In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: December 4, 2018

ERIC REED and JEANNA REED, as Parents and Natural Guardians of I.R., a minor,	*	PUBLISHED
	*	No. 08-650V
Petitioners,	*	Chief Special Master Dorsey
v.	*	ProQuad Measles, Mumps, Rubella, and Varicella ("MMRV") Vaccine; Autism Spectrum Disorder ("ASD"); Encephalopathy; Mitochondrial Dysfunction; Mitochondrial Disorder.
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	
Respondent.	*	

Anne Carrion Toale, Maglio Christopher and Toale, Sarasota, Florida, for petitioners.
Ryan Daniel Pyles, U.S. Department of Justice, Washington, D.C., for respondent.

ENTITLEMENT DECISION[1]

On September 15, 2008, Eric Reed and Jeanna Reed ("petitioners"), parents and guardians of I.R., a minor, filed a Short-Form Autism Petition for Compensation under the National Vaccine Injury Compensation Program ("the Program").[2] The case was included

[1] The undersigned intends to post this Decision on the United States Court of Federal Claims' website. **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), petitioners have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access. Because this Decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services).

[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10 et seq. ("Vaccine Act" or "the Act"). Hereafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

among the pending claims in the Court's Omnibus Autism Proceeding ("OAP").[3] At the conclusion of the OAP test cases, petitioners filed an amended petition alleging that the combined measles, mumps, rubella, and varicella ("MMRV" or "ProQuad"[4]) vaccine that I.R. received at 12 months on December 30, 2005, caused I.R. to "suffer from immunodeficiency disorder, bowel disease, pathological neuroinflammation, seizure disorder, mitochondrial disease, and the resulting features of autism spectrum disorder ('ASD')." Amended ("Am.") Petition dated Feb. 6, 2012, at ¶ 34 (ECF No. 16). Petitioners also alleged at the time that I.R. suffered a table injury, "post-MMR encephalitis." Id. at ¶ 35.[5] However, petitioners subsequently filed a second amended petition alleging that I.R. "suffered a significant aggravation of a preexisting condition, a mitochondrial disorder, causally related to the ProQuad vaccine administered on December 30, 2005," which in turn caused I.R. to "suffer from immunodeficiency disorder, bowel disease, pathological neuroinflammation, seizure disorder, mitochondrial dysfunction and the resulting features of autism spectrum disorder." Second Am. Petition dated Mar. 16, 2015, at ¶¶ 43-44 (ECF No. 85); see also Joint Pre-hearing ("Prehr'g") Submission dated Apr. 3, 2015, at 7 (ECF. No. 98).

An entitlement hearing was held on April 28-29, 2015, and June 22-24, 2016, followed by post-hearing briefing. After a review of the entire record, including medical records, affidavits, videotape evidence, expert reports, medical literature, hearing testimony, and other submissions, the undersigned finds that the evidence does not support a finding that petitioners are entitled to compensation. Accordingly, for the reasons discussed herein, compensation is denied.

I. Factual Background

The undersigned has considered all the evidence in this case and the record as a whole. The following summaries are by no means a complete recitation of the relevant facts and evidence reviewed. See § 300aa–13(a) (stating that the special master should consider the "record as a whole").

[3] The Omnibus Autism Proceeding consisted of a large group of petitions alleging that certain childhood vaccinations cause or contribute to the development of a serious neurodevelopmental disorder known as "autism spectrum disorder" or "autism." For complete information concerning the autism proceedings, please see www.uscfc.uscourts.gov/omnibus-autism-proceeding.

[4] ProQuad, a vaccine for the prevention of measles, mumps, rubella, and varicella, is recommended for children 12 months through 12 years of age. ProQuad, Merck Vaccines, https://www.merckvaccines.com/Products/ProQuad (last visited Nov. 7, 2018).

[5] While petitioners alleged a table encephalopathy in their amended petition, this allegation was abandoned in their second amended petition. See Second Am. Petition dated Mar. 16, 2015 (ECF No. 85).

A. Stipulated Facts

The parties agreed to 29 paragraphs of stipulated facts, set forth in the joint pre-hearing submission filed on April 3, 2015. Joint Prehr'g Submission at 1-6. Although not repeated here, the stipulated facts are incorporated in the Decision as if fully set forth. See id. The summary of additional facts below includes some of the facts set forth in the stipulated submissions, as well as additional relevant facts that pertain to I.R.'s medical history and the experts' opinions.

B. Summary of Additional Relevant Facts from the Medical Records

I.R. was born on December 29, 2004. Petitioners' Exhibit (Pet. Ex.) 4 at 6. He was conceived through in vitro fertilization ("IVF") and his mother was induced into labor at 38 weeks. Id. Prior to delivery, I.R.'s mother was placed on bed rest due to preeclampsia and high blood pressure. Pet. Ex. 2 at 9. At birth, I.R. experienced respiratory depression. Pet. Ex. 4 at 7. APGAR scores at one and five minutes were four and nine, respectively. Id. at 6. Although I.R. experienced breathing problems within the first five minutes of birth, his condition improved and he met all the benchmarks of a healthy newborn. Id. at 7.

i. I.R.'s Medical History Prior to 12-Month Vaccinations

As an infant, I.R. had trouble feeding, was colicky, and had a number of illnesses. See, e.g., Pet. Ex. 9 at 42. On January 19, 2005, he was noted to have excessive gas, and several days later, he had vomiting and diarrhea. Pet. Ex. 15 at 3-4. On January 26, 2005, he was reported to have episodes of crying and screaming. Id. at 5. Zantac was prescribed. Id. In February 2005, I.R.'s stomach problems persisted and he had another episode of diarrhea that lasted for two days. Id. at 6-7. In March 2005, he had periods of low grade fever, fussiness, and screaming. Id. at 8. Later that month, he had another low-grade fever and diarrhea. Id. at 9.

I.R.'s records do not reveal episodes of illness during the summer of 2005. By mid-October of that year, however, he was ill again, with colds "back to back" and a cough for one month. Pet. Ex. 15 at 11-12; see also Pet. Ex. 9 at 37. During his 9-month visit on October 13, 2005, I.R. was noted to suffer from a "nasty cough." Pet. Ex. 9 at 37. I.R.'s mother contacted his pediatrician's office with further complaints about his colds on October 27 and 31, 2005. Pet. Ex. 15 at 11-12. She expressed concern specifically about his "productive cough" and "constant drainage from nose." Id. at 11.

I.R.'s illnesses continued through November. Pet. Ex. 9 at 35-36; Pet. Ex. 15 at 13-14. During a sick visit with his pediatrician on November 1, 2005, I.R. exhibited coughing, fever, and decreased appetite. Pet. Ex. 9 at 36. On November 16, 2005, I.R. again suffered from a productive cough and loss of appetite, accompanied by fever and diarrhea. Pet. Ex. 15 at 14. On November 18, 2005, the intermittent fever, cough, and diarrhea persisted. Id. at 13. At this time, I.R. was described by his parents as being more fatigued and "sick off and on for weeks." Id.

Records from a November 19, 2005 sick visit also note a recent history of fever, diarrhea, and a "bad cough." Pet. Ex. 9 at 35.

ii. I.R.'s Medical History Following 12-Month Vaccinations

At I.R.'s one-year well-child exam on December 30, 2005, his pediatrician, Dr. Brooke Scherer, noted that I.R. was healthy. Pet. Ex. 9 at 34. I.R.'s 12-month vaccinations for mumps, measles, rubella, and varicella ("ProQuad") and for Haemophilus influenza type B and Hepatitis B ("COMVAX"[6]) were also administered. Id. Nine days later, on January 8, 2006, I.R. had a high fever, above 103°, for several days. Pet. Ex. 15 at 17. I.R.'s pediatrician indicated that the fever could have been a reaction to the ProQuad vaccine.[7] Id. at 16.

On February 3, 2006, approximately one month after these vaccinations, I.R.'s mother called the pediatrician's office to report that I.R. had a fever and a rash on his face and trunk. Pet. Ex. 15 at 15. The registered nurse who spoke with I.R.'s mother suggested that the rash was likely roseola[8] based on the mother's description. Id. On February 24, 2006, I.R. was diagnosed with pityriasis rosea.[9] Pet. Ex. 9 at 33. The rash persisted and led to a return visit on March 23, 2006. Id.

On March 26, 2006, I.R. was seen at the emergency room for fever and vomiting that began the previous day. Pet. Ex. 4 at 2-3. I.R. had some blueness around his lips and hands and his fever was 101°. Id. He was diagnosed with viral gastroenteritis and fever. Id. Four days later, on March 30, 2006, I.R. had his 15-month well-child visit. Pet. Ex. 9 at 32. No developmental abnormalities were noted and I.R. was assessed as a healthy 15 month old. Id.

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[6] COMVAX, which has since been discontinued, is a vaccine for the prevention of Haemophilus influenza type B and Hepatitis B. Licensed Biological Products with Supporting Documents, U.S. Food & Drug Admin., https://www.fda.gov/BiologicsBloodVaccines/ucm133705.htm (last visited Nov. 7, 2018).

[7] I.R.'s mother reported the fever by telephone. I.R. was not seen by his pediatrician.

[8] Roseola is "a type of rose-colored rash seen most often in an infectious disease such as measles or other exanthematous diseases." Dorland's Illustrated Medical Dictionary 1654 (32d ed. 2012) ("Dorland's").

[9] Pityriasis rosea is "a common, acute or subacute, self-limited, exanthematous disease of unknown etiology, whose onset is marked by a solitary pink, reddish, or tan plaque called a herald patch, usually on the trunk . . . ; subsequent lesions are similar to this but smaller, with vesicular borders, tending to peel and produce a scaly collarette." Dorland's at 1451.

At the visit, I.R. received the diphtheria-tetanus-acellular pertussis ("DTaP") and 7-valent pneumococcal conjugate vaccine ("PCV7" or "Prevnar 7"[10]) vaccines. Id.

In April and May of 2006, I.R. visited his pediatrician's office numerous times. See generally Pet. Ex. 5; Pet. Ex. 9. On April 11, 2006, the medical record indicates he had been sick for about a week and a half, with symptoms of fever, cough, and sleeplessness. Pet. Ex. 9 at 31. On April 24, 2006, he had a rash "all over trunk," which had been present "x 3 days." Pet. Ex. 9 at 30. He also had swelling of the face, red ears, and ear drainage. Id. His diagnoses included right-sided otitis media. Id. On April 27, 2006, I.R. returned and was diagnosed with bilateral otitis media, conjunctivitis, and petechiae on his earlobes. Pet. Ex. 9 at 29. At a series of three visits between May 2 and 4, 2006, I.R. was again diagnosed with otitis media and given an injection of Ceftriaxone, an antibiotic. Pet. Ex. 9 at 26-28. On May 5, 2006, I.R. saw an ear, nose, and throat ("ENT") specialist at the Ear Institute of Chicago, who diagnosed bilateral ear infections and perforated ear drums. Pet. Ex. 6 at 11. I.R.'s past history of fevers ranging from 103° to 105° were attributed to ear infections. Id. Because of I.R.'s repeated illnesses, the ENT specialist recommended immunoglobulin testing for possible immunodeficiency. Id. I.R.'s immunoglobulins A and G were both documented as below normal.[11] Pet. Ex. 4 at 65-66. At a follow-up visit on May 12, 2006, I.R. was improved, had no fever, and was described as playful and active. Pet. Ex. 6 at 10.

Due to his recurrent acute otitis media with high fevers, I.R. had tympanostomy tubes inserted on May 23, 2006. Pet. Ex. 6 at 3-4. I.R.'s preoperative diagnosis was recurrent acute otitis media and bilateral middle ear effusion. Id. at 3. The surgeon's operative report documents that I.R. had a history of "recurrent acute otitis media over the past several months developing recurrent high fevers." Id.

Following his operation, I.R. travelled with his family to Florida for vacation. On May 26, 2006, while in Florida, I.R.'s father called the pediatrician to report that I.R. had a fever of 103.5°. Pet. Ex. 6 at 9. The pediatrician instructed I.R.'s family to take him to an emergency department. Pet. Ex. 12 at 3-6. The treating physician in Florida ordered a complete blood count ("CBC"), which was normal, and diagnosed I.R. with a viral infection. Id.

On June 2, 2006, I.R.'s mother called his pediatrician to report that he had petechiae on his ear lobe. Pet. Ex. 15 at 44. She called again on June 10, 2006, reporting that I.R. had "3 good days last week with no [symptoms]" but that he had developed a low-grade fever a few days before and was "acting tired." Id. at 43. On June 14, 2006, I.R.'s mother reported that I.R.

[10] Prevnar 7 is a pneumococcal conjugate vaccine for the prevention of pneumococcal disease and is recommended for all babies and children younger than two years of age. Pneumococcal Vaccination: What Everyone Should Know, Ctrs. for Disease Control & Prevention, https://www.cdc.gov/vaccines/vpd/pneumo/public/index.html (last visited Nov. 7, 2018). Prevnar 13 is the latest iteration of this vaccine. Id.

[11] But see infra Section VI.B.ii.e.

had a floppy appearance and was stumbling a lot. Id. at 41. He was also irritable, vomiting, and had a low-grade fever. Id. The following day, I.R. presented to his pediatrician for a sick visit and was noted to be irritable, imbalanced, and fatigued. Pet. Ex. 9 at 24. The pediatrician recommended I.R. be seen by an immunologist; he also ordered a head and sinus CT scan, the results of which were normal. Id.

At his 18-month well-child exam on June 27, 2006, I.R. was noted to stumble less often, and his petechiae had cleared. Pet. Ex. 9 at 23. At that visit, his parents reported that I.R. had a 10-word vocabulary. Id. No developmental concerns were noted, and I.R. was described as "healthy." Id. Between that visit and July 18, 2006, I.R. experienced ear drainage, which was treated with medication and ear wicks. Id. at 20.

In August 2006, I.R. underwent an immunology evaluation at Loyola Clinic for Asthma, Allergy, and Clinical Immunology. Pet. Ex. 11 at 2. Although his IgG2 was below normal, it was attributed to "a frequent delay in immunity seen in young boys." Id. at 6-7. Based on the tests and evaluations, the immunologist concluded that I.R.'s immune system responded normally to environmental challenges relative to his age. Id. at 7.

I.R.'s two-year well-child exam was December 28, 2006. Pet. Ex. 9 at 17. He presented with no health problems. Id. He could say at least 20 words. Id. Again, no developmental concerns were noted. Id. In January 2007, I.R. had bilateral otitis media, ear drainage, and cough, and was treated with ear drops and antibiotics. Id. at 16. I.R. had no other significant health problems in January or February 2007.

iii. Evaluation and Diagnosis of Autism

I.R.'s mother first expressed concern about his speech development on March 30, 2007, more than a year after the vaccinations in question, when I.R. was seen for a follow-up appointment after an ear infection. Pet. Ex. 9 at 15. I.R. was 27 months of age. Id. He was saying 20 words, but many were difficult to understand. Id. I.R. also seemed frustrated with his inability to communicate. Id. The pediatrician diagnosed a speech delay and recommended that he be evaluated through the Early Intervention Program. Id.

On April 18, 2007, I.R. (28 months old) was evaluated by Jump Start Development ("Jump Start"). Pet. Ex. 9 at 61-66. The evaluation included a parental interview, clinical observation, and testing with the Battelle Developmental Inventory.[12] Id. The examiners concluded that I.R. had a delay in personal and social skills and referred him for occupational therapy. Id. at 66.

[12] Battelle Developmental Inventory is a comprehensive development test focused on cognitive, adaptive, motor, communication, and personal-social behavior. It is most often used to determine if a child is eligible for therapy services. See generally Abbey T. Berls & Irene R. McEwen, Battelle Developmental Inventory, Physical Therapy, Aug. 1999, at 776-783.

On May 1, 2007, occupational therapists documented that I.R. had a delay with grasping and visual motor integration. Pet. Ex. 9 at 75. They recommended occupational therapy in a clinical setting and a "sensory diet." Id. at 76. To rule out hearing problems as a cause for his language difficulties, I.R. was referred to the Sertoma Speech and Hearing Center for testing and evaluation. Pet. Ex. 7 at 2. He passed all screening tests and was deemed not hearing impaired. Id. at 2-3.

On July 24, 2007, I.R. (31 months old) was referred for an evaluation at Advocate Illinois Masonic Medical Center. Pet. Ex. 9 at 47. The records note that I.R.'s parents were concerned about his speech delay that began "after four months of illness," as well as his "difficult behaviors that may be due to autism." Id. at 47. I.R.'s language development history was reported as follows:

> [I.R.'s] first words were at 1 year of age, then he had 15 words at 15 months, but while sick he had no new words and for a long time had the same 15-20 words. He has had slow progression since he was ill, and now has about 40 words with a few 2-word utterances.

Id. at 48. Dr. Michael Cupoli, M.D., and other examiners[13] assessed I.R.'s developmental and behavioral skills to determine whether he was delayed as compared to his peers[14] and to measure his age equivalency.[15] Id. at 49. I.R. exhibited a significant delay in both cognitive and social-emotional skills. Id. Based on the testing, he was diagnosed with a sensory processing disorder, disruptive behavior disorder, and mixed language disorder, and was recommended for occupational therapy. Id. at 52. I.R. was also evaluated for autism through informal observation, which yielded unclear results. Id. The examiners recommended that I.R. undergo further testing to discern whether he had a definitive diagnosis of autism. Id. They also encouraged metabolic and genetic testing for I.R. Id.

On October 12, 2007, I.R. (33 months) was evaluated for "diagnostic clarification" at the Children's Research Triangle. Pet. Ex. 10 at 5. I.R. had difficulty maintaining eye contact and engaging with the examiners. Id. at 7-8. The examiners concluded that I.R.'s developmental delays were characteristic of autistic disorder. Id. at 8. Based upon his Childhood Autism

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[13] Dr. Michael Cupoli is a developmental and behavioral pediatrician. The other examiners included occupational therapists Lori N. Osborne, Ph.D., and Deborah Margulis, M.S.; physical therapist Lara Miller; and developmental therapist Melba Carter. See Pet. Ex. 9 at 47.

[14] I.R. was 45% delayed in cognitive skills, according to the Mullen Scale of Learning. Pet. Ex. 9 at 49. He was 42-52% delayed in social-emotional development measured by an informal observation through the Childhood Autism Rating Score ("CARS") and the Hawaii Early Learning Profile. Id. I.R.'s gross motor skills showed no delay. Id.

[15] I.R.'s level of cognitive skills was assessed as equivalent to a 17-month old and his social-emotional skills were between 15 and 18 months. Pet. Ex. 9 at 49.

Rating Score ("CARS")[16] of 39, I.R. was placed in the severe autistic range. Id. Upon completion of the evaluation, I.R. was diagnosed with "Autistic Disorder." Id. at 9. Early Intervention through the Early Childhood Program was recommended. Id.

Shortly before I.R.'s third birthday, on November 8, 2007, he was seen at the Pfeiffer Treatment Center, where he underwent biochemical testing.[17] Pet. Ex. 8 at 24. After discussing I.R.'s medical and nutritional history, the physician recommended that I.R. start a gluten and casein[18] free diet and take methyl-B-12 injections. Id. at 32. On December 12, 2007, the Pfeiffer Treatment Center notified I.R.'s parents that his lab results showed a zinc deficiency and elevated copper levels. Id. at 48.

At his three-year well-child exam on December 28, 2007, I.R.'s pediatrician noted that his speech was improving. Pet. Ex. 9 at 11. I.R. was assessed as a well child with autism. Id. At his four-year visit on January 15, 2009, I.R.'s pediatrician documented that his autism was less severe. Pet. Ex. 29 at 14.

iv. Genetic Testing and Evaluations for Mitochondrial and Immunological Disorders

After I.R. received his diagnosis of autism, he underwent testing to identify a causal or contributing underlying genetic or mitochondrial disorder. On June 26, 2009, I.R. saw Dr. Marvin R. Natowicz during a stay in the pediatric epilepsy unit at the Cleveland Clinic. Pet. Ex. 29 at 63. Dr. Natowicz was asked to evaluate I.R. to determine a "possible genetic and/or metabolic basis" for his ASD. Id. Prior diagnostic testing was reviewed and reported as follows: cranial CT scan (June 2006) normal; blood lymphocyte karyotype (2007) normal; Fragile X syndrome testing (2007) negative; CBC (2006, 2007, 2009) negative; comprehensive serum chemistry panel (2007, 2009) negative; serum CK (2007) normal; serum TSH and free T4 (2007) normal; blood ammonia (2009) normal; IgG (2006) low at 563; IgM (2006) normal; IgA (2006) low at less than 47; IgG, IgM, and IgA (2006) normal. Id. at 66-67.

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[16] CARS is a scale used by clinicians to measure the indicators of autism. Ctr. for Autism Research, http://www.carautismroadmap.org/childhood-autism-rating-scale/ (last visited Nov. 7, 2018).

[17] The Pfeiffer Treatment Center (now the Pfeiffer Medical Center) focuses on treating biochemical imbalances in children through vitamin, minerals, and other nutrient supplements. Pfeiffer Medical Ctr., http://www.hriptc.org/index.php (last visited Nov. 7, 2018).

[18] Casein is a protein present in all mammals' milk. The most common foods that contain casein are milks, ice cream, sour cream, yogurt, butter, lunchmeats, and cheese. A casein-free diet eliminates all foods that contain ingredients that have mammals' milk. What is Casein?, Talk About Curing Autism, http://www.tacanow.org/family-resources/what-is-casein/ (last visited Oct. 9, 2018).

I.R.'s physical examination was normal except for findings of a "large body size w/o disproportionate macrocephaly" and mild hyper-extensibility of hips and fingers. Pet. Ex. 29 at 67-68. Neurological examination was notable for his "neurodevelopmental phenotype, . . . mild diffuse hypotonia and a question of mild gross motor clumsiness." Id. at 68. Dr. Natowicz noted that I.R.'s clinical history, physical exam, and prior diagnostic evaluation did not suggest any basis for his ASD. Id. I.R.'s motor clumsiness and "possible intolerance of fasting raise[d] a question of an underlying metabolic basis for his condition," but Dr. Natowicz stated that a metabolic condition was not a certainty since no other history or lab data strongly supported a metabolic cause. Id. In addition to considering a metabolic cause, Dr. Natowicz also wondered whether I.R. might have a "monogenic non-syndromic process," given his history of staring episodes and his EEG pattern. Id. Lastly, Dr. Natowicz proposed the possibility of an "underlying chromosomal" disorder, noting that the prior chromosomal studies lacked the "substantial power to detect subtle cytogenic lesions." Id.

Dr. Natowicz ordered diagnostic tests to screen for metabolic causes or risk factors for I.R.'s ASD, but no such causes or risk factors were found. Pet. Ex. 29 at 68-69. Blood lactate levels, pyruvate levels, the plasma acylcarnitine profile, urinalysis, the urinary acylglycine profile, urinary organic acid analysis, urinary guanidinoacetate analysis, and creatine analysis were all normal. Id. Plasma amino acid analysis revealed mildly increased plasma glycine[19] and a relative increase in plasma alanine, but the "absolute level of alanine was normal." Id. DNA sequencing of the SCN1A gene was normal, although Dr. Natowicz did not rule out other genetic mutations. Id. The oligonucleotide-based chromosomal microarray analysis and cranial MR were also normal. Id. The EEG showed "benign focal epileptiform discharges of childhood." Id. Testing also did not reveal chromosomal abnormalities. Id. While acknowledging the limits of diagnostic testing, Dr. Natowicz concluded that it was unlikely that I.R. had a metabolic disorder because the tests did not reflect evidence of "organic acidemias and mitochondrial cytopathies, disorders of mitochondrial fatty acid beta-oxidation, [or] disturbances of creatine synthesis and transport." Id. He encouraged I.R.'s parents to revisit the issue of genetic etiologies in the future, given ongoing research and development in the area of ion channel defects caused by genetic mutations. Id.

On September 24, 2009, I.R. was seen by Dr. Richard E. Frye at University of Texas Physicians in Houston. Pet. Ex. 25 at 132-34. Dr. Frye noted I.R.'s abnormal EEG and history of immunoglobulin abnormalities, and recommended testing for cerebral folate deficiency and medication to treat the abnormal discharges seen on the EEG. Id. at 134. Numerous diagnostic tests were ordered, including a lumbar puncture. Id. at 88-98.

After the above testing revealed low levels of IgG, I.R. underwent a second immunological evaluation, this one by Dr. Sudhir Gupta, Chief of Immunology at the University of California, Irvine. Pet. Ex. 29 at 103. In a letter dated December 18, 2009, Dr. Gupta noted

[19] The increase in plasma glycine was not thought significant because I.R. had been receiving dimethylglycine. Pet. Ex. 29 at 69.

I.R.'s "impressive history of recurrent acute and chronic otitis media treated with several courses of antibiotic." Id. Given I.R.'s history of ear infections, decreased levels of IgG, and the fact that he lacked antibodies to polio even though he received the polio vaccine, Dr. Gupta diagnosed I.R. with "hypogammaglobulinemia with specific antibody deficiency" and recommended IVIG treatments. Id. Dr. Gupta did not express an opinion about whether I.R. had a mitochondrial disorder.

On February 25, 2010, Dr. Frye held a conference call with I.R.'s mother and physicians regarding analysis of I.R.'s cerebrospinal fluid ("CSF").[20] Pet. Ex. 25 at 85. Dr. Gupta confirmed "elevations in cytokines" consistent with an inflammatory process; Dr. Krigsman (a GI physician) noted "inflammation in the GI tract"; and Dr. Frye noted "decreased BH4 [consistent with] inflammation." Id. Dr. Frye also thought I.R. might possibly have a "secondary mito deficiency due to inflammation," but added that it was "probably mild considering the few mito markers found." Id. Thus, as of February 25, 2010, Dr. Frye considered the possibility of a mitochondrial deficiency, but had not diagnosed I.R. with a mitochondrial disorder due to the paucity of diagnostic markers.

To complete his evaluation for a metabolic or mitochondrial disorder, I.R. underwent a right quadriceps muscle biopsy in February 2011. Pet. Ex. 25 at 18. The biopsy showed "very good differentiation of [muscle] fiber types," but no necrosis, regeneration, or phagocytosis. Id. The biopsy did not show "'ragged-red' or 'ragged-blue' fibers." Id. Electron microscopy revealed "several accumulations of intermyofibrillar enlarged mitochondria," but "no crystalloid inclusions." Pet. Ex. 21 at 2. Mitochondrial respiratory chain enzyme analysis ("ETC") performed on the muscle revealed increased citrate synthase activity, suggesting "mitochondrial proliferation," a possible "adaptive response to mitochondrial dysfunction." Pet. Ex. 22 at 3.

Genetic testing for the PTEN mutation[21] detected a benign sequence variant. Pet. Ex. 27 at 4. A screening panel for common mutations and deletions in mitochondrial DNA, performed in May 2011, found no abnormal mutations. Id. at 12. In October 2011, Dr. Frye ordered a Transgenomic NuclearMitome Test, a "comprehensive gene panel for variants in 448 nuclear genes important for mitochondrial function." Pet. Ex. 30 at 4. The test revealed that I.R. had "a variant of unknown significance in KIAA0196, a gene with autosomal dominant disease

[20] Of note, serology studies also performed on I.R.'s CSF in February 2010 revealed that no antibodies were detectable for Rubeola (measles) or Rubella. Pet. Ex. 25 at 86.

[21] "The PTEN gene provides instructions for making an enzyme that is found in almost all tissues in the body. The enzyme acts as a tumor suppressor, which means that it helps regulate cell division by keeping cells from growing and dividing too rapidly or in an uncontrolled way." PTEN gene, Genetics Home Reference, U.S. Nat'l Library of Med., https://ghr.nlm.nih.gov/gene/PTEN# (last visited Nov. 7, 2018).

inheritance," and that [t]his genotype could be consistent with spastic paraplegia type 8."[22] Id. at 1. The test also showed that I.R. is a "carrier for a predicted deleterious variant in the POLG, a gene with autosomal recessive and autosomal dominant disease inheritance."[23] Id.

On August 31, 2011, using the Morava criteria,[24] Dr. Frye concluded that I.R. had "a probable mitochondrial disorder." Pet. Ex. 25 at 7. Dr. Frye gave I.R. a score of 7 points, including 3 points for his history of regression and seizures, 2 points for elevated alanine, and 2 points for the abnormal electron microscopy skeletal muscle biopsy findings. Id.

C. Summary of Affidavits, Fact Testimony, and Additional Evidence

Both of I.R.'s parents provided detailed affidavits about I.R.'s health and development prior to the December 30, 2005 vaccinations and the changes they observed over the ensuing months and years. See Pet. Exs. 16-17. Additionally, Mrs. Reed provided oral testimony during the first day of hearing on April 28, 2015. See Transcript ("Tr.") at 10-102. Home videos were also submitted into the record. See Pet. Exs. 138-44.

i. Jeanna Reed Affidavit

Mrs. Reed recounted that prior to receiving the ProQuad and COMVAX vaccines on December 30, 2005, when he was one year old, I.R. was meeting or exceeding "[a]ll of his developmental milestones." Pet. Ex. 16 at 1. She recalled that "[h]e understood commands, he waved, he said 'mama, dada, banana' to name a few words." Id. He was an "absolutely healthy one year old." Id.

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[22] "Spastic paraplegia type 8 is part of a group of genetic disorders known as hereditary spastic paraplegias. These disorders are characterized by progressive muscle stiffness (spasticity) and the development of paralysis of the lower limbs (paraplegia)." Spastic paraplegia type 8, Genetics Home Reference, U.S. Nat'l Library of Med., https://ghr.nlm.nih.gov/condition/spastic-paraplegia-type-8 (last visited Nov. 7, 2018).

[23] "The POLG gene provides instructions for making the active piece, called the alpha subunit, of a protein called polymerase gamma (pol γ). . . . Pol γ is a DNA polymerase, which is a type of enzyme that 'reads' sequences of DNA and uses them as templates to produce new DNA." POLG gene, Genetics Home Reference, U.S. Nat'l Library of Med., https://ghr.nlm.nih.gov/gene/POLG (last visited Nov. 7, 2018). DNA polymerases play important roles in the replication of cells' genetic material and the repair of DNA and have an important function in mitochondria. Id. "Mitochondria each contain a small amount of DNA, known as mitochondrial DNA (mtDNA), which is essential for the normal function of these structures. Pol γ is the only DNA polymerase that is active in mitochondria and that can replicate mtDNA." Id.

[24] The Morava criteria are discussed further below. See infra Section VI.C.i. They are part of a "consensus mitochondrial disease scoring system . . . established to facilitate the diagnosis in patients with a suspected mitochondrial disorder." Pet. Ex. 71 at 1.

A week later, on January 7, 2006, I.R. "came down with a 103+ fever," which "went up to 104+" the following day. Pet. Ex. 16 at 1. Because Mrs. Reed was concerned about his temperature, as well as his unsteadiness when walking, she contacted the pediatrician's office. Id. She called the pediatrician's office again on January 9, when a rash that "looked like the chicken pox" appeared on his body. Id. She was "reassured this was normal." Id.

In early February 2006, I.R. developed another high fever, which resolved after three days, and then a rash on his face and trunk. Pet. Ex. 16 at 2. On February 3, 2006, Mrs. Reed called the pediatrician's office to report his condition and inquire about the rash. Id. She recalled being "reassured by the nurse that it was most likely Roseola and that it would resolve." Id. A few weeks later, I.R. developed a rash on his back "that seemed to be spreading in patches[,] and his cheeks . . . were also very red." Id. Additionally, he seemed fatigued and lacked coordination. Id. At an office visit on February 24, 2006, I.R. was diagnosed with pityriasis rosea. Id. The rash persisted over the next month and spread to his shoulders. Id. At an office visit on March 23, 2006, I.R.'s pediatrician continued the diagnosis of pityriasis rosea and reassured that "it would resolve within eight to ten weeks." Id.

On March 26, 2006, I.R. was taken to an emergency room for fever, vomiting, and blue-appearing lips and hands, and was diagnosed with viral gastroenteritis and fever. Pet. Ex. 16 at 2. I.R. attended his 15-month checkup a few days later, on March 30, 2006, and was noted to be "developmentally fine" and "overall a healthy 15[-]month old." Id. At that visit, he received DTaP and Prevnar vaccines. Id.

Beginning in April and extending through May, I.R. had a series of illnesses, with numerous calls and visits to his pediatrician's office. Pet. Ex. 16 at 2-3. The day after his March 30 visit, Mrs. Reed recalled I.R. having "dark red circles under his eyes" and a "puffy and swollen" face. Id. at 2. Over the next few weeks he continued to have facial swelling and developed cough, fever, and rash, as well as otitis media and conjunctivitis. Id. None of the prescribed treatments, including eye drops, Amoxicillin, and Benadryl, had much effect. Id. On April 26, 2006, I.R. had "dark purple dots that looked like blood and . . . 'splotches' on the bottom of his earlobes." Id. Mrs. Reed sent pictures to I.R.'s pediatrician and took I.R. for an office visit the following day. Id. I.R. was diagnosed with petechiae and a complete blood count was ordered. Id. The next morning, the I.R. "woke up with petechiae on his forearm down to his hand." Id. Despite this development, I.R.'s blood results returned normal, providing "a moment of relief." Id.

I.R.'s fever returned a few days later with more severe symptoms. Pet. Ex. 16 at 3. On May 2, 2006, I.R. was seen by his pediatrician, who determined the best treatment was to administer a series of antibiotic injections over three consecutive days. Id. The antibiotic appeared to help. Id. On May 5, 2006, I.R. was seen by an ENT for evaluation of his recurrent ear infections. Id. at 4. The ENT "ordered an immunoglobulin analysis to evaluate for possible immunodeficiency." Id. The results showed below normal levels of immunoglobulin A and G. Id. At a follow-up visit, the ENT recommended ear tubes be inserted to relieve I.R.'s ear

problems. Id. The procedure was performed on May 23, 2006. Id. Another immunoglobulin test was performed, but this one returned with normal results. Id.

While vacationing in May 2006, I.R.'s fever and petechiae returned, and he suffered diarrhea. Pet. Ex. 16 at 4. He was examined at a nearby emergency room and diagnosed with another "viral syndrome." Id. Throughout the month of June 2006, I.R. continued to experience a variety of symptoms, including fever, petechiae, diarrhea, vomiting, poor appetite, irritability, and lethargy. Pet. Ex. 16 at 4. By his 18-month checkup on June 27, 2006, he "seemed to be getting better" physically, although his behavior was "becoming a bit more challenging." Id. The month of July 2006 saw fewer illnesses, and I.R. was "very active." Pet. Ex. 16 at 5. The results of an immunology consult and testing at Loyola Medical Hospital on July 24, 2006, returned as "normal for his age." Id.

By I.R.'s second birthday in late December 2006, changes in his behavior were starting to cause concern. Pet. Ex. 16 at 5. Mrs. Reed recalled that he had difficulty sitting still and "was very frustrated with his speech." Id. She also remembered that "[t]ime outs were not [an] effective" form of discipline and that he "seemed to like the physical side of punishment." Id. For instance, when they "would put him on the step he would throw himself on it." Id.

Mrs. Reed's affidavit also described at length her family's subsequent efforts to diagnose I.R.'s condition and care for him. Pet. Ex. 16 at 5-10. She testified similarly during the hearing, though with some additional detail. Tr. 10-101.

ii. Eric Reed Affidavit

Mr. Reed explained that due to his work schedule, his interactions with I.R. were mostly limited to evenings and weekends. Pet. Ex. 17 at 1. He indicated that Mrs. Reed watched I.R.'s development and progress every moment on a daily basis. Id. Nonetheless, Mr. Reed indicated that he did notice that I.R. tended to get really sick a couple days after regular doctor's visits and vaccinations, noting in particular that I.R. had episodes of 104° to 105° fevers for several days in a row. Id. After noticing this trend, Mr. Reed indicated that he also noticed I.R.'s development begin to taper off. Id. at 2. Mr. Reed recalled that his speech declined and that he stopped using words he had been using on a regular basis. Id. He placed this changed at between about one year of age and eighteen months of age. Id. Mr. Reed also indicated that he observed a change in temperament as well, noting that after his vaccinations he became hard to manage and very erratic. Id. Additionally, Mr. Reed described the efforts that his family made to address I.R.'s condition. Id. at 2-3. Mr. Reed did not testify during the hearing.

iii. Home Videos

In addition to oral and written testimony, petitioners provided extensive video footage showing I.R. at home and engaged in daily family activity from about six months of age to shortly after his second birthday. Specifically, the videos were filed on seven discs marked as

petitioners' Exhibits 138 through 144 and include footage from July 10, 2005, to January 23, 2007.

II. Procedural Background

Petitioners filed their claim on September 15, 2008. The case was included in the OAP.[25] Supporting evidence was also filed in the form of medical records, labeled as Exhibits 1-15 (ECF No. 6), and affidavits, labeled as Exhibits 16-17 (ECF No. 7).

On December 12, 2008, respondent filed his Rule 4(c) Report, stating that the case was not appropriate for compensation. Respondent's Report ("Resp. Rept.") dated Dec. 12, 2008 (ECF No. 8). Over the next three years, petitioners filed additional medical records, labeled as Exhibits 18-19 (ECF No. 9), Exhibit 20 (ECF No. 12), Exhibit 21 (ECF No. 13), and Exhibits 22-29 (ECF No. 14). Petitioners filed an amended petition on February 6, 2012. Amended ("Am.") Petition dated Feb. 6, 2012 (ECF No. 16).

Thereafter, another special master received the case and set a deadline for petitioners to file an expert report. See Order dated Feb. 7, 2012 (ECF No. 18). Petitioners subsequently filed more records, labeled as Exhibits 30-31 (ECF Nos. 19, 22), and eventually the expert report of Andrew W. Zimmerman, M.D., designated as Exhibit 32 (ECF No. 27). The special master

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[25] The OAP was created to manage more than 5,400 petitions alleging that autism or autism spectrum disorder was caused by either the measles, mumps, and rubella ("MMR") vaccine or thimerosal, an ethylmercury preservative used in multi-dose vials of vaccines. See Autism General Order #1, 2002 WL 31696785 (Fed. Cl. Spec. Mstr. Jul. 3, 2002). Three special masters conducted separate proceedings in test cases involving these two theories of autism causation. All found that the petitioners had not provided preponderant evidence of causation, indicating that the cases were "not a close case." King v. Sec'y of Health & Human Servs., No. 03-584, 2010 WL 892296, at *90 (Fed. Cl. Spec. Mstr. March 12, 2010) (emphasis removed).

Motions for review were denied in all three cases. Two of the three decisions in the Theory 1 test cases were appealed to the Federal Circuit. Cedillo v. Sec'y of Health & Human Servs., No. 98-916, 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), aff'd, 89 Fed. Cl. 158 (2009), aff'd, 617 F.3d 1328 (Fed. Cir. 2010); Hazelhurst v. Sec'y of Health & Human Servs., No. 03-654, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), aff'd, 88 Fed. Cl. 473 (2009), aff'd, 604 F.3d 1343 (Fed. Cir. 2010). Petitioners in the third test case did not appeal the Court of Federal Claims' decision. Snyder v. Sec'y of Health & Human Servs., No. 01-162, 2009 WL 332044 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), aff'd, 88 Fed. Cl. 706 (2009). Petitioners did not seek review of the special masters' decisions in the Theory 2 test cases. Dwyer v. Sec'y of Health & Human Servs., No. 02-1202, 2010 WL 892250 (Fed. Cl. Spec. Mstr. March 12, 2010); King v. Sec'y of Health & Human Servs., No. 03-584, 2010 WL 892296 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); Mead v. Sec'y of Health & Human Servs., No. 03-215, 2010 WL 892248 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). For a comprehensive discussion of the OAP and proceedings after the conclusion of the test case litigation, see Sturdivant v. Sec'y of Health & Human Servs., No. 07-788, 2016 WL 552529 (Fed. Cl. Spec. Mstr. Jan. 21, 2016).

ordered petitioners to file a supplemental expert report from Dr. Zimmerman because the one submitted appeared to "not attribute the alleged vaccine-related injury to a vaccine." Order dated Aug. 15, 2012 (ECF No. 28).

The following month, petitioners filed the results of amino acid testing performed by Richard I. Kelley, M.D., Ph.D., and his interpretation of those results. Pet. Ex. 33 (ECF No. 30).[26] On October 15, 2012, petitioners filed Dr. Zimmerman's supplemental expert report. Pet. Ex. 34 (ECF No. 31).

On February 1, 2013, respondent filed the expert reports of Bruce H. Cohen, M.D., and Max Wiznitzer, M.D., along their curriculum vitae ("CV") and other supporting materials. Resp. Exs. A-E (ECF No. 34). On February 8, 2013, respondent filed a supplemental Rule 4(c) Report, maintaining his position that this case was not appropriate for compensation and should be dismissed. See Resp. Suppl. Rept. dated Feb. 8, 2013 (ECF No. 37).

On February 28, 2013, the special master convened a telephonic status conference to discuss petitioners' claim. During the discussion, petitioners' counsel asked that a hearing in this case be delayed until she had an opportunity to further consult with experts. The special master granted petitioners' request and ordered the filing of regular status reports until petitioners deemed the case ready for hearing. See Order dated Feb. 28, 2013 (ECF No. 38). For nearly a year and a half, petitioners filed status reports documenting their efforts to obtain additional expert evidence. They also filed more medical records during this period, identified as Exhibits 35-38 (ECF Nos. 40-41, 43).

On August 14, 2014, petitioners filed the expert report of Dmitriy Niyazov, M.D. Pet. Ex. 39 (ECF No. 52). Petitioners subsequently filed Dr. Niyazov's CV as Exhibit 40 (ECF No. 54) and supporting medical literature as Exhibits 41-65 (ECF No. 56). On October 29, 2014, respondent filed the expert report of Shawn E. McCandless, M.D., along with his CV and supporting medical literature. Resp. Exs. F-G (ECF No. 59). On December 1, 2014, petitioners filed the transcript of a proceeding of the Committee to Review Adverse Effects of Vaccines. Pet. Ex. 66 (ECF No. 61). The proceeding, which featured respondent's expert Dr. Cohen, occurred on August 26, 2009.

On December 5, 2014, petitioners filed a status report stating that the case was now ready for an evidentiary hearing. Petitioners planned to present the testimony of Drs. Zimmerman and Niyazov. See Status Report dated Dec. 5, 2014 (ECF No. 62). The special master ordered respondent to file a status report indicating which experts she intended to present at hearing.[27] Order dated Dec 9, 2014 (ECF No. 63). In the interim, the undersigned received the case. See Order Reassigning Case dated Dec. 11, 2014 (ECF No. 64).

[26] The Exhibit was previously filed incompletely (ECF No. 29).

[27] The status report was not filed.

On January 7, 2015, respondent filed a supplemental expert report from Dr. Cohen. Resp. Ex. H (ECF No. 66). The following day, the undersigned convened a status conference to discuss possible hearing dates and to confirm which experts would testify. Additionally, the undersigned afforded petitioners time to file a supplemental expert report in response to Dr. Cohen's supplemental report, provided it did not delay the hearing. See Order dated Jan. 8, 2015 (ECF No. 67). On January 26, 2015, in response to the parties' feedback, the undersigned ordered the entitlement hearing for April 28-29, 2015, and set pre-hearing deadlines. Prehr'g Order dated Jan. 26, 2015 (ECF Nos. 69, 70 (revised)).

From January through April 2015, petitioners filed additional evidence, including medical and other records, demonstrative materials, and supporting literature.[28] Likewise, respondent filed additional supporting literature.[29] On March 16, 2015, petitioners filed a second amended petition. Second Am. Petition dated filed Mar. 16, 2015 (ECF No. 85). That same day, petitioners moved for leave to file the report of an expert specializing in the retrospective review of home videos in cases of early autism. Motion ("Mot.") dated Mar. 16, 2015 (ECF No. 84).

On March 25, 2015, petitioners and respondent filed their pre-hearing memoranda. (ECF Nos. 90-91). The following day, the undersigned convened a pre-hearing status conference to discuss the upcoming hearing, as well as petitioners' pending motion to file the additional expert report. At the conclusion of the conference, the parties requested an opportunity to confer and to file a status report proposing next steps, including whether the hearing should be postponed. The undersigned granted the parties' request but ordered petitioners to file the videos they planned to have their expert analyze. See Order dated Mar. 26, 2015 (ECF No. 95).

On March 31, 2015, petitioners filed a joint status report informing the undersigned that the parties wished to proceed as scheduled. Joint Status Report dated Mar. 31, 2015 (ECF No. 96). Petitioners also noted that they and respondent had agreed to "table" the issue of video analysis. Id. Petitioners, however, reserved the right to present a video expert at a later date, and respondent reserved the right to challenge the merits of any motion by petitioners to add such an expert. Id.

On April 3, 2015, petitioners filed a Joint Pre-hearing Submission setting forth stipulated facts, disputed facts, issues not in dispute, and issues remaining to be resolved. Joint Submission dated Apr. 3, 2015 (ECF No. 98). The parties also reiterated their agreement to table the video

[28] Pet. Ex. 67 (ECF No. 68); Pet. Exs. 68-84 (ECF No. 71); Pet. Exs. 85-93 (ECF No. 77); Pet. Exs. 94-97 (ECF No. 78); Pet. Ex. 98 (ECF No. 79); Pet. Ex. 99 (ECF No. 80); Pet Exs. 100-106 (ECF No. 81); Pet. Exs. 107-109 (ECF No. 86); Pet. Exs. 110-119 (ECF No. 87); Pet. Ex. 120 (ECF No. 88); Pet. Ex. 121 (ECF No. 99); Pet. Ex. 122 (ECF No. 102); Pet. Ex. 123 (refiling of Exhibit 73) (ECF No. 105).

[29] Resp. Ex. H, Tabs 1-9 (ECF No. 72); Resp. Ex. H, Tabs 10-18 (ECF No. 73); Resp. Ex. J (ECF No. 101); see also Resp. Ex. C, Tabs 1-4 (refiled) (ECF No. 92); Resp. Ex. H, Tabs 2, 4-9 (refiled) (ECF No. 93); Resp. Ex. H, Tabs 10-13, 15, 16, 18 (refiled) (ECF No. 94).

analysis issue, adding that neither would offer any testimony about the home videos at hearing. Id. at 1. In light of this agreement, the parties further agreed that petitioners need not file the home videos. Id.

On April 22 and 24, 2015, a few days before the hearing, respondent filed the testimony of Diane Griffin, M.D., Ph.D., an immunologist.[30] Respondent stated that the testimony, which was taken during the OAP, was responsive to petitioners' argument "that the MMR vaccine has an immunosuppressive effect." Notice of Filing dated Apr. 22, 2015, at 1 (ECF No. 101). Respondent argued that the testimony, which was precisely on point, was appropriately filed in the current case, as it had been "part of the OAP." Id. Respondent also noted that petitioners had not "designated an immunologist or virologist to address their assertions," and that none of their current experts had addressed their argument regarding the immunosuppressive effect of the MMR vaccine. Id. Petitioners did, however, specifically rely on one of Dr. Griffin's articles. Id.

The following day, petitioners filed a motion to strike Dr. Griffin's testimony. Mot. dated Apr. 25, 2015 (ECF No. 104). Petitioners argued that the testimony was irrelevant and would "confuse the task of fact-finding" in this case. Id. at 2. They additionally asserted that the admission of the testimony "would be a failure of due process" because they would be unable "to confront and cross-examine the witness." Id.

At the commencement of the entitlement hearing on April 28, 2015, the undersigned heard oral arguments from the parties concerning petitioners' motion to strike. The undersigned granted petitioners' motion on the basis that respondent had filed the Exhibit outside the time frame set forth in the pre-hearing order. See Order dated May 1, 2015 (ECF No. 106). The undersigned, however, granted respondent permission to resubmit the testimony if, at the conclusion of the hearing, he determined it was still needed. Id.

The hearing proceeded for two full days, recessing on April 29 with testimony remaining. During the proceeding, petitioners offered the testimony of Mrs. Reed and Dr. Niyazov, and respondent offered that of Drs. McCandless and Cohen. The parties also produced evidence during the hearing that had not been entered into the record.[31] The undersigned ordered these documents to be filed within 30 days. See Order dated May 1, 2015 (ECF No. 107).

On May 7, 2015, the undersigned convened a status conference to inquire about the availability of the parties' counsel and experts to reconvene and conclude the hearing. See Order dated May 8, 2015 (ECF No. 109). The parties provided several possible dates and discussed

[30] Resp. Ex. I (ECF Nos. 101, 103) (subsequently stricken pursuant to order dated May 1, 2015 (ECF No. 106)). An unrelated medical article, filed as Exhibit J, was not stricken.

[31] Pet. Ex. 124 (ECF No. 108); Pet. Exs. 125-34 (ECF No. 116); Pet. Exs. 135-37 (ECF No. 117); Resp. Exs. K-N (ECF No. 118).

which experts would offer testimony. Id. at 1. Respondent had not decided whether he would move for the admission of Dr. Griffin's transcript testimony and requested more time to make a determination. Id. Petitioners renewed their objection and advised that they would likely obtain an opposing expert if the testimony was admitted. Id. Finally, petitioners stated that they did not intend to obtain a video analysis expert to opine concerning I.R.'s development or to submit any video evidence. Id. at 2.

On May 27, 2015, the parties requested hearing dates of September 9-10, 2015. See Order dated May 27, 2015 (ECF No. 115). Petitioners now stated that it was their intention to call an unidentified video expert, as well as Drs. Zimmerman and Niyazov. Id. Respondent stated that Drs. Cohen and Wiznitzer would testify, as well as an expert responsive to petitioners' video expert. Id. In view of the number of experts testifying, and the parties' difficulty managing their time during the previous hearing, the undersigned informed the parties that an additional day of hearing was necessary to ensure receipt of all anticipated testimony. Id.

On June 9, 2015, the parties confirmed their availability to reconvene the hearing on September 9-11, 2015, in Washington, D.C. See Order dated June 10, 2015 (ECF No. 119). Petitioners also identified Ashley Freuler, Ph.D., as their video analysis expert. Id. The undersigned set deadlines for the submission of Dr. Freuler's expert report, and a responsive report from a yet-to-be-identified expert for respondent. Id. On July 10, 2015, petitioners filed Dr. Freuler's expert report and CV as Exhibits 145-46 (ECF No. 124) and supporting medical literature as Exhibits 147-70 (ECF No. 125). Petitioners also filed select home video footage as Exhibits 138-44 (ECF No. 123).

On June 22, 2015, respondent submitted a status report stating her desire to resubmit Dr. Griffin's transcript testimony. Status Report dated June 22, 2015 (ECF No. 120). Petitioners again moved to "exclude inadmissible evidence." Mot. dated June 22, 2015 (ECF No. 121). Respondent filed a timely response. Resp. Resp. to Mot. dated July 9, 2015 (ECF No. 122).

On July 16, 2015, the undersigned convened a telephonic status conference to discuss the pending hearing. See Order dated July 20, 2015 (ECF No. 126). The parties confirmed that their experts remained available to testify; however, Dr. Freuler, petitioners' video analysis expert, would have to testify via videoconferencing. Id. at 1. After an extended discussion about this development, the undersigned advised that Dr. Freuler's testimony would not be conducive to long-distance videoconferencing and that petitioners would have to devise an alternate plan.[32] Id. As for the identity of respondent's video analysis expert, respondent reported that Dr. Wiznitzer had been selected and that his report was forthcoming. Id. Finally, the undersigned addressed petitioners' renewed motion to exclude Dr. Griffin's testimony. Id. at 2. The parties agreed that a decision on the motion should be stayed pending further proceedings, but that the transcript testimony would remain excluded at the hearing. Id.

[32] The parties agreed to consider a change of venue to enable Dr. Freuler to testify in person. Order dated July 20, 2015, at 1 (ECF No. 126).

On July 29, 2015, the parties informed the undersigned that the hearing would need to be rescheduled. See Order dated July 31, 2015 (ECF No. 127). The undersigned ordered a joint status report in 30 days proposing new dates. Id. On August 28, 2015, respondent filed Dr. Wiznitzer's responsive video analysis report and supporting articles as Exhibit O, Tabs 1-5 (ECF No. 130).[33] That same day, the parties chose February 4-5, 2016, as the new dates, and confirmed Washington, D.C., as the location.[34] See Order dated Aug. 31, 2015 (ECF No. 131). They advised, however, that because of certain scheduling conflicts with two experts, an additional proceeding would be needed.[35] Id.

On December 16, 2015, petitioners informed the undersigned that their video expert, Dr. Freuler, had unexpectedly resigned from the case due to a personal crisis. See Order dated Dec. 18, 2015 (ECF No. 138). Petitioners had retained another expert to review the videos and prepare a report. Id. As a consequence of this development, the parties were no longer prepared for the hearing in February and proposed that the hearing now be held on June 22-24, 2016. Id. The undersigned approved these dates and rescheduled the hearing. See Prehr'g Order dated Jan. 12, 2016 (ECF No. 140).

Over the next several months, the parties filed additional evidence and various pre-hearing submissions.[36] On February 22, 2016, petitioners filed the report of their new video expert, Kaitlyn Wilson, Ph.D., along with her CV, as Exhibits 176-77 (ECF No. 142). Supporting literature was subsequently filed as Exhibits 178-84 (ECF No. 143). On March 24, 2016, respondent filed a second supplemental expert report from Dr. Wiznitzer, along with supporting literature, as Exhibit P, Tabs 1-3 (ECF No. 144). Petitioners filed a pre-hearing brief on May 6, 2016 (ECF No. 145), and respondent filed one on May 31, 2016 (ECF No. 149).

On June 8, 2016, the undersigned convened a pre-hearing status conference. See Order dated June 10, 2016 (ECF No. 153). The parties confirmed that they were prepared to resume the entitlement hearing. Id. at1. During the conference, the undersigned learned that petitioners' counsel had not provided respondent's counsel with certain hearing-related materials, including a detailed list of the video segments to be discussed by petitioners' video expert. Id. at 2. The

[33] Petitioners elected to not file a reply supplemental expert report from Dr. Freuler. Status Report dated Sept. 4, 2015 (ECF No. 132).

[34] Subsequently, the parties requested that the hearing be rescheduled for February 3-4, 2016. See Order dated Sept. 8, 2015 (ECF No. 133).

[35] The parties selected June 22-23, 2016, for a third proceeding with the two experts. See Order dated Nov. 9, 2015 (ECF No. 137).

[36] Pet. Exs. 171-73 (literature) (ECF No. 139); Pet. Exs. 174-75 (medical records) (ECF No. 141); Pet. Exs. 185-91 (literature) (ECF No. 148); Pet. Exs. 192-93 (updated CV for Dr. Niyazov; literature) (ECF No 152); Pet. Ex. 194 (medical records) (ECF No. 154); Pet. Exs. 195-97 (literature and demonstrative exhibit) (ECF No. 155).

undersigned reminded the parties that "'ambush' tactics have no place in the Vaccine Program," and she instructed them to share such information prior to the hearing.[37] Id. Respondent's counsel stated that he did not have an illustrative presentation prepared for the hearing but would share it with opposing counsel if one was created. Id. In any case, respondent's counsel agreed to file a list of the video clips to be discussed by his expert.[38] Id. The undersigned also briefly discussed respondent's request to refile the testimony of Dr. Griffin and petitioners' renewed motion to exclude. Id. The undersigned informed the parties that a decision on this issue would not be made until the hearing concluded, and as such, the testimony would remain excluded from the hearing. Id. The undersigned also acknowledged respondent's objection to petitioners' submission of additional articles unrelated to the video testimony and unreferenced by any of their experts. Id. Respondent requested and was granted relief to supplement the record, if necessary, after the hearing. Id.

On the morning of the first day of the continued hearing, petitioners filed a motion in limine to exclude, postpone, or limit the planned video testimony. Mot. in Limine dated June 22, 2016 (ECF No 157). Petitioners argued that they had been unfairly prejudiced when, in compliance with the undersigned's order, they filed a streamlined list "of actual presentation footage" to be shown at the hearing, while respondent subsequently designated all of the video footage for possible use. Id. at 1-2. Petitioners asserted that this allowed respondent to better prepare for the cross-examination of petitioners' video expert and the direct examination of his own expert, while precluding petitioners from doing the same. Id. at 2-3. Petitioners proposed several remedies, involving various combinations of excluding, postponing, or limiting the anticipated testimony. Id. at 3. The undersigned addressed petitioners' pending motion at the start of the hearing. Tr. 563-73. Following a lengthy discussion, the parties reached a compromise agreement that allowed both parties to present their video testimony as anticipated. Id.

The hearing thereafter proceeded as planned from June 22 to 24, 2016, in Washington, D.C., with Drs. Niyazov, Zimmerman, and Wilson testifying for petitioners, and Drs. Cohen and Wiznitzer testifying for respondent. Following the hearing, the undersigned ordered petitioners to report whether they intended to offer rebuttal testimony, and whether they wished to file a post-hearing brief. The parties were also ordered to submit any evidence produced during the hearing but not yet filed into the record.[39] See Order dated June 27, 2016 (ECF No. 158).

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[37] That same day, petitioners' counsel filed a list of the video clips Dr. Wilson intended to display and discuss during the hearing. Status Report dated June 8, 2016 (ECF No. 151).

[38] Respondent filed the list of video clips Dr. Wiznitzer intended to reference during his testimony. Status Report dated June 20, 2016 (ECF No. 156).

[39] Pet. Exs. 198-202 (responsive report of Dr. Wilson; literature) (ECF No. 166); Pet. Ex. 203 (Dr. Wilson's PowerPoint presentation) (ECF No. 167); Pet. Ex. 204 (compilation of mitochondrial exhibits) (ECF No. 173); Pet. Ex. 205 (mutation database) (ECF No. 177); Resp. Exs. Q-R (ECF No. 168); Resp. Ex. S (demonstrative video clips) (ECF No. 169).

On August 16, 2016, petitioners filed a status report stating they did not intend to provide rebuttal testimony from Drs. Zimmerman or Wilson. Status Report dated Aug. 16, 2016 (ECF No. 175). However, they were undecided about refuting respondent's recently filed Exhibit R (a printout of a database of mutations in DNA polymerase gamma (POLG) discussed at hearing) and they requested additional time to make that decision. On September 15, 2016, petitioners filed a rebuttal to Exhibit R from Dr. Niyazov, along with supporting materials.[40]

On September 30, 2016, respondent requested and was granted an opportunity to file a supplemental report from Dr. Cohen responsive to Dr. Niyazov's rebuttal report addressing Exhibit R. See Order dated Sept. 30, 2016 (ECF No. 185). The supplemental report and supporting literature were filed on October 28, 2016.[41] On October 31, 2016, petitioners filed a motion to strike Dr. Cohen's supplemental report and supporting literature. Mot. dated Oct. 31, 2016 (ECF No. 187). A response and reply were filed in due course. Resp. Resp. to Mot. dated Nov. 22, 2016 (ECF No. 189); Pet. Reply to Resp. Resp. to Mot. dated Dec. 2, 2016 (ECF No. 190).

On January 9, 2017, petitioners filed their post-hearing brief. Pet. Posthr'g Br. dated Jan. 9, 2017 (ECF No. 193). On April 5, 2017, respondent file his post-hearing brief. Resp. Posthr'g Br. dated Apr. 5, 2017 (ECF No. 196). Petitioners filed a reply post-hearing brief on April 28, 2017. Pet. Reply Posthr'g Br. dated Apr. 28, 2017 (ECF No. 198). The evidentiary record is now closed and the case is ripe for adjudication.

III. Rulings on Pending Motions

Two evidentiary motions remain pending in this case. They are (1) petitioners' motion to exclude Dr. Griffin's testimony, and (2) petitioners' motion to strike Dr. Cohen's supplemental report, Exhibit T, including accompanying tabs 1 through 4. These motions are resolved within the analysis below. The motion to exclude Dr. Griffin's testimony is addressed in Section VI.B.i, below. For the reasons discussed there, petitioners' motion to exclude Dr. Griffin's testimony is DENIED as MOOT. The motion to strike Dr. Cohen's supplemental report is addressed in Section VI.C.ii, below. For the reasons discussed there, petitioners' motion is DENIED.

IV. Standards for Adjudication

A. Petitioners' Burden in Vaccine Program Cases

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law

[40] Pet. Exs. 206-09 (ECF No. 181).

[41] Resp. Ex. T, Tabs 1-4 (ECF No. 186).

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

To establish causation-in-fact, a petitioner must show by a preponderance of the evidence that but for the vaccination, the petitioner would not have been injured, and that the vaccination was a substantial factor in bringing about the injury. Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1338 (Fed. Cir. 2010); Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999). Proof of actual causation must be supported by a sound and reliable "medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'" Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010) (quoting Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994)); see also Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992) ("[P]etitioners must show a medical theory causally connecting the vaccination and the injury."). "[A] petitioner must demonstrate the reliability of any scientific or other expert evidence put forth to carry their burden. Expert testimony, in particular, must have some objective scientific basis in order to be credited by the Special Master." Jarvis v. Sec'y of Health & Human Servs., 99 Fed. Cl. 47, 54-55 (2011) (citing Moberly, 592 F.3d at 1322; Cedillo, 617 F.3d at 1339; Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999)).

Causation is determined on a case-by-case basis, with "no hard and fast per se scientific or medical rules." Knudsen, 35 F.3d at 548. A petitioner may use circumstantial evidence to prove the case, and "close calls" regarding causation must be resolved in favor of the petitioner. Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1280 (Fed. Cir. 2005).

To receive compensation under the Program, petitioners must prove either (1) that I.R. suffered a "Table Injury" – i.e., an injury listed on the Vaccine Injury Table – corresponding to a vaccine that he received, or (2) that I.R. suffered an injury that was actually caused by the vaccine (or vaccines) he received. See §§ 13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Petitioners must show that a vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Although the Vaccine Table includes an injury of encephalopathy (or encephalitis) suffered five to 15 days after administration of the MMRV vaccine or one of its components, petitioners did not pursue the Table Injury. Moreover, to qualify as a Table Injury, the encephalopathy petitioners claims I.R. suffered would have to satisfy the more narrow definition of encephalopathy contained in the Qualifications and Aids to Interpretation ("QAI") section of

the Vaccine Injury Table.[42] See 42 C.F.R. § 100.3(c)(2). Here, the medical records and expert reports do not support an allegation of a Table encephalopathy, even if petitioners had decided to pursue that allegation.

Because petitioners cannot show that I.R. suffered a Table injury, they must prove that a vaccine or vaccines I.R. received caused his injury. To do so, they must show by preponderant evidence (1) a medical theory causally connecting a vaccine and I.R.'s injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that a vaccine was the reason for his injury ("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between a vaccine and his injury ("Althen Prong Three"). Althen, 418 F.3d at 1278; § 13(a)(1) (requiring proof by a preponderance of the evidence).

Since Althen, the Federal Circuit has addressed the causation-in-fact standard in several additional rulings, which have affirmed the applicability of the Althen test and afforded further instruction for determining causation-in-fact. In Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006), the court cautioned Program fact-finders against narrowly construing the second element of the Althen test, confirming that circumstantial evidence and medical opinion, sometimes in the form of notations of treating physicians in the vaccinee's medical records, may in a particular case be sufficient to satisfy that second element of the Althen test. Both Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006), and Walther v. Sec'y of Health & Human Servs., 485 F.3d 1146, 1149-50 (Fed. Cir. 2007), discussed the issue of which party bears the burden of ruling out potential non-vaccine causes. DeBazen v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1350-52 (Fed. Cir. 2008), explored what evidence the special master may consider in deciding the initial question of whether the petitioner has met her causation burden. The issue of the temporal relationship between vaccination and the onset of an alleged injury was further discussed in Locane v. Sec'y of Health & Human Servs., 685 F.3d 1375, 1380-81 (Fed. Cir. 2012), and W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1358 (Fed. Cir. 2013). Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322-23 (Fed. Cir. 2010), concluded that the "preponderance of the evidence" standard that applies to Vaccine Act cases is the same as the standard used in traditional tort cases, so that conclusive proof involving medical literature or epidemiology is not needed, but demonstration of causation must be more than "plausible" or "possible." Both Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009), and Porter v. Sec'y of Health & Human Servs., 663 F.3d 1242, 1253-54 (Fed. Cir. 2011), considered when a determination concerning an expert's credibility may reasonably affect the outcome of a causation inquiry. Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1345-46 (Fed. Cir. 2010), found that it was appropriate for a special master to determine the reliability of

[42] As explained in Waddell, "[t]he scope of the medical term 'encephalopathy' is more expansive than the narrower, statutory definition set forth in the Table." Waddell v. Sec'y of Health & Human Servs., No. 10-316, 2012 WL 4829291, at *12 (Fed. Cl. Spec. Mstr. Sept. 19, 2012). Encephalopathy as generally used means "any degenerative disease of the brain." Dorland's at 614. "The QAI definition of acute encephalopathy simply does not encompass every type of brain dysfunction to which the broader meaning of 'encephalopathy' applies." Blake v. Sec'y of Health & Human Servs., No. 03-31, 2014 WL 2769979, at *6 (Fed. Cl. Spec. Mstr. May 21, 2014).

a diagnosis before analyzing the the likelihood of vaccine causation. Lombardi v. Sec'y of Health & Human Servs., 656 F.3d 1343, 1351-52 (Fed. Cir. 2011), and Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364-65 (Fed. Cir. 2012), both again explored the importance of assessing the accuracy of the diagnosis that supports a claimant's theory of causation. Doe 11 v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1356-58 (Fed. Cir. 2010), and Deribeaux v. Sec'y of Health & Human Servs., 717 F.3d 1363, 1369 (Fed. Cir. 2013), both discuss the burden of proof necessary to establish that a "factor unrelated" to a vaccine may have caused the alleged injury.

Where, as here, petitioners in a cause-in-fact or "off Table" case seek to prove that their vaccination aggravated a pre-existing injury, the court must apply three additional factors originating from the standard for assessing aggravation claims in "Table" injury cases. See Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144 (Fed. Cl. 2009). The additional Loving factors require petitioners to demonstrate aggravation by addressing (1) the vaccinee's condition prior to the administration of the vaccine, (2) the vaccinee's current condition, and (3) whether the vaccinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. Id.

Another important aspect of the causation-in-fact case law under the Vaccine Act concerns the factors that a special master should consider in evaluating the reliability of expert testimony and other scientific evidence. In Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579 (1993), the Supreme Court listed certain factors that federal trial courts should utilize in evaluating proposed expert testimony concerning scientific issues. In Terran, 195 F.3d at 1316, the Federal Circuit ruled that it is appropriate for special masters to utilize the Daubert factors as a framework for evaluating the reliability of causation-in-fact theories presented in Program cases.

B. Law Governing Factual Determinations

The process for making factual determinations in Vaccine Program cases begins with consideration of the medical records. See § 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." § 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) (emphasizing that it is within the special master's discretion to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony given at a later date).

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). Curcuras v. Sec'y of Health & Human Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993); Doe/70 v. Sec'y of Health & Human Servs., 95 Fed. Cl. 598, 608 (2010) ("Given 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). This presumption is based on the linked propositions that (1) sick people visit medical professionals; (2) sick people honestly report their health problems to those professionals; and (3) 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. 11-685, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); Curcuras, 26 Cl. Ct. 537, 543 (1992), aff'd, 993 F.2d 1525 (Fed. Cir. 1993) ("It 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, they should be afforded substantial weight. See Lowrie v. Sec'y of Health & Human Servs., No. 03-1585, 2005 WL 6117475, at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony – especially where such testimony conflicts with the record evidence. Curcuras, 993 F.2d at 1528; see also Murphy v. Sec'y of Health & Human Servs., 23 Cl. Ct. 726, 733 (1991) (favorably citing the special master's determination that "oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight"), aff'd, 968 F.2d 1226 (Fed. Cir. 1992).

However, compelling oral testimony may be more persuasive than written records in some situations, 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) ("[L]ike 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 ("Written records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent.") (quoting Murphy, 23 Cl. Ct. at 733). Ultimately, a special master must evaluate the witness' credibility before determining the weight to afford such testimony. See Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); 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. 90-2808, 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 of Health & Human Servs., 110 Fed. Cl. 184, 203-04 (2013), aff'd, 746 F.3d 1334 (Fed. Cir. 2014). In determining whether to afford greater weight to contemporaneous medical records than to contrary testimony, there must be evidence that this decision was the result of a rational determination. Burns, 3 F.3d at 416-17.

V. Expert Testimony

Petitioners allege that I.R. "suffered a significant aggravation of a preexisting condition, a mitochondrial disorder, causally related to the ProQuad vaccine administered on December 30, 2005," which in turn caused I.R. "to suffer from immunodeficiency disorder, bowel disease, pathological neuroinflammation, seizure disorder, mitochondrial dysfunction and the resulting features of autism spectrum disorder." Second Am. Petition at ¶¶ 43-44. Regarding this proposition, the following expert evidence was heard.

A. Petitioners' Experts

i. Dmitriy Niyazov, M.D.

Dmitriy Niyazov, M.D., was proffered by petitioners without objection as an expert in the areas of genetics and mitochondrial medicine. Tr. 114.

a. Education and Background

Dr. Niyazov earned his undergraduate degree in biology from the University of California at Los Angeles in 1996 and his M.D. from the University of Rochester School of Medicine in 2001. Pet. Ex. 192 at 1; Tr. 105-06. He completed residencies in otolaryngology and medical genetics at Emory University School of Medicine. Id. Dr. Niyazov is licensed to practice medicine in the state of Louisiana and is a diplomate of the American Board of Medical Genetics. Id.

Currently, Dr. Niyazov is section head of medical genetics in the department of pediatrics at the Ochsner Clinic Foundation in New Orleans, Louisiana. Pet. Ex. 192 at 1; Tr. 105. He is also an instructor in the combined medical student and residency program at Ochsner Clinic and Tulane University School of Medicine and a senior lecturer for the joint medical student program between Ochsner Clinic and the University of Queensland School of Medicine. Pet. Ex. 192 at 2; Tr. 106. Dr. Niyazov specializes in mitochondrial medicine as a branch of genetics. Tr. 106. Previously, he was a research associate in the departments of human genetics and biomedical engineering at Emory University School of Medicine. Pet. Ex. 192 at 2.

Dr. Niyazov is a fellow of the American College of Medical Genetics and is also affiliated with the American Society of Human Genetics and the Mitochondrial Medicine Society. Pet. Ex. 192 at 1. He is a member of the editorial board of both Clinical Syndromology and the Journal of Molecular Genetics and Metabolism. Id. Dr. Niyazov lists 30 publications on his CV, as well as numerous presentations. Pet. Ex. 192 at 2-13; Tr. 106-07.

b. Opinion

Applying two different sets of diagnostic criteria, as well as noting the presence of a heterozygous POLG mutation (explained below), Dr. Niyazov opined that I.R. "experienced developmental regression and autism, caused by a vaccine reaction, which exacerbated his deficient cellular energy metabolism due to his POLG mutation." Pet. Ex. 39 at 4. Dr. Niyazov also asserted that "it's more likely than not that [I.R.]'s infection rate increased with more vaccinations because his immune system was weakened by the vaccinations and his [mitochondrial disorder]. Even if infections played a role in [I.R.]'s regression and autism, the vaccinations were a substantial factor in causing the injury without which it wouldn't have occurred." Id. at 5. Dr. Niyazov further opined:

> When a stress event such as infection or vaccine (both of which carry antigens) enters the body it produces inflammatory response and catabolism which requires a significant amount of ATP. Immune response to vaccines has been shown to last for weeks and months and vaccination was unequivocally demonstrated to cause oxidative stress in humans. Developmental regression is a hallmark of [mitochondrial disorders] but a certain magnitude of threshold need to be exceeded to trigger decompensation and ATP depletion. Each individual affected person has his or her own threshold based on a variety of cumulative factors over a period of time such as degree and duration of an impact in relationship to this person's percentage of mitochondrial heteroplasmy in different organs and tissues. Moreover, owing to its waxing and waning nature, [mitochondrial disorders] can cause mitochondrial dysfunction that can reach this threshold more than once[,] often triggered by a catabolic stressor as in the case of [I.R.]'s vaccinations which served as catabolic events that expedited the threshold of his regression after both 12- and 15-month shots.[43]

Pet. Ex. 39 at 5-6 (internal citations omitted).

[43] Although Dr. Niyazov's report references vaccines other than the ProQuad vaccine that I.R. received on December 30, 2005, petitioners allege that only the ProQuad vaccine caused any injury. See Second Am. Petition at ¶¶ 43-44. Furthermore, consideration of I.R.'s other vaccinations would not change the undersigned's analysis.

ii. Kaitlyn Wilson, Ph.D.

Kaitlyn Wilson, Ph.D., was proffered by petitioners without objection as an expert in speech-language pathology and as an expert in Retrospective Video Analysis ("RVA") in autism. Tr. 621.

a. Education and Background

Dr. Wilson earned her undergraduate degree in communication sciences and disorders from Florida State University in Tallahassee, Florida, in 2004 and a master's degree and doctorate in speech and hearing sciences from the University of North Carolina at Chapel Hill in 2006 and 2012, respectively. Pet. Ex. 177 at 1. In 2014, she completed a post-doctoral fellowship at the Kennedy Krieger Institute, where she worked in the Center for Autism and Related Disorders. Id. at 2. She is licensed by the Maryland State Board of Audiologists, Hearing Aid Dispensers, and Speech-Language Pathologists. Id. She is also certified as a speech-language pathologist by ASHA, the American Speech-Language-Hearing Association. Id.

Currently, Dr. Wilson is an assistant professor and clinical supervisor in the department of audiology, speech-language pathology, and deaf studies at Towson University. Pet Ex. 177 at 1. Previously, she worked for six years, dating back to her time as a graduate research assistant with Dr. Grace Baranek from 2004 to 2006, with the Program in early Autism Research, Leadership, and Service ("PEARLS") based at the University of North Carolina Chapel Hill. Id. at 3; Tr. 585, 594, 597.

Dr. Wilson is a peer reviewer for several publications, including the Journal of Early Intervention, the Journal of Autism and Developmental Disorders, and the Journal of Speech, Language, and Hearing Research. Pet Ex. 177 at 8. She is a member of both the International Society for Autism Research and the American Speech-Language Hearing Association. Id. She lists seven journal articles and two book chapters on her CV, as well as numerous presentations. Id. at 4-6.

b. Opinion

Upon review of the video footage filed in this case, Dr. Wilson opined that "I did not find clear markers of autism in the earliest home videos provided for [I.R.]. Many children who will later be diagnosed with autism exhibit characteristics, or red flags, prior to their first birthday. I begin to see clear (vs. ambiguous or possible) markers that raise red flags for autism starting around 15 months of age and after. . . . Later videos primarily focused on the baby brother and the context became increasingly non-continuous." Pet. Ex. 176 at 4.

iii. Andrew Zimmerman, M.D.

Andrew Zimmerman, M.D., was proffered by petitioners without objection as an expert in pediatric neurology with specialty in autism. Tr. 681.

a. Education and Background

Dr. Zimmerman earned his undergraduate degree in Germanic languages and literatures from Princeton University in 1966 and this M.D. from Columbia University in 1970. Pet. Ex. 125 at 1; Tr. 678-80. He completed a residency in pediatrics at C.S. Mott Children's Hospital, University of Michigan Hospitals, in 1972 and a residency in neurology at Johns Hopkins Hospital in 1977. Pet. Ex. 125 at 1. He is licensed to practice medicine in Maryland and Massachusetts and is board certified in pediatrics as well as psychiatry and neurology, with special competence in child neurology. Id. at 13.

Currently, Dr. Zimmerman is an associate professor in epidemiology at Johns Hopkins Bloomberg School of Public Health as well as an associate professor of pediatrics and neurology at Harvard Medical School. Pet. Ex. 125 at 2. He is also a clinical professor of pediatrics at the University of Massachusetts Medical School. Id. Dr. Zimmerman is a staff physician at both Johns Hopkins Hospital (pediatric neurology) and Kennedy Krieger Institute (neurology and developmental medicine). Id. He is also the Director of Medical Research for the Center for Autism and Related Disorders at Kennedy Krieger Institute. Id. He has had numerous prior academic and hospital appointments. Id. at 1-2.

Dr. Zimmerman has been a conference organizer for Autism Speaks, past President of Medical Staff at Kennedy Krieger Institute, and a panel member for the National Institutes of Health Development Conference on Neurofibromatosis. Pet Ex. 125 at 3. He is a member of, inter alia, the American Academy of Neurology as well as the American Academy of Pediatrics, for which he was a member of the Executive Committee for the Section on Neurology from 1998 to 2001. Id. He is a peer reviewer for many publications, including the New England Journal of Medicine, Pediatrics, the Journal of Autism and Developmental Disorders, Autism Research, and the Journal of Child Neurology. Id. at 4-5. He lists 78 peer-reviewed publications on his CV, as well as numerous presentations. Id. at 16-22; Tr. 680-81.

b. Opinion

Dr. Zimmerman opined that "[i]t is my opinion, based on a reasonable degree of medical certainty, that [I.R.]'s autistic regression following immunizations can be explained by the underlying genetic, metabolic and immune abnormalities that have been carefully documented in his medical record." Pet. Ex. 32 at 1. Dr. Zimmerman explained the basis for his opinion as follows:

> From my previous experience and subsequent studies by others, it is apparent that certain abnormalities of cellular mitochondrial energy metabolism are associated with a susceptibility to developmental regression leading to autism. The relationship of immune dysfunction to mitochondrial abnormalities in such children is not known, but may also be related to the underlying genetic abnormality and compounds their susceptibility to metabolic stress during infections or with certain immunizations.

Id.

With regard to the facts of this case, Dr. Zimmerman opined:

> [I.R.]'s initial reaction to vaccination on January 18, 2006 at 12 months of age, with a rash and temperature of 104° (diagnosed as roseola), was followed by recurrent infections for 5 months. Neurological symptoms became clinically evident at 17 months in postural unsteadiness and ataxia of gait, then regression in both language and social skills around 24 months of age. The evolution of immunological stress following immunization, combined with the underlying mitochondrial disorder, led to the diagnosis of autism.

Pet. Ex. 32 at 1.

B. Respondent's Experts

i. Shawn McCandless, M.D.

Shawn McCandless, M.D., was proffered by respondent as an expert in clinical genetics, as well as mitochondrial and metabolic disorders and general pediatrics. Tr. 334. The undersigned accepted him as an expert in mitochondrial disorders, including respiratory chain disorders. Tr. 343.

a. Education and Background

Dr. McCandless earned his undergraduate degree in chemistry from Westminster College in 1984 and his M.D. from Temple University School of Medicine in 1988. Resp. Ex. L at 1. He initially completed a residency in pediatrics at the University of Wisconsin Hospital and Clinics from 1988 to 1991, before later completing a residency in medical genetics and a fellowship in biochemical genetics at University Hospitals of Cleveland through Case Western Reserve University. Id. He is licensed to practice medicine in the state of Ohio and is certified in clinical biochemical genetics by the American Board of Genetics and in clinical genetics by the American Board of Medical Genetics. Id. at 1-2; Tr. 329. He is also board certified in pediatrics. Tr. 329.

Currently, Dr. McCandless is an associate professor of genetics, pediatrics, and pathology at Case Western Reserve University and University Hospitals Case Medical Center, where is he

also the director of the Center for Human Genetics, residency director of the department of genetics, medical director of the Prader-Willi Syndrome Clinic, and associate director of the Center for Inherited Disorders of Energy Metabolism. Resp. Ex. L at 1-2. Prior to joining Case Western Reserve University, he was an assistant professor of pediatrics in the division of genetics and metabolism at the University of North Carolina School of Medicine. Id. at 1.

Dr. McCandless has served numerous professional committees and organizations. He is a section editor for the Medical Genetics Inservice Exam on behalf of the Association of Professors of Human and Medical Genetics. Resp. Ex. L at 3. He is chair of both the Genetics Education Committee at the University Hospitals Case Medical Center and the Newborn Screening Committee at University Hospitals of Cleveland, as well as a member of the Laboratory Subcommittee of the Ohio Newborn Screening Advisory Council. Id. He is also a peer reviewer for several journals, including the Journal of Inherited Metabolic Diseases, Genetics in Medicine, Pediatrics, and the American Journal of Medical Genetics. Id. at 2. His CV lists 36 peer-reviewed articles, along with various other publications and one patent. Id. at 4-12.

b. Opinion

Dr. McCandless agreed with Dr. Niyazov's assessment that I.R. had a likely deleterious POLG mutation but disputed that a heterozygous POLG mutation could cause disease. Resp. Ex. F at 4-5. With regard to the potential for a mitochondrial disorder diagnosis based on I.R.'s medical history, Dr. McCandless observed:

> I find no records supporting myopathy, nor is there clear documentation by an objective observer of loss of neurodevelopmental milestones, with the possible exception of the balance problem . . . . Development of ataxia is not really regression, as defined by a loss of previously attained milestones, as ataxia does not represent an earlier developmental stage. Rather, ataxia should be considered a new neurological finding. I find no convincing documentation of many [of] the cardinal signs of MRI changes in the brain, mitochondrial diseases, myopathy, cardiomyopathy, hearing loss, diabetes, autonomic dysfunction, significant hypotonia, hematological problems or kidney disease.

Id. at 4.

Dr. McCandless disputed Dr. Niyazov's application of the mitochondrial disorder diagnostic criteria and criticized Dr. Niyazov for conflating mitochondrial dysfunction with mitochondrial disease (or disorder). Resp. Ex. F at 5-6. Dr. McCandless opined that "[i]n this case, the sum of testing that reflects mitochondrial function is normal, and the likelihood that this child has a primary mitochondrial disease is extremely low." Id. at 5.

Additionally, Dr. McCandless disputed Dr. Niyazov's suggestion that there is a causative link between mitochondrial dysfunction, immunological dysfunction, and oxidative stress that

could explain how a vaccine induces autistic regression. Resp. Ex. F at 6. He also disputed Dr. Zimmerman's assertion that vaccines may induce autistic regression in a child with mitochondrial disease. Id. at 7.

ii. Bruce Cohen, M.D.

Bruce Cohen, M.D., was proffered by respondent and admitted without objection both as an expert in neurology with special qualification in child neurology and as an expert in mitochondrial disease. Tr. 449.

a. Education and Background

Dr. Cohen earned his undergraduate degree in Chemistry from Washington University in St. Louis, Missouri, in 1978 and his M.D. at the Albert Einstein College of Medicine at Yeshiva University in New York, New York, in 1982. Resp. Ex. K at 1. After medical school, Dr. Cohen completed both a pediatric residency and a pediatric neuro-oncology fellowship at the Children's Hospital of Philadelphia, as well as a pediatric neurology residency at Columbia Presbyterian Medical Center. Id. Dr. Cohen is licensed to practice medicine in the state of Ohio. Id. at 2. He is a fellow of the National Board of Medical Examiners and the American Board of Psychiatry and Neurology with special competence in child neurology. Resp. Ex. K at 2; Tr. at 441.

Currently, Dr. Cohen serves as the director of neurology and the director of the Neurodevelopmental Science Center at the Children's Hospital Medical Center of Akron, where he maintains a clinical practice. Resp. Ex. K at 2; Tr. 443-44. He is also a professor of pediatrics at Northeast Ohio Medical University, specializing in child neurology, mitochondrial disease, and neuromuscular disease. Resp. Ex. K at 2; Tr. 443-44. He has had prior academic and medical appointments with Case Western Reserve University, Hillcrest Hospital, Cleveland Clinic, and Ohio State University. Resp. Ex. K at 2. He has been involved with mitochondrial disorder patient care since 1983. Tr. 444.

Dr. Cohen is a member of, inter alia, the American Academy of Neurology, the Child Neurology Society, the Mitochondrial Research Society, and the Mitochondrial Medicine Society. Resp. Ex. K at 2; Tr. 443. He is a past president of both the Professors of Child Neurology and the Mitochondrial Medicine Society. Resp. Ex. K at 2. He has served on a multitude of committees and advisory groups, both nationally and at the Cleveland Clinic, and is on the editorial board of four academic journals. Id. at 3-5. Dr. Cohen listed 91 peer-reviewed articles on his CV, as well as 30 book chapters and an edited journal volume. Id. at 33-40. He co-authored several of the medical journal articles extensively discussed in this case.

b. Opinion

Dr. Cohen agreed that "[a] subset of children with autism do have mitochondrial disease," but countered that "there is insufficient medical evidence to suggest any link between vaccines and mitochondrial regression." Resp. Ex. A at 7-8. He noted that I.R.'s clinical features of autism improved over time and are "most consistent with the diagnosis of pervasive

developmental disorder" with "no evidence of a single encephalopathic event." Id. at 7. Dr. Cohen opined that "[t]he medical evaluation performed does not indicate this patient has a mitochondrial illness" and further that "[t]he analyte screening (chemical biomarkers) did not indicate any ongoing systemic mitochondrial dysfunction." Id. at 5-6. He further opined:

> [T]he child does not display any classic features of a child with mitochondrial disease: brain lesions on MRI consistent with a metabolic process, movement disorder, apneas, ptosis, external ophthalmoplegia, retinitis pigmentosa, optic atrophy, high-frequency hearing loss, cardiomyopathy, cardiac conduction defect, exocrine pancreatic failure, liver disease, myopathy, or neuropathy. Although pervasive development disorders and autism can be seen in mitochondrial disorders, those children have either additional clinical features or diagnostic biochemical-genetic-histological features that extend beyond the EEG finding, epilepsy (although epilepsy has not been confirmed in this case), or a single episode of regression (which is known to occur in autism).

Id. at 6-7. Dr. Cohen additionally disputed that "immunizations cause enough oxidative stress (metabolic stress or immunological stress) to trigger mitochondrial dysfunction resulting in a clinical demise." Id. at 7.

iii. Max Wiznitzer, M.D.

Max Wiznitzer, M.D., was proffered by respondent as an expert in pediatric neurology with specialty in autism, including autism diagnosis and developmental pediatrics. Tr. 793. Petitioners did not object to Dr. Wiznitzer's admission as an expert in pediatric neurology and autism.[44] Tr. 779, 783.

a. Education and Background

Dr. Wiznitzer received his B.S. in medical education in 1975 and a medical degree in 1977, both from Northwestern University. Resp. Ex. Q at 1. He completed a residency in pediatrics in 1980 at the Children's Hospital Medical Center in Cincinnati, Ohio. Id. He then completed a one-year fellowship at the Cincinnati Center for Developmental Disorders, a three-year fellowship in pediatric neurology at the Children's Hospital of Philadelphia, and a two-year fellowship at the Albert Einstein College of Medicine in New York, where he studied higher cortical functions. Id. at 1-2. Dr. Wiznitzer is certified by the American Board of Pediatrics. Id. at 5. He also received certification from the American Board of Psychiatry and Neurology, with a special qualification in Child Neurology. Id. In 2004, the American Board of Psychiatry and Neurology certified his competence in neurodevelopmental disabilities. Id. He maintains licenses to practice medicine in Ohio, Pennsylvania, and New York. Id.

[44] However, petitioners do challenge Dr. Wiznitzer's qualifications specific to his opinion competing against the opinion of their expert, Dr. Wilson, with regard to review of the home videos filed in this case. Pet. Posthr'g Br. at 18-20. This issue is addressed in Section VI.A.i.C, below.

Currently, Dr. Wiznitzer is a professor of pediatrics and neurology at Case Western Reserve University. Resp. Ex. Q at 2. He is also an associate pediatrician and neurologist at University Hospitals of Cleveland. Id. Dr. Wiznitzer has received appointments to practice at several hospitals for various lengths of time, including the Department of Neurology of Montefiore Medical Center in New York; the Department of Neurology at Bronx Municipal Hospital Center; and Rainbow Babies and Children's Hospital in Cleveland. Id. He has served as a consultant in pediatrics and neurology at several other hospitals as well. Id. At Rainbow Babies and Children's Hospital, Dr. Wiznitzer served as Co-Director of the Rainbow Autism Center in 1991; Chief of the Division of Pediatric Neurology from 1992 to 1995; and the Director of the Rainbow Autism Center from 1992 through 2010. Id. at 2-3.

Dr. Wiznitzer has been a reviewer of articles for many medical journals, most notably for Pediatric Neurology, Lancet Neurology, and the Journal of Child Neurology, where he also served on the editorial boards. Resp. Ex. Q at 6. He has served on a multitude of medical advisory groups at the local, state, and national levels. Id. at 6-9. Dr. Wiznitzer has published 73 medical articles and 11 book chapters. Id. at 13-20.

b. Opinion

Dr. Wiznitzer disputed that I.R.'s autism could be explained by his vaccinations. Resp. Ex. C at 12. He opined that I.R. was properly diagnosed with autism before age three and that he does not have any history of regression, persistent unsteadiness, or ataxia. Id. at 11-12. He further opined that there is no correlation between I.R.'s illnesses and the appearance of his autistic features, and noted that language delay is known to be an initial manifestation of autism spectrum disorders. Id. Dr. Wiznitzer also opined that I.R.'s subsequent improvement, with a later diagnosis of pervasive development disorder not otherwise specified (PDD-NOS), is consistent with "a known developmental trajectory for autistic disorder." Id. at 11. Upon subsequent review of the video footage filed in this case, Dr. Wiznitzer opined, in contrast to Dr. Wilson, that I.R. "clearly showed ASD signs in 2005 and prior to his MMR and varicella vaccinations on 12/30/05 and showed no obvious functional deterioration in the months after that time." Resp. Ex. O at 3.

VI. Findings of Fact

Before reaching the substance of petitioners' medical theory regarding causation, a number of disputed factual points must be resolved. In particular, three significant aspects of I.R.'s health status remain in dispute. These are the onset and course of I.R.'s autism, his immune status, and his metabolic status. Petitioners assert that I.R. was neuro-typical during his first year of life and prior to administration of his 12-month vaccines. They further allege that he experienced a regression after those vaccinations. Petitioners also allege that I.R.'s ProQuad vaccine, which includes MMR, caused a temporary immunosuppression and, moreover, that I.R. has experienced longstanding immunodeficiency. Finally, petitioners allege that I.R. has a mitochondrial disorder or dysfunction. The undersigned will address each of these assertions in turn.

A. The Onset and Course of I.R.'s Autism

Among the factual disagreements in this case, the parties disagree regarding the onset, course, and nature of I.R.'s autism. In order to fully evaluate petitioners' claim of vaccine causation, it is first necessary to determine when I.R.'s autism first manifested and whether I.R. experienced a developmental regression following his vaccinations.

i. The undersigned finds that I.R.'s autism manifested prior to his first birthday and prior to the vaccinations at issue.

A significant point of factual dispute in this case relates to the age at which I.R.'s autism first manifested. Petitioners contend that I.R. was developmentally typical until one year of age, after which he began showing signs of autism following his allegedly injury-causing vaccinations, which became clear by 15 months of age. Pet. Posthr'g Br. at 40-41. Respondent contends that I.R.'s autism actually manifested much earlier, during his first year of life and prior to the vaccinations at issue in this case. Resp. Posthr'g Br. at 18-20.

Record evidence touching on this issue includes medical records, baby book entries, parental and expert testimony, and home videos. However, most of the attention paid to the question of when I.R.'s autism manifested has been devoted to analysis of the home videos, which show I.R. in his home environment from about six months of age until shortly after his second birthday. Resolving this factual issue requires weighing the testimony and opinions of several competing experts.[45]

Upon the undersigned's review of the record evidence as a whole, including the video footage filed in this case, the undersigned finds preponderant evidence that I.R.'s autism began to manifest by the time he reached 12 months of age, prior to the vaccinations alleged to have caused his injuries.

a. Early Detection of ASD

As described in the factual history above, concerns about I.R.'s development were first raised to his pediatrician at about 27 months of age, when Mrs. Reed expressed concern about I.R.'s speech development. After several evaluations, he was subsequently diagnosed as autistic at about 33 months of age. However, age of diagnosis is not equivalent to age of onset or manifestation, and in any event, both parties contend that I.R.'s autism manifested well before 27 months of age. Rather, children are most commonly diagnosed as autistic at about two years of age due to the fact that parents and pediatricians are not able to pick up on the more subtle early manifestations of autism. See Tr. 658.

[45] Petitioners had filed a motion to exclude, postpone, or limit respondent's expert testimony regarding the home videos. Mot. in Limine dated June 22, 2016 (ECF No. 157). Petitioners argued that respondent was overbroad in designating video clips for presentation at the hearing, resulting in unfair surprise. Id. The parties resolved the issue by agreeing to a modified order of witness presentation. Tr. 563-72.

Symptoms of autism are age dependent and diagnosis of ASD relies on the ability to reliably detect more subtle behaviors that emerge during infant development. Pet. Ex. 150 at 1. For example, the common symptoms of restricted interests and repetitive behaviors are not expected until two to three years of age. Tr. 857. Earlier studies suggested that an accurate autism diagnosis was not possible prior to two years of age. Pet. Ex. 150 at 1; Tr. 801-02. However, more recent studies have established that onset can actually be discerned much earlier. For example, one 2010 paper explained:

> Retrospective studies have demonstrated that children with early-onset ASD differ from age-matched children with delayed and typical development in orienting to name, gaze to faces, joint attention, and affect sharing. Differences are most evident in the second year of life but some studies have detected signs of ASD before the first birthday. This early onset pattern is thought to occur in the majority of individuals with ASD.

Resp. Ex. P, Tab 2 at 1. Experts for both parties (Dr. Wilson for petitioner and Dr. Wiznitzer for respondent) agree that the age at which a reliable diagnosis can be made is moving, and that more subtle signs of autism can often be observed as early as the first year of life. Pet. Ex. 176 at 3; Tr. 660-61, 668-69, 795-96. Dr. Wilson in particular views RVA research as a driving force in lowering the age of first diagnosis. Tr. 593, 668-69.

In describing what autistic behaviors might be visible during the first year of life, Dr. Wilson summarized: "[D]uring the first year of life, children with autism (when compared to typically developing children) are distinguished by reduced social interaction, absence of social smiling, lack of facial expression, failure to orient to name, lack of joint attention, decreased orienting to faces, and abnormal muscle tone, posture and movement patterns."[46] Pet. Ex. 176 at 3 (internal citations omitted) (quoting Pet. Ex. 145 at 2). During the hearing, Dr. Wilson further explained these symptoms with reference to a list created by Autism Speaks! regarding "red flag" behaviors that may indicate a child is at risk for autism. Tr. 637. Specifically, Dr. Wilson highlighted the following:

- No big smiles or other warm, joyful expressions by six months or thereafter;
- No back-and-forth sharing of sounds, smiles, or other facial expressions by nine months;
- No babbling at all by 12 months;
- No back-and-forth gestures such as pointing, showing, reaching, or waving by 12 months;
- No words by 16 months;
- No meaningful two-word phrases by 24 months;
- Any loss of speech, babbling, or social skills at any age.

[46] Additional behaviors were listed in a more qualified manner as "hav[ing] been mentioned as potentially being diagnostic." Pet. Ex. 176 at 3. Dr. Wilson also cited repetitive play as a sign of autism generally but did not cite an age of onset for that behavior. Id. Dr. Wiznitzer opined, however, that repetitive behaviors and restricted interests do not present in the first year of life and may not present until age two to three. Tr. 857.

Id.

Dr. Witznitzer did not challenge Dr. Wilson's description of these early signs of autism but stressed some caveats. Dr. Wiznitzer opined that patterns are more significant than isolated behaviors. Tr. 797-800. He also indicated that the relevant question regarding these red flag behaviors is not "you do the act or you don't do the act," but rather the quality of the interaction and social intent. Tr. 801-02. Both experts agree that a child ultimately diagnosed as having autism will display typical behaviors some of the time. Tr. 654-55, 801-02.

Additionally, experts for both parties agreed that hyporesponsiveness to pain is a possible "red flag" sign of autism. Resp. Ex. O at 2; Pet. Ex. 176 at 8. Specifically, Dr. Wilson opined that additional red flags for autism include "lack of response to pain and lack of response to loud sounds." Pet Ex. 176 at 8. She indicated that "[t]hese characteristics are not indicative of autism on their own, but in conjunction with the other atypical traits noted, they become consistent with autism features." Id.

b. Retrospective Video Analysis Generally

Since I.R. was not evaluated for autism until later in life, the most significant source of evidence regarding his first-year behavior is home videos filmed by his parents, reviewed through the lenses of RVA. Petitioners characterize RVA as "a respected and scientifically valid research method which has been instrumental in guiding current early identification of autism." Pet. Posthr'g Br. at 14 (citing Pet. Ex. 165). Respondent's expert, Dr. Wiznitzer, likewise opined that RVA can be useful in determining autism onset, so long as there is sufficient footage to discern patterns of behavior. Tr. 794. And indeed, RVA has been used in prior cases within this Program and has been found to be a useful diagnostic tool. See, e.g., R.K. v. Sec'y Health & Human Servs., No. 03-632, 2015 WL 10936124, at *67-69 (Fed. Cl. Spec. Mstr. Sept. 28, 2015), mot. for rev. denied, 125 Fed. Cl. 57, aff'd, 671 F. App'x 792 (mem.).

Numerous RVA studies related to autism have been filed in this case. See, e.g., Pet. Ex. 107 (Osterling); Pet. Ex. 109 (Baranek); Pet. Ex. 147 (Adrien); Pet. Ex. 148 (Adrien); Pet. Ex. 150 (Baranek); Pet. Ex. 151 (Baranek); Pet. Ex. 153 (Bernabei); Pet. Ex. 161 (Maestro); Pet. Ex. 169 (Werner); Resp. Ex. O, Tab 1 (Palomo), Tab 3 (Costanzo), Tab 4 (Ozonoff), Tab 5 (Maestro). In addition, both parties have filed and cited a 2009 literature review article that surveys prior RVA studies and discusses their utility. Pet Ex. 165 (Saint-Georges). Methodology and objective vary quite a bit among the different studies. Nonetheless, all of these studies involve trained screeners viewing home video footage to determine whether autistic-like behaviors are evidenced. A significant advantage of RVA is that it allows for ecological validity. That is, the reviewer is able to observe a child in his usual environment, where he or she is more comfortable and behaving in his or her usual manner. Pet. Ex. 109 at 2.

Nonetheless, RVA has significant limitations. The most notable limitations of home video review are uncertainty regarding whether the videos are representative of a child's overall behavior (parents may selectively film pleasant or favorable situations such as reaching milestones); a risk that the cross-section of observable behaviors may not be adequate to analyze infrequent or context-dependent situations; and a tendency by parents to use compensatory

strategies to coax more social behavior from their children. See, e.g., Pet. Ex. 165 at 7; Pet. Ex. 150 at 10-11. An additional concern related to study methodology, discussed more fully below, is the difficulty of overcoming subjective interpretive differences among video reviewers when analyzing the footage.

c. Retrospective Video Analysis in This Case

Petitioners' testifying expert on RVA was Kaitlyn Wilson, Ph.D. Dr. Wilson holds a Ph.D. in speech and hearing sciences and has participated in multiple studies regarding RVA intended to identify early manifestations of autism. During the hearing, Dr. Wilson was admitted without objection as an expert in speech and language pathology and in use of RVA with regard to autism. Tr. 621. Upon review of the video footage available in this case, Dr. Wilson opined that the first atypical behavior I.R. exhibited occurred when he hit his head and had a minimal reaction on January 5, 2006, when he was between 12 and 13 months of age. Pet. Ex. 176 at 6, 8; Tr. 629-30. She further opined that it was not until approximately 15 months of age that I.R.'s autism became clear and apparent.[47] Pet. Ex. 176 at 8.

Respondent presented competing expert testimony from Dr. Max Wiznitzer, a pediatric neurologist with special interest in autism. Dr. Wiznitzer's testimony was admitted without objection as being expert in pediatric neurology with a specialty in autism and developmental pediatrics, including diagnosis.[48] Tr. 779, 783. Dr. Wiznitzer's review of the video footage, as well as the medical records and other evidence, led him to conclude that, although I.R.'s condition became more apparent in his second year of life, he showed early signs of autism prior to 12 months of age and that what he experienced was a slow evolution of atypical behaviors increasing over time. Resp. Ex. O at 2-3; Tr. 831-32, 840-42.

Upon review of the videos filed in this case, as well as the competing expert opinions, a number of considerations lead the undersigned to conclude that Dr. Wiznitzer's opinion is more persuasive on the whole. First, the undersigned finds that Dr. Wiznitzer has presented persuasive testimony regarding potential red flag findings within the first year of life that Dr. Wilson has not persuasively addressed in her own review of the videos at issue. Second, the undersigned finds that Dr. Wilson failed to identify I.R.'s first instance of hyporesponsiveness. Third, the

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[47] The record also contains a report filed by petitioners from an additional RVA expert, Dr. Freuler. Pet. Ex. 145. However, Dr. Freuler did not ultimately testify in this case, providing no opportunity for respondent to cross-examine. Moreover, her report is largely cumulative of Dr. Wilson's opinion. Thus, the undersigned does not give Dr. Freuler's report significant weight and will not discuss Dr. Freuler's report at length. Nonetheless, it has been considered as part of the following analysis. Like Dr. Wilson, Dr. Freuler did not report any "red flag" findings prior to 12 months of age. Pet. Ex. 145 at 5-7. Both Dr. Wilson and Dr. Freuler identified minimal reactions to a head bump January 5, 2006, and a balloon pop on January 25, 2006, as the first two atypical behaviors observed. Pet. Ex. 145 at 5-7; Pet. Ex. 176 at 6. Some of their observations regarding subsequently dated videos differ.

[48] However, petitioners do challenge Dr. Wiznitzer's credentials regarding RVA. Pet. Posthr'g Br. at 18-20. This point is further addressed below.

undersigned finds it significant that while Dr. Wiznitzer's opinion accords with what is known of autism onset, Dr. Wilson struggled to reconcile her findings with these facts. The undersigned will address each of these points in turn and will then address additional arguments raised by petitioners in their post-hearing brief.

1. Dr. Wiznitzer provided persuasive observations regarding the video footage.

During the course of the hearing, each expert showed several video clips and provided their analysis. In total, there are video clips from 12 different dates during I.R.'s first year of life for which there is competing expert testimony in the record.[49] In addition, there were video clips highlighted by each expert for which there is no directly competing expert testimony from the other party.[50] Interpreting these videos is very challenging. In many instances these two experts drew different conclusions based on very subtle distinctions. However, the undersigned is persuaded that Dr. Wiznitzer has raised instances of potential signs of autism visible during the first year of life.

For example, in a video dated August 25, 2005, according to Dr. Wiznitzer, I.R. shows a lack of good eye contact and babble, fails to respond to his name being called several times, and doesn't look at another person who takes an object from him. Resp. Ex. O at 4; Tr. 813-14. In contrast, Dr. Wilson opined during the hearing regarding the same video that I.R. laughed, pulled to stand, and responded to his name with eye contact. Tr. 641. In her report, she identified typical behaviors of mouthing objects and making vowel sounds. Pet. Ex. 176 at 5. Upon the undersigned's review, both experts are accurately discussing different aspects of the same video. For instance, although Dr. Wilson is correct that at one point I.R. responded to his name, Dr. Wiznitzer is also correct that a different point in the video shows I.R. repeatedly failing to do so.

Dr. Wiznitzer also testified that a series of video clips from July 2005, when I.R. was about six to seven months old, demonstrated instances of limited eye contact, a lack of facial

[49] These clips are dated: July 12, 2005; July 15, 2005; July 18, 2005; August 21, 2005; August 25, 2005; October 6, 2005; October 30, 2005; November 15, 2005; November 20, 2005; November 26, 2005; December 20, 2005; and December 29, 2005. Although the undersigned has reviewed all of the videos filed in this case, this decision will explicitly address only a few examples.

[50] Dr. Wilson testified regarding videos dated July 10, 2005; July 22, 2005; September 16, 2005; October 31, 2005; November 6, 2005; and November 24, 2005. Dr. Wiznitzer testified regarding videos dated July 23, 2005; August 9, 2005; September 4, 2005; November 25, 2005; and December 10, 2005. Additionally, Dr. Wiznitzer extended his review of the videos far beyond the first year of life. While Dr. Wilson testified only regarding video clips up to I.R.'s first birthday (and her report additionally includes observations through August 2006), Dr. Wiznitzer also testified regarding later clips dated January 5, 2006; January 7, 2006; January 10, 2006; January 25, 2006; February 17, 2006; February 26, 2006; March 26, 2006; March 31, 2006; April 3, 2006; August 2, 2006; August 16, 2006; August 18, 2006; August 27, 2006; October 5, 2006; and December 29, 2006.

expression, and a lack of alerting (e.g., no reaction to sneeze).[51] Tr. 807-10. That is, he opined to a lack of the dynamic, sustained interaction that would typically be expected. Id. He also testified that a video clip from December 10, 2005, just weeks prior to I.R.'s first birthday, additionally demonstrated minimal vocalizations, and vocalizations limited in their range, that suggest a developing language issue. Tr. 821-22. Although Dr. Wilson identified competing typical behaviors from the same time periods in her report (Pet. Ex. 176 at 4), she did not directly address the behaviors identified by Dr. Wiznitzer.[52]

In another instance, the undersigned found that Dr. Wilson's opinion was not persuasive in itself. For example, in one instance Dr. Wiznitzer cast doubt on Dr. Wilson's observation of typical behavior without necessarily offering a strong competing opinion. In a video dated December 20, 2005, Dr. Wilson opined that I.R. engaged in a waving gesture directed at his mother. Tr. 645. Dr. Wiznitzer, however, opined that typical versus atypical behavior is difficult to discern from the video. Tr. 822-23. Dr. Wiznitzer characterized the video as showing an unprompted up and down of I.R.'s arm and suggested that he could not see an intent for attention. Resp. Ex. O at 6; Tr. 822-23.

The undersigned is not persuaded by Dr. Wilson's opinion on this point, in part because it was inconsistently offered. When Dr. Wilson first discussed this December 20 clip at the hearing, she described it as a "social gesture of waving directed towards mom" without qualification. Tr. 645. Later, in testimony rebutting Dr. Wiznitzer's opinion, she conceded that due to I.R.'s early age the wave was "not perfectly executed," but maintained her view that it represented a social gesture. Tr. 651-52. In her earlier report, however, Dr. Wilson described the clip only as "possible" waving and smiling, seeming to acknowledge that the action was ambiguous.[53] Pet. Ex. 176 at 6.

Upon the undersigned's review of the entirety of video footage, neither expert has a monopoly on correct interpretation.[54] However, on the whole, the undersigned is not persuaded

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[51] This refers to the following video clips presented during the hearing: July 23, 2005, at 6:48:15 to 6:48.38; July 27, 2005, at 10:12:00 to 10:12:20; and July 27, 2005, at 10:13:50 to 10:14:55.

[52] Dr. Wilson's report identifies a range of expressions, including smiles and concern, on July 27, 2005, but does not address the video footage discussed by Dr. Wiznitzer from July 15 or July 23. Pet. Ex. 176 at 4. Her only observation regarding the December 10, 2005 video is that his first steps were age appropriate. Id. at 6.

[53] Nonetheless, she did code it as a typical rather than ambiguous behavior.

[54] The undersigned stresses that it would not be practical to describe the competing opinions regarding every video in evidence in this case. There is simply too much footage. However, the undersigned's opinion is based on review of the video footage as a whole. The above-described opinions are only a few examples of instances where the undersigned finds Dr. Wiznitzer more persuasive. There are more. Additionally, there are other instances not cited where Dr. Wilson has credibly challenged Dr. Wiznitzer's observations. For example, as stressed in petitioners' post-hearing brief, the undersigned agrees that Dr. Wiznitzer's observation that I.R. did not smile

that Dr. Wilson has fully accounted for all of the possible red flag behaviors present in the video clips as presented by Dr. Wiznitzer (also including the hyporesponsiveness discussed separately below). Rather, the undersigned finds that Dr. Wiznitzer's competing testimony is credible and that, coupled with the video evidence, it provides preponderant evidence that I.R.'s autism predated his first birthday. See, e.g., R.K., 2015 WL 10936124, at *65 (similarly noting that "[o]n the whole, however, I attach less weight to Dr. Megson's report than I do to Dr. Miller's testimony because Dr. Megson's characterizations of the videos run counter to what I observed while viewing them").

2. Dr. Wilson failed to identify the first appearance of hyporesponsiveness.

Another significant issue weighing against Dr. Wilson's interpretation of the video evidence is her misplacement of the onset of I.R.'s hyporesponsive behavior. Dr. Wilson opined that, having reviewed all of the video footage in this case, the first "red flag" incident was a "minimal response" to pain when I.R. fell and hit his head on January 6, 2006. Pet. Ex. 176 at 6; Tr. 627-29. And indeed, as previously noted, experts for both parties agree that hyporesponsiveness to pain is a possible "red flag" sign of autism. Resp. Ex. O at 2; Pet. Ex. 176 at 8. Yet Dr. Wilson failed to record, or "code," two substantially similar incidents occurring prior to I.R.'s first birthday.[55] Thus, the undersigned finds that Dr. Wilson has misplaced the onset of this behavior. The onset of hyporesponsiveness within the first year of life further supports Dr. Wiznitzer's opinion in this case, while also casting doubt on the accuracy of Dr. Wilson's opinion.

In the video identified as a red flag by Dr. Wilson, I.R. is toddling around in a hallway near a staircase on January 5, 2006. He is between 12 and 13 months old. As he moves around, he loses his balance and falls sideways, striking his head against the wall. A thudding noise is audible, but I.R. has no apparent reaction.

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at his mother in the video on October 31, 2005, should not be credited as an atypical behavior since I.R. was distressed by his Halloween costume. Pet. Posthr'g Br. at 22. However, other examples listed in petitioners' post-hearing brief are less persuasive. For example, petitioners assert that Dr. Wiznitzer opined that I.R. demonstrated an "inadequate wave." Id. As described above, the question was not whether I.R.'s wave was adequately executed, but whether the behavior was intended to be a wave. The undersigned agrees that the video is ambiguous in that regard.

[55] In fact, I.R.'s baby book suggests a third instance. In an entry for September 15, 2005 (when I.R. was about eight to nine months old), Mrs. Reed wrote: "Swimming/learned to paddle/you love to splash/fell on your chin/bleeder in the pool – but you never cry." Pet. Ex. 73 at 12. Dr. Wiznitzer classified this as evidence of hyporesponsiveness. Tr. 863-64. Dr. Wilson declined to opine on the entry, because she had not reviewed the baby book. Tr. 655-56.

A very similar incident occurred on August 25, 2005, when I.R. was approximately eight to nine months old. In the video of that date, I.R. can be heard striking his head.[56] As in the later January 6, 2006 video, there is an audible thud as his head strikes a hard surface. I.R. shows no reaction to the strike. Mrs. Reed can be heard gasping audibly. Moreover, she expresses surprise that I.R. is not reacting, saying "it's so painful, it has to be . . ." Pet. Ex. 139.

As compared to the January 5, 2006 incident, the August 25, 2005 video reflects an incident just as likely to be painful, and I.R.'s reaction is every bit as muted in the earlier video as it is in the later January 5, 2006 video. However, in her expert report, Dr. Wilson's only observation about the August 25, 2005 video is that I.R. can be heard making vowel sounds. Pet. Ex. 176 at 5. Her only testimony regarding this video concerned observations – challenged by Dr. Wiznitzer – that he laughs, responds to his name, and pulls to stand. Tr. 641.

Additionally, the videos in evidence show that on November 15, 2005, when I.R. was about 10 to 11 months old, I.R. again fell and hit his head while playing with a window curtain. As with the videos of August 25, 2005, and January 6, 2006, there is an audible thud when his head strikes the hard surface, despite the camera in this instance being some distance away. As with the August 25, 2005 video, Mrs. Reed again makes a comment on film that suggests surprise at I.R.'s lack of reaction. Like the August 25, 2005 incident, the undersigned finds that the video shows an incident as likely to have caused I.R. pain as the January 5, 2006 incident. Again, I.R.'s reaction is equally muted. Yet Dr. Wilson's observations regarding this video make no mention of the head bump or of I.R.'s muted reaction. In her report, comment on the November 15, 2005 video is limited to observations regarding his playing of peekaboo and his response to his name. Pet. Ex. 176 at 5. Her testimony regarding this video addresses only I.R.'s affect while playing peekaboo. Tr. 650.

During the hearing, the undersigned questioned Dr. Wilson about these prior first-year falls. Dr. Wilson explained that she felt the falls occurring during the first 12 months of life were not painful falls. Tr. 672. She further suggested that she has observed in her clinical practice and in parenting that a crying response to such a fall is often conditioned by the parents and onlookers reacting in such a way as to elicit that response. Id. She speculated that I.R.'s parents may not be the type of parents that encourage a crying response. Id. With regard to the specifics of her review of the videos, Dr. Wilson indicated that "[w]hen I did note that it looked like a painful fall, you know, you hear a bang or something like that." Tr. 672-73. Dr. Wilson did seem to acknowledge that Mrs. Reed appeared concerned by the falls on the video, but ultimately suggested that in contrast to the fall on January 5, 2006, the prior falls were "just a stumble, no reason for a cry really." Tr. 673.

This testimony does not align with the undersigned's review of the videos. The various impacts described above were not significantly distinguishable in their severity. Moreover, as noted above, contrary to Dr. Wilson's suggestion that I.R.'s parents may not be the types to elicit a crying response, Mrs. Reed did appear to express concern about the falls and did, in particular,

[56] Although the camera pulls away a moment before I.R.'s head strikes the hard surface, the video clearly shows that I.R. is about to fall.

audibly respond each time I.R. hit his head, though she did not react to the extent of intervening in I.R.'s activities.

Most significantly, and again contrary to Dr. Wilson's suggestion, the undersigned noted that each of the prior falls resulted in an audible noise similar to the noise heard upon the January 5, 2006 fall; yet this was Dr. Wilson's stated basis for distinguishing one fall from another. Accordingly, the undersigned does not find any basis in the record for Dr. Wilson's decision to categorize or code the August 25, 2006 and November 15, 2006 falls differently than the January 5, 2006 fall. Thus, the undersigned finds that Dr. Wilson has misidentified the onset of I.R.'s hyporesponsiveness, which actually occurred prior to I.R.'s first birthday.[57]

The undersigned finds Dr. Wilson's misidentification of the August 25 and November 15 falls significant for two reasons. First, although Dr. Wilson opined that hyporesponsiveness alone is not indicative of autism, her opinion was predicated on the complete absence of any "red flag" type behaviors during I.R.'s first year of life. Specifically, Dr. Wilson opined in pertinent part:

> Other red flags noted after [I.R.]'s first birthday included his lack of response to pain and his lack of response to loud sounds (e.g., balloon popping in video 4). These characteristics are not indicative of autism on their own, but in conjunction with the other atypical traits noted, they become consistent with autism features. The pattern of behaviors noted in this qualitative analysis shows a clear emergence of autism characteristics following [I.R.]'s first birthday, with no clear cause for concern prior to 12 months of age.

Pet. Ex. 176 at 8 (emphasis original). Second, at no point did Dr. Wilson offer any additional explanation of how her opinion would change – or more to the point, not change – if she accepted any of Dr. Wiznitzer's competing observations or if the undersigned otherwise found that certain of I.R.'s autistic behaviors emerged prior to 12 months of age.

Thus, having concluded that I.R. demonstrated the same hyporesponsive behavior identified by Dr. Wilson, but as early as eight to nine months of age, the undersigned is left with an expert opinion that is premised on an incorrect factual assumption. It is, therefore, far less persuasive as a whole. See, e.g., Hennessey v. Sec'y of Health & Human Servs., 2009 WL 1709053, at *42 (Fed. Cl. Spec. Mstr. May 29, 2009) ("When experts disagree, . . . [o]bjective factors, including the qualifications, training, and experience of the expert witnesses and the extent to which their proffered opinions are supported by reliable medical research, other testimony, and the factual basis for their opinions, are all significant in determining what testimony to credit and what to reject."). As the Supreme Court has noted, a trial court is not required to accept medical or scientific opinion "that is connected to existing data only by the ipse dixit of the expert," because the "court may conclude that there is simply too great an

[57] Of note, Dr. Wiznitzer cited the November 15, 2005 head bump in his supplemental expert report as an example of hyporesponsiveness similar to the January 5, 2006 incident. Resp. Ex. O at 2. He did not, however, offer an opinion regarding the August 25, 2005 fall.

analytical gap between the data and the opinion proffered." Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997).

Additionally, separate and apart from her ultimate conclusion regarding the trajectory of I.R.'s autism, this issue calls into question the reliability and credibility of Dr. Wilson's review of the videos and each of her resulting observations. Specifically, the undersigned's review of the record evidence described above suggests that Dr. Wilson did not in all instances acknowledge or characterize similar events similarly across the multiple videos in this case. This is particularly problematic, because Dr. Wilson's opinion is premised on her claimed expert demonstration that there is a complete absence of atypical behaviors prior to 12 months of age, whereas Dr. Wiznitzer has opined that such behaviors were present during that earlier period, only more subtle. Yet, the undersigned's own review reveals that Dr. Wilson's underlying assertion is not necessarily credible, because her observations are not consistent between the two periods even with regard to incidents that are readily comparable and not at all subtle.[58] As the Federal Circuit noted, "[a]ssessments as to the reliability of expert testimony often turn on credibility determinations, particularly in cases . . . where there is little supporting evidence for the expert's opinion." Moberly, 592 F.3d at 1325-26; see also Snyder, 88 Fed. Cl. at 718 (quoting Ryman v. Sec'y of Health & Human Servs., 65 Fed. Cl. 35, 40-41 (2005)) (noting that special masters perform a gatekeeping function when determining "whether a particular petitioner's expert medical testimony supporting biological probability may be admitted or credited or otherwise relied upon").

3. Dr. Wiznitzer's opinion accords with known patterns of ASD onset.

The undersigned further stresses that the persuasiveness of Dr. Wiznitzer's observations is bolstered by the fact that his opinion is fully consistent with known patterns of ASD onset. Dr. Wilson, in contrast, struggled to articulate how her findings in this case square with what is known about autism.

As noted above, Dr. Wiznitzer stressed that patterns of behavior are more significant to determining ASD onset than isolated behaviors. Resp. Ex. P at 2. He also persuasively testified that the pattern of ASD onset he observed in I.R.'s case is consistent with one of the known, major patterns of ASD onset, namely subtle or insidious onset of atypical behaviors during the first year of life followed by divergence of social behaviors, becoming more evident around 18-24 months of age. Tr. 859-60. In particular, Dr. Wiznitzer identified a pattern of behavior during I.R.'s first year of life including quiet or somber behavior, decreased eye contact, less

[58] The undersigned also notes that although Dr. Freuler discussed hyporesponsiveness in her report, Dr. Freuler coded the January 5, 2006 video as atypical not due to hyporesponsiveness, but because of unsteady gait and motor dyspraxia. Pet. Ex. 145 at 6. This may explain why Dr. Freuler similarly did not code the prior falls as atypical. It is clear from Dr. Wilson's report, however, that it is the hyporesponsiveness to pain, rather than the unsteadiness that led to the fall, which caused Dr.Wilson to code the January 5, 2006 fall as atypical. Pet. Ex. 176 at 6, 8. Thus, even if Dr. Freuler was consistent in opining that none of the falls were concerning for hyporesponsiveness, Dr. Wilson's observations remain inconsistent.

interaction, and a paucity of expected language and vocalization for a child of his age. Tr. 840-42. These observations are fully consistent with the "red flag" items presented by Dr. Wilson and with the literature filed in this case, and are consistent with what is typically known as early onset autism.[59] Tr. 637; see generally Pet. Ex. 165 (describing early onset autism as including social and communicative impairments at a lower rate in the first year, with increasing socio-interactive difficulties and loss of previously seen behaviors as poorer social interest evolves in the second year). Moreover, by highlighting later videos as well, Dr. Wiznitzer persuasively demonstrated how these patterns of behavior became more evident over time.

In contrast, Dr. Wilson has presented findings in this specific case that are potentially at odds with her characterization of her prior RVA study experience, which forms the basis for her expertise. That is, Dr. Wilson explained that RVA researchers should be able to discern the signs of autism earlier than parents or clinicians. Tr. 661. She also noted that prior studies have predicted autism with 94% accuracy at nine to 12 months of age. Tr. 665-67 (citing Pet. Ex. 150 (Baranek)). Yet Dr. Wilson identified no signs of ASD prior to twelve months of age, despite the fact that I.R. is known to have been subsequently diagnosed as autistic.

Asked by the undersigned during the hearing whether it is typical that children later diagnosed as having autism would not show many significant red flag-type behaviors between nine to 12 months of age (i.e., I.R.'s presentation as posited by Dr. Wilson's testimony), Dr. Wilson replied that "I would say it's unusual." Tr. 663. Dr. Wilson did not provide any explanation during the hearing of what significance should be attached to the fact that her findings are unusual or why, in light of that characterization, her conclusion should be credited over Dr. Wiznitzer's competing expert opinion.[60] Indeed, when asked if she would include trajectories of autism as part of her expertise, Dr. Wilson effectively demurred, stating only that she has read about it in the literature but has not included it in her research. Tr. 670.

Following the hearing, Dr. Wilson provided a supplemental report. Pet Ex. 198. In that report, she expressed that "[t]here is currently no simple answer to the question of how common early onset autism is in relation to late onset autism." Id. Citing one review article by Ozonoff, et al., and one Medwire News report, Dr. Wilson further expressed that patterns of ASD onset

[59] In their post-hearing brief, petitioners were critical of the fact that Dr. Wiznitzer did not independently provide any objective or published criteria by which to compare I.R.'s behavior. Pet. Posthr'g Br. at 14 n.25. This is not entirely true. Although not stressed in his opinion, Dr. Wiznitzer cited medical literature regarding this point in his second supplemental report. Resp. Ex. P at 2. In any event, the undersigned notes that she had no difficulty matching Dr. Wiznitzer's observations to the first-year signs of autism described by Dr. Wilson.

[60] In her report, Dr. Freuler went a step further, suggesting not just that I.R. represents an unusual case at the margins of RVA reliability, but actually positing that the unusual lack of red flag behaviors is suggestive of an atypical pattern of autism. Pet. Ex. 145 at 5. Dr. Freuler wrote that I.R. demonstrated a pattern of development that "support[s] an atypical trajectory of autistic features. In my experience of reviewing hundreds of hours of early home movies of infants and toddlers who went on to have a diagnosis of autism, I have very rarely (if ever) seen a lack of ANY red flags in the first year of life prior to an onset of clinical symptoms." Id.

are more complex and varied than simple groups of onset patterns. Id. (citing Pet. Ex. 199 (Ozonoff 2008) and Pet. Ex. 200 (Mahendra 2012)).[61]

The Ozonoff article notes that "[t]here is evidence that the traditionally defined categories of early onset and regressive autism are overly narrow prototypes" and that "[t]here is ample evidence of other ways in which symptoms emerge that are not captured by these prototypes." Pet. Ex. 199 at 7. Nonetheless, when discussing a hypothesized additional onset pattern wherein intact early social development gives way to a later failure to progress, the authors stated that "[n]o empirical research has been conducted on this pattern and very little is known about whether it differs from other onset patterns in phenotypic features unrelated to symptom emergence." Id. at 6. The authors propose:

> [S]ymptom emergence may better be characterized as a continuum. The two extremes of this continuum are anchored by traditional defined prototypical early onset and regressive cases, but many intermediate phenotypes containing mixed features and varying degrees of early deficits, subtle diminishments, failures to progress, and frank losses are also possible. We propose that variable combinations and timings of these processes across children lead to symptoms exceeding the threshold for diagnosis at different points in the first 24 months for different children . . . .

Id. at 7.

Dr. Wilson concluded her supplement report by noting that "autism is a highly complex developmental disorder with multiple genetic factors and patterns of progression. The [RVA] methodology I used to examine I.R.'s early home videos cannot rule out late onset autism, but does offer valuable information about the likelihood (or not) of early onset autism." Pet. Ex. 198. Given her findings in this case – in which, given I.R.'s subsequent history, she effectively concludes there is late onset autism – this is an equivocal conclusion. Moreover, Dr. Wilson conceded during the hearing that RVA is still an evolving methodology. She acknowledged that in terms of screening for earlier diagnosis, "we're not there yet in every way." Tr. 660-61. She further explained that notwithstanding the success of RVA studies, "we still need more information." Tr. 667-68. Ultimately, she also acknowledged, perhaps consistent with her findings in this case, that it is easier to pick up on autism at later ages "across the board," regardless of methodology.[62] Tr. 668.

ii. Petitioners' Additional Arguments

Petitioners raise several additional arguments in their post-hearing brief as to why Dr. Wilson's opinion should be accorded greater weight than Dr. Wiznitzer's. The undersigned does not find these arguments persuasive. Moreover, even if fully credited, none of these arguments

[61] The Mahendra report is not a study and to the extent it does discuss prior studies, it does not discuss them by name or even confirm whether the studies discussed were published.

[62] Dr. Wiznitzer likewise stressed that diagnosis at one year of age is very difficult. Tr. 795-96.

is sufficient to overcome the undersigned's findings with regard to the substance of Dr. Wilson's opinion. Nonetheless, the undersigned addresses each in turn.

a. First Year Medical Records

In their post-hearing brief, petitioners note that I.R.'s medical records report completely normal development during the first year of life. Pet. Posthr'g Br. at 13. Specifically, petitioners cite I.R.'s four-month, six-month, nine-month, and 12-month well-child visits. Pet. Ex. 9 at 34-39. Petitioners also stress that Dr. Niyazov and Dr. Cohen both opined based on the medical records that I.R. had normal development in his first year.[63] Pet. Posthr'g Br. at 6 (citing Tr. 118, 228, 511-12).

The undersigned does take notice of the fact that I.R.'s pediatric medical records reflect normal development through at least 12 months of age. Indeed, this fact was stipulated by the parties prior to the hearing. Joint Prehr'g Submission at 1. However, this fact does not carry a great deal of significance. Dr. Wilson testified that parents and clinicians commonly do not become concerned about potential signs of autism until about 18 months to two years of age. Tr. 658-59. Dr. Wiznitzer similarly testified that children are typically referred for autism evaluation after 18 to 24 months of age and that earlier referrals are less common. Tr. 881. Moreover, Dr. Wiznitzer testified that the 12-month developmental screening in this case did not account for the types of social behaviors he observed upon his review of the videos filed in this case. Tr. 904-05. And indeed, petitioners note in their post-hearing brief that due to her concerns regarding I.R.'s health status and her uncertainty as a first-time parent, Mrs. Reed recognized some of I.R.'s developmental issues only in hindsight. Pet. Posthr'g Br. at 36-37.

Thus, the fact that I.R.'s medical records do not reflect the signs of autism discussed by Dr. Wiznitzer is not surprising. Moreover, in light of the extensive expert evidence presented in this case, the videos filed from I.R.'s first year of life remain the most illuminating evidence regarding whether he demonstrated atypical behaviors prior to his first birthday. In that regard, petitioners' own expert confirmed that there was more than the usual amount of video footage available in this case and that the amount was sufficient to detect atypical behaviors. Tr. 621-22. Although the medical records provide some corroboration for Dr. Wilson's opinion, that corroboration is not very meaningful in light of her own testimony that parents and clinicians do not typically recognize the early signs of autism.

b. Experts' Credentials

Petitioners also allege a qualifications gap between Drs. Wilson and Wiznitzer, favoring petitioners' own expert. Petitioners argue, in effect, that Dr. Wilson's history of participating in RVA studies makes her more qualified to judge the videos filed in this case and determine the age of onset for I.R.'s autism. Petitioners do not go so far as to argue that Dr. Wiznitzer's

[63] In the testimony cited by petitioners, Dr. Niyazov did not specifically address the basis for his opinion regarding I.R.'s first year development. Although I.R. did have office visits with Dr. Niyazov, these visits occurred later in life. Therefore, Dr. Niyazov's opinion is necessarily based on record review or later parental report.

testimony should be precluded, but implicitly argue that Dr. Wilson's opinion should be afforded greater weight. Pet. Posthr'g Br. at 18 n.33. The undersigned disagrees.

Dr. Wilson's bona fides in the specific area of RVA are well established. She worked for six years with the Program in early Autism Research, Leadership, and Service ("PEARLS") based at the University of North Carolina Chapel Hill, which is recognized as one of five main research groups driving study in this field. Tr. 585, 594, 597; Pet. Ex. 165 (Saint Georges) at 5. Dr. Wilson described the extensive training necessary to participate as a coder in the PEARLS research and estimates that she has observed video footage of over 100 children. Tr. 576-77, 595-602. Dr. Wilson is published in this area as well. Tr. 602-10; Pet. Ex. 181 (Watson).

In contrast, Dr. Wiznitzer has not published in this area and has not suggested that he has participated in any RVA studies. He described himself as "familiar" with the literature. Tr. 792. Rather, Dr. Wiznitzer's experience with RVA stems from his use of video review as part of his clinical practice. Resp. Ex. 0 at 2; Tr. 792-93. Dr. Wiznitzer himself characterized his use of video review as "occasional" and estimated that he reviews patient video about once a month. Tr. 893. However, Dr. Wiznitzer noted that he has been doing so for many years, characterizing the timeframe as dating back to when videos were available only on VCR cassette tapes. Tr. 792. In addition to his academic appointments, Dr. Wiznitzer has been a continuously practicing clinician since 1984. Resp. Ex. Q at 2-3.

Regarding that clinical experience, petitioners stress that Dr. Wiznitzer testified that he does not currently have any patient under 18 months of age and that patients are usually 18 months old by the time they are referred to him. Pet. Posthr'g Br. at 18-19 (citing Tr. 881, 883). Dr. Wiznitzer testified, however, that he has evaluated less than ten patients under the age of one for autism, but several dozen children 12-15 months old. Tr. 881. Dr. Wiznitzer also specifically confirmed in his testimony that his experience with video review, which he has been doing for decades to assist in diagnosis, involves videos recorded when his patients were younger, including during the first year of live. Tr. 792, 896-97. Dr. Wiznitzer estimates that up to 30% of his practice is devoted to children with autism. Tr. 880.

Petitioners further stress that Dr. Wiznitzer does not see well babies, suggesting that he has "almost no experience evaluating 0-12 month olds who are 'typical.'" Pet. Posthr'g Br. at 26 (citing Tr. 886). Dr. Wiznitzer testified, however, that as a pediatric neurologist he regularly consults on cases involving infants for a variety of issues. Tr. 885. Dr. Wiznitzer clarified that he sees infants with suspected neurological concerns, but that many of these conditions do not affect their development. Tr. 886. Additionally, he noted that he is trained not only in pediatrics, but in developmental pediatrics. Tr. 885. In any event, Dr. Wiznitzer also persuasively explained that knowing normal social behavior, and variations on social behavior, are an inherent part of making an autism diagnosis in the clinical context. Tr. 789-90.

Importantly, to the extent that the above points raised by petitioners arguably reveal significant nuances regarding the relevancy of Dr. Wiznitzer's clinical experience, these points also highlight Dr. Wilson's comparative lack of clinical experience. Dr. Wilson's CV lists only two years of clinical experience in speech-language pathology at Kennedy Krieger from 2006 to 2008. Pet. Ex. 177 at 1. She testified that her duties in her current teaching position, which she

has held since 2014, also involve supervision of graduate students engaged in clinical speech-pathology work. Tr. 575. And in any event, although Dr. Wilson has identified a clear research interest in early identification of autism, she has not demonstrated that any of her clinical, as opposed to research, experience involves patients in the 0-12 month age range.[64]

Moreover, Dr. Wilson seemed to acknowledge that her observations may be limited by her particular field. With specific regard to this case, she acknowledged that petitioners' other RVA expert, Dr. Freuler, may have picked up on additional atypical behaviors by virtue of her training in occupational therapy. Tr. 632-33. Dr. Wilson also admitted that she has not personally researched trajectories of autism. Tr. 670. This is significant, because diagnosis of autism is a clinical exercise that extends far beyond speech pathology. See, e.g., King, 2010 WL 892296, at *79 (noting that "autism is considered both a neurologic and a psychiatric disorder" and that "psychologists are also often the specialists who diagnose autism"); see also Snyder, 2009 WL 332044, at *32 ("With the exception of Rett's disorder, all ASDs are diagnosed by comparing behavioral symptoms exhibited by a child against an established set of broad diagnostic criteria. The diagnosis is made by direct observation, videos of the child, and from parental reports, as there is no biochemical test for ASD.").

These points go to the core of the difference between these two experts. While Dr. Wilson clearly has research experience and training specific to RVA that Dr. Wiznitzer lacks, Dr. Wiznitzer has a depth and breadth of clinical experience in pediatric neurodevelopment and autism that Dr. Wilson cannot match. Dr. Wiznitzer persuasively asserted that, notwithstanding the research methodologies involved in RVA studies, video review itself can be an extension of clinical care and diagnosis. Tr. 903. Petitioners, on the other hand, have not established that the video format itself in any way prevents Dr. Wiznitzer from utilizing the full breadth of his clinical skills. Thus, the undersigned disagrees that Dr. Wilson's testimony is entitled to greater weight based on her credentials. While these two experts have different strengths, the undersigned stresses that both are qualified to opine in this case regarding the manifestation of I.R.'s autism.

c. Expert Methodology

Petitioners also argue that Dr. Wilson's opinion should be credited over Dr. Wiznitzer's competing opinion, because Dr. Wilson used an established methodology for RVA. Petitioners assert that "Dr. Wilson testified that specialized training, expertise and procedures, for example, using multiple coders who had attained 90% accuracy in coding, ensured 'reliability' and prevented errors resulting from ignoring context or by focusing on irrelevant behaviors." Pet. Prehr'g Br. at 23. Petitioners further stress that "[r]eliability is the fundamental measuring stick for the admissibility of expert testimony in the Vaccine Program, thus an expert methodology designed for its reliability and accuracy, rather than a more casual 'call it as I see it' approach, is the one this Court should credit."[65] Id. at 24. The undersigned does not credit petitioners'

[64] Her expert report states only that she has "clinical experience with individuals with autism across age ranges." Pet. Ex. 176 at 2.

[65] Dr. Wiznitzer, in contrast, contended that the value in Dr. Wilson's methodology lies in

argument because, notwithstanding her familiarity with RVA procedures, Dr. Wilson's participation in this case differed significantly from her participation in RVA studies.

First, it is important to understand that Dr. Wilson discussed reliability in several distinct ways. The 90% reliability referenced in petitioners' brief refers to Dr. Wilson's testimony that as part of the training process, potential RVA coders must show their ability to reach 90% agreement against a previously vetted master code. Tr. 598-600. This was characterized during the hearing as a test that functions as a barrier to entry as an RVA coder. Tr. 599. Although that accomplishment certainly speaks to Dr. Wilson's experience in this area, that figure represents a one-time training threshold, not an ongoing accuracy rating, and it in no way suggests that Dr. Wilson will necessarily be 90% accurate in any given instance.

Dr. Wilson also discussed the fact that RVA studies can achieve a confidence level of 95%.[66] Tr. 661-63. In describing the process utilized in the studies she has participated in, however, she explained that each video is observed by two coders, a primary coder and a reliability coder. Tr. 614-15. To be considered scientifically valid, the reviewers must reach 80% agreement in their coding. Tr. 619. When they fail to achieve 80% agreement on the proper coding, the two coders re-review the videos and confer to resolve the differing interpretations. Tr. 615-16. This is called consensus coding. Dr. Wilson further explained that, should the consensus coding fail to achieve 80% agreement, protocol requires that a third coder be introduced to help resolve the conflicting data. Tr. 619.

Dr. Wilson's testimony is significant then for revealing the extent to which the reputation of RVA studies for reliability is built upon the use of multiple reviewers to reach a consensus. Indeed, consistent with Dr. Wilson's testimony, the undersigned's review of the medical

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maintaining consistency among reviewers for research purposes and that it is far less meaningful in this context, which is more akin to an extension of clinical care. Tr. 790, 903. Petitioners are critical of this argument, contending that it is not true that RVA studies are standardized so that they can be compared, because RVA study designs can be very different. Pet. Posthr'g Br. at 23 n.35. Petitioners point out that Dr. Wiznitzer provided no evidence to support his assertion that standardization is the reason for RVA methodology. Id. at 23. This is an overly cramped reading of Dr. Wiznitzer's testimony. Specifically, Dr. Wiznitzer testified that "you need to lay foundations for how people are going to do it so you can compare one research study to the other." Tr. 790. He went on to explain by way of further example that when studying autism, use of the common diagnostic criteria is important to ensure that the population being targeted for study is adequately defined so that subsequent readers can properly evaluate the study. Tr. 791. The undersigned understands the sum and substance of Dr. Wiznitzer's testimony on this point to be that any research study must necessarily have a standardized and disclosed methodology so that the results may be scrutinized and potentially challenged. It is not a fair reading of his testimony to suggest that he was asserting that all RVA studies have the same methodology.

[66] Dr. Wilson stressed that this confidence level applies to the group as a whole and not to each individual subject. Tr. 663. In other words, Dr. Wilson explained that statistically speaking, there is a 95% chance that they have not erred in grouping the subjects of the study. Id.

literature filed in this case reveals that, despite variations in methodology among RVA studies, consensus coding or reliability reviewing in some form is overwhelmingly used to vet the coding data to at least some degree. Dr. Wilson additionally acknowledged that in her own experience participating in RVA studies she has personally fallen below 80% agreement in some categories and found it necessary to engage in consensus coding. Tr. 616. Following the consensus coding, she reports that she achieved up to 88-93% agreement. Id. And although she testified that she has never had to use a third coder, she acknowledged that the need can arise, noting that "it was put in place for a reason, I'm sure." Tr. 619.

Nonetheless, petitioners stress Dr. Wilson's use of a detailed operational coding manual previously used in her RVA gesture study, suggesting that the manual and checklist necessarily make her observations more reliable. Pet. Posthr'g Br. at 24. Petitioners further observe that Dr. Wiznitzer acknowledged the validity of that paper's methodology. Id. at 24-25. However, Dr. Wilson's testimony describes a process wherein coders who use such manuals, and who would necessarily have achieved a 90% reliability score following training, may see their interpretations swing significantly from their own review to consensus review (i.e., from less than 80% agreement to 93% agreement) before any final conclusion is drawn for research purposes. Yet, notably, no such collaborative review process took place in this case as between the competing expert opinions presented.[67]

This dramatically reduces the significance of both Dr. Wilson's reported achievement of 90% accuracy as a threshold for becoming a coder and of the overall reliability of RVA studies in general. Dr. Wilson's own testimony about RVA methodology in the studies she has participated in reveals that the checklist or coding approach alone is not considered sufficient to ensure scientific reliability. Rather, these RVA studies rely on consensus coding to help overcome subjective interpretative differences that routinely arise even among researchers using the same operating manual and checklist and viewing the same videos. Moreover, these studies – to the extent that they seek only 80% agreement between coders – do not even purport to entirely overcome these subjective differences. Indeed, Dr. Wilson's own RVA gesture study, cited by petitioners, cautions that "[a]nother potential methodological limitation is that coders used a consensus coding procedure for all data due to challenges in reaching high levels of point-by-point agreement with the coding system as they coded low-frequency behaviors." Pet. Ex. 181 at 12. Thus, it cannot fairly be said, when dealing with a single reviewer in a single instance, that the checklist or coding manual eliminates the "call it as I see it" subjectivity petitioners assign to Dr. Wiznitzer's analysis.

Moreover, to the extent petitioners' argument includes a corresponding criticism of Dr. Wiznitzer for not using a checklist or other predetermined methodology, the undersigned does not find that to be a compelling argument where Dr. Wiznitzer has, in fact, identified more

[67] To the extent petitioners suggest that Dr. Freuler's report could stand in as a form of reliability coding, at least as far as their agreement regarding the first 12 months of life, the undersigned notes that the record evidence also includes Dr. Wiznitzer's competing observations, which are at odds with Dr. Wilson's opinion. This continues to raise the question of what sort of interpretive swing could result, in a different, non-adversarial context, were Dr. Wiznitzer and Dr. Wilson to engage in consensus coding.

atypical behaviors than Dr. Wilson. If the argument had been that it was Dr. Wiznitzer who potentially missed atypical behaviors, his lack of a checklist or other methodology would be important for questioning his rigor and would provide some possible explanation of how those behaviors were missed. But where, as here, the issue is that Dr. Wiznitzer has identified additional suspect behaviors over and above those identified by Dr. Wilson, those observations can be confirmed, discussed, and weighed on substance and should not be dismissed solely because they were derived from Dr. Wiznitzer's unquantifiable clinical judgment rather than from a predetermined method of video review. That is, the relevant reliability consideration regarding Dr. Wiznitzer's observations is not how he arrived at them, but whether those observations align with what can be seen on the videos and what is known about autism and autistic behaviors.

In their post-hearing brief, petitioners acknowledged Dr. Wiznitzer's testimony regarding his methodology for reviewing the videos. Pet. Posthr'g Br. at 27. Specifically, Dr. Wiznitzer explained that he (1) reviewed the tapes to determine if there were patterns of behavior or only isolated events, (2) questioned if the behaviors were appropriate developmentally, and (3) looked at the intent or purpose of the behavior in terms of behavioral response, social interaction, and joint attention. Tr. 898-99. Notably, Dr. Wilson describes her review method in substantially similar terms.

In her report, Dr. Wilson explained that "I completed a qualitative retrospective video analysis through careful review of each home video . . . [that] included identification of behaviors as 'units of analysis' that reflected developmental milestones and/or unusual or atypical behaviors." Pet. Ex. 176 at 3 (citations omitted). Dr. Wilson noted that "[d]uring viewing, I took detailed notes based on my clinical experience and current scientific knowledge of both typical and atypical behaviors and developmental patterns." Id. at 3-4. And indeed, when asked by petitioners' counsel on direct examination how she determined what behaviors were significant without a predesigned study, Dr. Wilson responded that her observations were based only on her overall experience with RVA. Tr. 626-27. In other words, Dr. Wilson's opinion in this case is only an extension of her understanding of RVA coding practices, not a replication of an RVA study procedure.

Moreover, to the extent that petitioners have stressed the qualitative contextual analysis that goes into Dr. Wilson's video review,[68] very little of that contextual analysis can be gleaned from Dr. Wilson's report.[69] When reviewing Dr. Wilson's video notes as included in her report, very few of her observations include sufficient detail to fully evaluate the contextual considerations Dr. Wilson is said to have factored into her conclusions. For example, citing three examples spanning July 10, 2005, to August 10, 2005, Dr. Wilson notes that I.R. "responds to sounds/voices often" and is "[d]istracted when not responding to name at times (TV, toys . . .

[68] Dr. Wilson indicated that she reviewed the videos a second time to screen for context. Pet. Ex. 176 at 3.

[69] Moreover, as described above, the undersigned did not in all instances agree with Dr. Wilson's description of the relevant context, particularly as regards her inconsistent identification of hyporesponsive behavior.

eventually turns to sound and goes to mom)." Pet. Ex. 176 at 4. Another note regarding December 24, 2005, says "overwhelming situation, no expressions, but attending to people and trying new things." Pet. Ex. 176 at 6. In each of these notes, Dr. Wilson coded I.R.'s behavior as typical, but her description includes references to related, but apparently qualifying or contradictory, behavior (i.e., instances of not responding to name and no expression). Thus, these findings include a significant degree of contextual judgment. However, there is insufficient explanation to evaluate how these contextual considerations may have been weighed.[70] In other instances, Dr. Wilson has coded behaviors as typical – rather than ambiguous – despite using language in her notes that suggests uncertainty regarding what the behavior at issue actually represents. For example, she classifies "possible initiation of peekaboo" on November 15, 2005, and "possible waving and smiling" on December 20, 2005, as typical. Pet. Ex. 176 at 5-6. However, the report lacks any explanation of how these seemingly ambiguous entries came to be affirmatively coded as "typical."

Thus, despite petitioners' well-founded assertion that RVA methodology is well respected in general, Dr. Wilson has not, in fact, fully brought that study methodology to bear in this case. The field's reputation or reliability writ large does not apply to a single reviewer operating in a single instance. The undersigned is therefore not persuaded that Dr. Wilson's approach to reviewing the videos at issue in this case is inherently superior to, or significantly less subjective than, that of Dr. Wiznitzer.

d. Hindsight Approach

Finally, petitioners note that Dr. Wiznitzer characterized his approach as both longitudinal and as an extension of clinical care. Pet. Posthr'g Br. at 21-23. Petitioners describe Dr. Wizinitzer's review as a "hindsight approach" and argue that it is "scientifically flawed," because having knowledge of a child's diagnosis can unwittingly create bias. Id. at 21. Petitioners stress that Dr. Wilson was blind to the specifics of I.R.'s medical history when she reviewed the videos and that an RVA paper that was not blind to ultimate diagnosis would not survive peer review.[71] Id. (citing Tr. 617); see also Pet. Ex. 176 at 3. Petitioners further stress

[70] Of these four videos, only the July 10, 2005 video clip was further discussed during the hearing.

[71] In their post-hearing brief, petitioners draw their focus on scientific validity too narrowly by focusing on what is peer-reviewable or appropriate for research purposes. Petitioners repeatedly suggest that Dr. Wiznitzer's approach to this case as an extension of clinical care is improper or unscientific, but do not explain why knowledge based on clinical care should be viewed as unscientific. Petitioners stress Dr. Wiznitzer's testimony that "I don't do an ADI [Autism Diagnostic Interview] on every single child with autism who comes into my office, or an ADOS [Autism Diagnostic Observation Schedule] on every child who comes into my office. . . . I know autism, and I know child development, and I know what the typical milestones are." Tr. 791. Citing this testimony, petitioners suggest that Dr. Wiznitzer failed to utilize a "scientifically recognized, and replicable, methodology" to review the videos. Pet. Posthr'g Br. at 23. However, the fact that observations from clinical care do not lead to replicable findings does not render them inaccurate or invalid when they are otherwise substantiated and not simply the expert's ipse dixit. Indeed, in this Program, treating physician opinions and treatment records,

that "Dr. Niyazov concurred that Dr. Wiznitzer's hindsight approach to the videos was 'improper,' because every child has behaviors that could be interpreted as autistic by someone aware of the autism diagnosis, looking back. Yet those same behaviors would not be suspect if the child did not have a present autism diagnosis." Pet. Posthr'g Br. at 21 (citing Tr. 960-61). The undersigned disagrees.

The question in this case was never whether I.R.'s later autism diagnosis was predictable at 12 months of age or earlier, or whether isolated behaviors are necessarily suggestive of autism. The question is whether there is preponderant evidence that I.R.'s autism began to manifest, albeit subtly, by 12 months of age. In other words, evaluating the evidence in this case is inherently an exercise in hindsight. In that regard, Dr. Wiznitzer's longitudinal approach – showing that the later, more evident signs of autism that factored into I.R.'s diagnosis could be seen in budding form in the earlier videos – is persuasive. Dr. Wiznitzer explained that first-year diagnosis of autism is challenging and that it can be difficult to know if early developmental differences are autism or not. Tr. 795-96. In that context, the fact that early behavioral differences did, in fact, become more apparent and lead to an autism diagnosis in this case is valuable information. Thus, what petitioners characterize as a potential source of bias is, in fact, necessary context.

This issue was persuasively addressed in a prior case. In R.K. v. Sec'y Health & Human Servs., petitioners' expert, a pediatric neurologist, was critical of respondent's expert's video analysis, arguing that early indications of developmental disability should not be viewed as predictors of autism. 2015 WL 10936124, at *67. The special master observed, however, that "there is a difference between engaging in diagnosis and recognizing with the benefit of hindsight that certain signs or symptoms are indicative of a subsequently diagnosed condition. . . . [T]he question is not whether the videos are diagnostic of [the child]'s ASD in themselves, but whether [the child]'s behavior in the videos is consistent with or contrary to petitioners' description of the timeline of onset." Id.

By misconstruing the critical question as one of predictive analysis and having Dr. Wilson conduct a blind review, petitioners effectively prevented Dr. Wilson from bringing the fullness of her expertise to bear in this case. This can be readily observed in Dr. Wilson's report, which is phrased in a tentative manner likely for this very reason. Dr. Wilson states that "I begin to see clear (vs. ambiguous or possible) markers that raise red flags for autism starting around 15 months of age and after." Pet. Ex. 176 at 4 (emphasis in original). She also concluded that

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which reflect clinical care, are often given significant weight. See, e.g., Capizzano v. Sec'y of Health & Human Servs., 440 F.3d. 1317, 1326 (Fed. Cir. 2006) (noting that "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). Moreover, as previously discussed, petitioners have not substantiated that the video format prevents Dr. Wiznitzer from utilizing his clinical knowledge in this case. Contrary to petitioners' intimation, the undersigned understands Dr. Wiznitzer's testimony to reveal that, notwithstanding whether he fully executes the ADI and ADOS in every instance, he does in fact include his knowledge of those standardized diagnostic tools in his clinical practice and in his review of the videos in this case.

"[t]he pattern of behaviors noted in this qualitative analysis shows a clear emergence of autism characteristics following [I.R.]'s first birthday, with no clear cause for concern prior to 12 months of age." Id. at 8 (emphasis original).

Had Dr. Wilson viewed these videos with full knowledge of I.R.'s subsequent history, she may have been better equipped to further scrutinize the behaviors she appears to have discounted because they were not "clear" predictors of autism. Such an opinion by Dr. Wilson would have been more helpful in resolving the question actually at issue in this case. As Dr. Wilson acknowledged, it is easier to pick up on autism at later ages "across the board," regardless of methodology. Tr. 668. Thus, her focus on "clear" manifestations of autism that are predictive of autism or would in themselves constitute "cause for concern" is not necessarily helpful in placing the onset of I.R.'s autism.[72] The potential for bias as a result of knowing I.R.'s full history is far less of a concern in this case than the risk that Dr. Wilson overlooked actual manifestations of I.R.'s autism due to her apparent focus on what is predictive rather than discernable in hindsight as a manifestation of autism.

iii. The undersigned finds that I.R.'s autism is not regressive.

In addition to disputing the onset of I.R.'s autism, the parties also disagree as to his subsequent course. Petitioners' experts, Drs. Niyazov and Zimmerman, both opined that I.R. experienced a post-vaccination regression. Pet. Ex. 32 at 1; Pet. Ex. 39 at 5; Tr. 223-24. Respondent's experts disagree. Tr. 408-09, 459, 840-42; Resp. Ex. C; Resp. Ex. O; Resp. Ex. P. Based on the record as a whole, the undersigned does not find preponderant evidence of a regression.

a. Contemporaneous medical records do not reflect a regression.

As noted above, I.R.'s first-year pediatric records reflect typical development, though not much detail is provided. Pet. Ex. 9 at 34-39. At I.R.'s 18-month well visit on June 27, 2006, his parents reported that he had a "10+" word vocabulary. Id. at 23. Later, on December 28, 2006, at I.R.'s two-year well visit, I.R. was reported to have 20 words. Id. at 17.

Mrs. Reed first expressed concern about I.R.'s speech development on March 30, 2007. Pet. Ex. 9 at 15. At that time, Mrs. Reed mentioned that he "really hasn't progressed," and I.R.'s physician noted "speech delay." Id. I.R. was reported to still have a 20-word vocabulary, but many words were difficult to understand and he appeared to be frustrated by his difficulty communicating. Id. He was noted to have only one two-word phrase. Id.

On April 18, 2007, at 28 months of age, I.R. had an Initial Global Developmental Evaluation at Jump Start Development. Pet. Ex. 9 at 61-66. The reason for the evaluation was a lack of expressive speech. Id. at 61. Based on the Battelle Developmental Inventory, I.R. was assessed as having adaptive skills within normal limits and above average motor skills, but was

[72] To the extent Dr. Wilson's report is couched in such qualified terms – expressing an opinion only regarding what is "clear" – it does not even necessarily contradict Dr. Wiznitzer's opinion that signs of I.R.'s autism began to emerge in subtle ways prior to that point.

delayed in personal and social skills (scoring at a 19 month age equivalent) as well as communication and cognitive skills (scoring at a 15 month age equivalent). Id. at 62. I.R. was noted to have about 15 words in his daily language. Id. at 65. I.R. was recommended for early intervention due to a 30% delay in his language and communication skills, personal social skills, and adaptive (sensory) skills. Id. at 66. I.R.'s parents did not report any loss of skills. No assessment of regression was made, nor was the history provided consistent with any loss of previously acquired skills.

The same day, I.R. was seen for a speech evaluation.[73] Pet. Ex. 9 at 67-70. The reported reason for evaluation was a concern that I.R. was not talking as much as other two year olds, though it was noted that "mom reports that she has many concerns regarding [I.R.]'s development." Id. at 67. Mrs. Reed reported that I.R. had "around 15-20 words" but that he was not always able to use those words to communicate wants and needs. Id. at 68. During the clinical observation, I.R. was observed "to use a few true words to communicate." Id. I.R. was assessed as having a 58% delay in play skills and pragmatics (scoring at a 12-month age equivalent) and a 65% delay in both language expression and receptive language (scoring at a 10 month age equivalent). Id. at 68-69. Again, no loss of skills was reported, and no assessment of regression was made.

About three months later, on July 26, 2007, I.R. was seen at 31 months of age at the Advocate Illinois Masonic Medical Center, Pediatric Development Center, for concerns about speech language delay and suspicion of autism. Pet Ex. 9 at 47-55. Consistent with prior evaluations, I.R.'s parents reported that a concern about language delay arose after about four to six months of illness. Id. at 47. They also reported that "his speech and social skills appeared to decrease after his illness," which seems to be the first suggestion of regression in I.R.'s medical records. Id. at 48. However, the evaluation later uses the phrase "lack of progression," rather than regression, to describe his status. Id. The evaluation also reflects: "His family reports that his first words were at 1 year of age, then he had 15 words at 15 months, but while sick he had no new words and for a long time had the same 15-20 words. He has had slow progression since he was ill, and now has about 40 words with a few 2-word utterances." Id.

I.R. was evaluated against a number of childhood development tests, including the Childhood Autism Rating Scale ("CARS"). Id. at 49. Although he received a CARS score consistent with autism and showed impairments in all three areas associated with autism (social interaction, communication, and rigid/repetitive behaviors), certain signs of social awareness during the evaluation suggested a need for further evaluation before a diagnosis could be made. Id. at 49-50. I.R.'s assessment did not include any diagnosis or conclusion consistent with regression.

[73] Both the April 18 global development report and the April 18 speech evaluation report list the same history, which includes a summary of I.R.'s period of illnesses from about 12 months through 18 months of age, but does not explicitly link those illnesses to the concerns about his development. Pet. Ex. 9 at 61, 67. An occupational therapy evaluation on May 1, 2007, included a similar history. Id. at 71-72.

On October 12, 2007, I.R. was seen at two years and nine months of age for a further evaluation to clarify his diagnosis following the July 26, 2017 evaluation. Pet. Ex. 10 at 5-9. He was evaluated by Nancy Keck, M.D., and Erin Telford, Psy.D. Id. The history provided by Mr. and Mrs. Reed was largely consistent with prior histories, except that they raised the possibility of regression. Id. After describing motor milestones as being "on target," the following was noted based on the parental interview: "He used to point to identify pictures until he got sick at approximately 12 to 15 months, when he seemed to lose skills. For instance, he had pointed at around 12 months of age but then stopped doing it." Id. at 5. The history also indicates that "[a]t approximately 18 months of age, [I.R.] seemed to lose words and his pediatrician referred him to Early Intervention."[74] Id. at 6.

Drs. Telford and Keck concluded that "[I.R.]'s developmental delays are characteristic of a child with autistic disorder." Pet. Ex. 10 at 8. They noted that he had a CARS rating of 39, which placed him in the severe autistic range and characterized his speech as "significantly delayed." Id. Nothing indicates that I.R.'s autism was considered regressive or that Drs. Telford and Keck believed I.R. to have experienced any loss of skills or regression. Indeed, their conclusion was that he had developmental delays consistent with autistic disorder. They stressed that "Autistic Disorder generally begins before age 3," but noted that developmental gains are possible and that some autistic children show increased social interactions as they get older. Id. at 8.

In March of 2009, I.R. was subsequently reevaluated at age 4 years and two months by Alexian Brothers Behavioral Health. Pet. Ex. 18. At that time, Mrs. Reed reported that "[c]urrent concerns include delays in language (i.e., echolalia, scripted speech), fine motor skills, and social skills." Id. at 2. She provided a history in which she indicated that "[I.R.]'s language development was normal until age 2 when he lost the single words he had mastered up until that point (i.e., about 10 single words)." Id. The evaluation further reflects that "[h]e also had severe ear infections that required myringotomy tubes to be placed at about 16 months of age. After these illnesses, his mother reported a change in his language and social skills." Id. The evaluation concluded:

> [I.R.] is an adorable little boy who presents with delayed language and fine motor skills, social difficulties, repetitive behaviors, and stereotyped interests. Based on this evaluation, [I.R.] meets the criteria for a diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified (PPD-NOS). PPD-NOS is a diagnosis along the autism spectrum, with symptoms in the mild range of severity. Based on [I.R.]'s developmental history and current functioning, he has clearly made marked improvements. The Autism diagnosis was more appropriate for him at a younger age when his symptoms were more severe.

[74] Mrs. Reed testified that this statement is accurate in that she reported a loss of words at 18 months of age, but she clarified that the referral to Early Intervention came later. Tr. 65-69. However, this is not consistent with the contemporaneous medical records. I.R.'s pediatrician explicitly recorded that Mrs. Reed reported that I.R. "hasn't progressed," which is distinct from a loss of words. Pet. Ex. 9 at 15.

Id. at 13. As with prior evaluations, nothing indicates that I.R.'s diagnosis included any loss of skills or regression.

Thereafter, subsequent medical records repeatedly referenced by petitioners report a history of regression. See, e.g., Pet. Ex. 28 at 7; Pet. Ex. 29 at 103; Pet. Ex. 84 at 8. Additionally, Mrs. Reed testified in April of 2015 that I.R. had lost words, but that she hadn't noticed it until her younger son began to develop speech. Tr. 59-60.

Notwithstanding the later reports of regression, based on the medical record as a whole, the undersigned does not find preponderant evidence that I.R. experienced regression. The medical records demonstrate that from the time Mrs. Reed first reported speech concerns to I.R.'s pediatrician in March 2007 through July 2007, I.R.'s parents were consistent in describing their concern as one of speech delay, noting that I.R. lacked progress during his period of illness and make slow progress after. No loss of developmental milestones was reported. Such medical records generally "warrant consideration as trustworthy evidence." Cucuras v. Sec'y of Health & Human Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). Greater weight is typically given to contemporaneous records. Vergara v. Sec'y of Health & Human Servs., No. 08-882, 2014 WL 2795491, at *4 (Fed. Cl. Spec. Mstr. May 15, 2014) ("Special Masters frequently accord more weight to contemporaneously-recorded medical symptoms than those recorded in later medical histories, affidavits, or trial testimony.")

It was only as time passed that I.R.'s parents began to introduce suggestions of regression. Notably, these reports were more remote in time from the events recalled. The later parental reports regarding regression do not have sufficient indicia of reliability to be credited over the contemporaneous medical records and their own earlier statements, which do not show speech regression. See, e.g., R.K., 2015 WL 10936124 (finding that later medical records, including parental recollections of autistic regression, cannot be credited over closer-in-time medical records that did not report regression); see also Reusser v. Sec'y of Health & Human Servs., 28 Fed. Cl. 516, 523 (1993) ("[W]ritten documentation recorded by a disinterested person at or soon after the event at issue is generally more reliable than the recollection of a party to a lawsuit many years later."); Cucuras, 993 F.2d at 1528 ("[O]ral testimony in conflict with contemporaneous documentary evidence deserves little weight.").

b. Expert opinions do not support a finding of regression.

Having reviewed I.R.'s medical records through 2012, including his multiple developmental and autism screenings, as well as the home video footage described above, Dr. Wiznitzer opined that there is no evidence of regression. Tr. 840-42; Resp. Ex. C; Resp. Ex. O; Resp. Ex. P. Rather, Dr. Wiznitzer opined that I.R. experienced a stagnation that became more apparent during his second year of life, a pattern consistent with early onset autism. Tr. 842. Dr. Wiznitzer further explained that there are several major patterns of ASD presentation. Tr. 859-60. Some children with ASD will show subtle or insidious onset in their first year of life with social behaviors diverging more fully or stagnating in the second year of life. Id. Those children showing regressive autism remain typically developing until their second year, when a true regression occurs. Id.

Dr. Zimmerman was unable to persuasively identify evidence of regression in I.R.'s contemporaneous records.[75] Tr. 753-60. Ultimately he agreed that I.R.'s "regression" was not a typical regression, but a stagnation or plateau. Tr. 753, 756. Nonetheless, he maintained his opinion that as a regression from the expected, I.R.'s stagnation in development constituted a regression. Id. Dr. Zimmerman's opinion is not persuasive in this regard. He acknowledged both that stagnation is a known pattern in ASD and that language stagnation is a fairly common symptom leading to diagnosis. Tr. 755. He also acknowledged that language delay is one of the most common presenting signs of autism. Tr. 759. Moreover, Dr. Zimmerman's interpretation of regression is not consistent with the opinions of petitioners' other experts. Dr. Niyazov agreed that stalling or stagnation is not the same as regression. Tr. 277-78. Though he opined that a stalling of development would be atypical autism, his expert report did distinguish regression from a plateau in development.[76] Tr. 277-78, 315-17; Pet. Ex. 39 at 5.

Additionally, Dr. Wiznitzer stressed that there are specific criteria for determining whether such a regression has occurred and opined that I.R. did not experience regressive autism. Tr. 840-43, 869; Resp. Ex. O at 2-3. He indicated that regression is a loss of social or language skills and that in the case of language skills it requires the demonstrated loss of at least five functional words. Tr. 869. Dr. Wiznitzer indicated that the types of symptoms that would lead him to suspect a mitochondrial disorder in an autism patient would be true regression, seizures, and cessation of walking and talking. Tr. 867.

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[75] Dr. Zimmerman acknowledged that he based the finding of a loss of language at two years on Mrs. Reed's report and could not confirm that medical records documented the loss. Tr. 752-53.

[76] In their post-hearing brief, petitioners cite Wiggins, et al., for the proposition that "different methodologies are likely to yield different results. For instance, the definition of regression varies in existent literature; some studies define autistic regression as a loss of skills only, whereas others include a leveling off of skills, or developmental plateau." Pet. Posthr'g Br. at 91 n.134 (quoting Pet. Ex. 64 at 3). The undersigned notes, however, that the Wiggins paper did not endorse the definition of regression as including developmental plateau. Rather, the article expressed that such variations in definition were a confounding factor when conducting a review of the literature. Critical of such definitions, the authors expressed concern that such definitions "confuse the relationship between regression and plateau in ASDs." Pet. Ex. 64 at 4. The Wiggins authors described regression as follows:

> [A] substantial minority of parents of children with ASD report a period of typical or slightly delayed development followed by the loss of previously acquired skills and the sudden appearance of autistic behavior patterns. This type of autistic regression has been distinguished from childhood disintegrative disorder (CDD), which typically emerged between 3 and 4 years of age and involves regression in multiple areas of functioning, including adaptive functioning. Children who regress around the second year of life are almost always diagnosed with an ASD after loss of skills.

Id. at 3 (internal citations omitted).

B. I.R.'s Alleged Immunodeficiency and the Immunosuppressive Effect of the MMR Vaccine

Petitioners assert as a factual matter that the MMR vaccine, like wild measles, causes immunosuppression. Pet. Posthr'g Br. at 82-84. Specifically, petitioners note that "Dr. Zimmerman testified that the measles vaccination is immunosuppressive, and people who receive the vaccine are more subject to infections during that time." Id. at 83 (citing Tr. 703). In fact, Dr. Zimmerman testified that he could not opine that I.R.'s condition was vaccine-caused without evidence that the measles vaccine was immunosuppressive. Tr. 771-72. Dr. Niyazov offered similar testimony. Tr. 236-37.

Additionally, both Drs. Niyazov and Zimmerman opined that immune dysfunction and mitochondrial function are intertwined. Tr. 252-53, 771-72. They indicated both that I.R. had evidence of immune dysfunction following his one-year vaccinations, and also that such immune dysfunction is further evidence of the underlying mitochondrial disorder that they opine contributed to I.R.'s alleged injury. In his report, Dr. Niyazov wrote: "Mitochondrial dysfunction has been implicated in immune dysregulation in autism spectrum disorders which further supports the fact that [I.R.]'s immunodeficiency has been a crucial element of his complex phenotype." Pet. Ex. 39 at 4 (citations omitted).

However, for the reasons discussed below, the undersigned finds no preponderant evidence that I.R. suffered immune dysfunction. Nor is there preponderant evidence that the measles vaccine, or any of I.R.'s vaccinations, has an immunosuppressive effect or that I.R. experienced immunosuppression in the months following his vaccinations.

i. The Immunosuppressive Effect of the MMR Vaccine and Petitioners' Motion to Exclude the OAP Testimony of Dr. Griffin

Petitioners filed several studies regarding the possibility of an immunosuppressive effect of either the wild measles virus, attenuated measles vaccines, or the rubella vaccine. See Pet. Ex. 95 (Moss 2004); Pet. Ex. 96 (Pukhalsky 2003); Pet. Ex. 101 (Hussey 1996); Pet. Ex. 102 (Munyer 1975); Pet. Ex. 103 (Smedmen). Respondent disputes petitioners' reliance on these articles. Resp. Posthr'g Br. at 26-28. Additionally, respondent sought, in response to this evidence, to introduce testimony from the OAP by Dr. Griffin, an expert in immunology and co-author of one of the studies filed by petitioners. See Pet. Ex. 95; Resp. Status Report dated June 22, 2015 (ECF No. 120). Petitioners argue that this testimony should be excluded. Pet. Mot. to Exclude Evidence dated June 22, 2015 (ECF No. 121).

Although petitioners have filed literature supporting the notion that the wild measles virus results in immunosuppression, the very same literature indicates that there is little to no evidence that the same is true of live attenuated vaccines. In particular, petitioners filed an excerpt from the 1994 Institute of Medicine ("IOM") report, Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality. Pet. Ex. 94. Petitioners highlight a passage from the section titled "Effect of Vaccines on the Immune System," which discusses various studies finding evidence, using skin and laboratory tests, of immune suppression following vaccination similar to the effects of various antigens. Id. at 3. These effects are

described variously as "less consistent and less prolonged than that following natural measles infection," "mild and inconstant," and "mild but measurable." Id. Upon review of these studies, however, the IOM concluded that "[a]t present, the data are insufficient to answer with certainty whether immunosuppression in the form of laboratory and skin test abnormalities after the receipt of a vaccine does, in fact, indicate a decrease in the capacity to resist infection. . . . To date, studies of current vaccines suggest that if immunization leads to an infection, it must do so infrequently."[77] Id. at 4.

Petitioners additionally cite a study by Munyer, et al., which found that in vitro stimulation of lymphocytes from post-vaccination blood samples revealed impaired response to stimulation with Candida antigen. Pet. Ex. 102 at 2 (Munyer 1975). Significantly, however, the authors noted:

> [N]o significant alteration was observed in the absolute number of lymphocytes in the peripheral blood of vaccinated subjects, either in comparison with base line (before vaccination) counts or with counts from a group of unvaccinated controls. Similarly, no decrease in either the percentage or the absolute number of peripheral blood T-lymphocytes was observed after vaccination.

Id. at 3. This observation makes it difficult to credit the study's in vitro findings as transferrable to an in vivo context. Additionally, the undersigned notes that the Munyer study was cited by the IOM in its above-discussed 1994 analysis of vaccine immunosuppression. Pet. Ex. 94 at 3, 5. As noted above, the IOM stressed at that time that previously produced laboratory data, including the Munyer study, was insufficient to suggest an actual decrease in the ability to resist infection.

Special masters routinely rely on IOM reports as trustworthy evidence. See, e.g., Crutchfield v. Sec'y Health & Human Servs., 125 Fed. Cl. 251 (2014) (emphasizing that "the court often has relied on the findings of the Institute of Medicine").[78] In this case, the

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[77] The Institute of Medicine is the medical arm of the National Academy of Sciences. The National Academy of Sciences ("NAS") was created by Congress in 1863 to advise the federal government on scientific and technical matters. See An Act to Incorporate the National Academy of Sciences, ch. 111, 12 Stat. 806 (1863). The Institute of Medicine is an offshoot of the NAS established in 1970 to provide advice concerning medical issues. When it enacted the Vaccine Act in 1986, Congress directed that the IOM conduct studies concerning potential causal relationships between vaccines and illnesses. See § 300aa–1 note.

[78] See also Isaac v. Sec'y Health & Human Servs., 108 Fed. Cl. 743, 768-79 (2013), aff'd, 540 F. App'x 999 (mem.) (affirming the special master's reliance on findings of the IOM); Porter v. Sec'y Health & Human Servs., 663 F.3d 1242, 1252 (Fed. Cir. 2011) (noting the special master's comment that "IOM reports are favored, although not dispositive, in the Vaccine Act Program," then affirming the special master's decision); Cedillo v. Sec'y Health & Human Servs., No. 98–916, 2009 WL 331968, at *94 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), aff'd, 89 Fed. Cl. 158 (2009), aff'd, 617 F.3d 1328 (Fed. Cir. 2010); Rodriguez v. Sec'y of Health & Human Servs., 67 Fed. Cl. 409, 410 (2005) (relying on an IOM report regarding vaccine causation of an injury);

undersigned finds that on balance the IOM report filed by petitioners weighs against a finding that the measles vaccine creates the type of clinically significant immunosuppressive effect that would create susceptibility to infection.[79] Although petitioners filed several articles post-dating this IOM report, none include findings that call the conclusion of the IOM report into doubt.

Hussey, et al., a 1996 study cited by petitioners for the proposition that measles and rubella vaccines depress immune response for many weeks, states that "[i]mmunosuppression leading to increased susceptibility to secondary infection is a well-recognized complication of natural measles, but there is no evidence that routine immunization with live attenuated measles virus vaccines leads to clinically important immune suppression." Pet. Ex. 101 at 1 (Hussey 1996). The Hussey study itself did produce some evidence, based on testing of 75 children, that immune suppression in the form of decreases in mitogen-induced lymphoproliferation were common at three months post vaccination among six and nine month old infants; however, these results were only statistically significant for one of two vaccine strains studied (the Schwarz strain). Id. at 5. Moreover, consistent with the conclusion of the IOM, the study did not assign any clinical significance to its findings. Indeed, the authors concluded by noting that "[w]hile perturbations of the immature immune system may have an effect on immune responsiveness, many studies have demonstrated that measles vaccine given at 9 months of age results in an overall reduction in childhood mortality." Id. at 6 (emphasis added). Smedman, et al., similarly included findings "consistent" with generalized immunosuppression after immunization, but also noted that "[t]he decrease in antigen-specific responses after measles immunization probably has

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Althen v. Sec'y Health & Human Servs., No. 00–170, 2003 WL 21439669, at *11 n.28 (Fed. Cl. Spec. Mstr. 2003) ("Due to the IOM's statutory charge, the scope of its review, and the cross-section of experts making up the committee reviewing the adverse events associated with vaccines, the court considers their determinations authoritative and subject to great deference."), rev'd on other grounds, 58 Fed. Cl. 270 (2003), aff'd, 418 F.3d 1274 (Fed. Cir. 2005); Terran v. Sec'y of Health & Human Servs., 41 Fed. Cl. 330, 337 (1998) (affirming the special master's reliance on conclusions of the IOM), aff'd, 195 F.3d 1302 (Fed. Cir. 1999), cert. denied, 531 U.S. 812 (2000); Cucuras v. Sec'y of Health & Human Servs., 993 F.2d 1525, 1529 (Fed. Cir. 1993) (noting that the special master had placed "a great deal of weight" on an IOM report in reaching a decision, then affirming the special master's decision); Stroud v. Sec'y of Health & Human Servs., 113 F.3d 1258 (Fed. Cir. 1997) (unpublished) (determining that a special master may rely on an IOM report that neither party filed as evidence).

[79] "Although Althen and Capizzano make clear that a claimant need not produce medical literature or epidemiological evidence to establish causation under the Vaccine Act, where such evidence is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury. . . . Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1380 (Fed. Cir. 2009) (citing Althen, 418 F.3d 1274; Capizzano, 440 F.3d 1317).

no negative health consequences for children given Schwartz strain vaccine of regular titre." Pet. Ex. 103 at 5. Additional later-published papers were also unavailing.[80]

Thus, upon review of the whole of the literature relied upon by petitioners, the undersigned concludes that the evidence does not support a finding that vaccines such as ProQuad, or any other vaccine alleged to have contributed to I.R.'s condition, have a clinically significant immunosuppressive effect. The above-discussed literature regarding the potential for such an effect with regard to the measles and rubella vaccines is preliminary or equivocal at best. Moreover, significant to the undersigned's conclusion, neither Dr. Zimmerman nor Dr. Niyazov is an immunologist and neither has the qualifications necessary to credibly opine regarding the significance of these studies or to extend their findings to this case.

Respondent has emphasized that the question of whether the MMR vaccine has an immunosuppressive effect was previously addressed during the OAP test cases. Resp. Posthr'g Br. at 26-27 (quoting Hazlehurst v. Sec'y Health & Human Servs., No. 03-654, 2009 WL 332306, at *106 (Fed. Cl. Spec. Mstr. Feb. 12, 2009)); see also Snyder v. Sec'y of Health & Human Servs., 2009 WL 332044, at *102-04. In those cases, based in part on the testimony of experts such as Dr. Griffin, the special masters were not persuaded that any period of clinically relevant immunosuppression follows administration of the vaccine-strain of the measles virus. Id. Respondent believes Dr. Griffin's testimony should also be considered in this case.

Petitioners argue, however, that introduction of OAP evidence is prejudicial (see Pet. Mot. to Exclude Evidence), and that the presence of a mitochondrial disorder in this case renders the OAP conclusions inapplicable because "there was no testimony in the OAP that MMR would not be sufficiently immunosuppressive to have clinical significance even in a person with only 50% of the POLG protein available to immune cells." Pet. Posthr'g Br. at 84 n.122 (emphasis in original). Respondent argues that the distinction drawn by petitioners is immaterial. Resp. to Mot. to Exclude Evidence at 3 (ECF No. 122).

[80] Petitioners filed a 2003 study regarding the rubella vaccine, but that study involved only 18 participants. Pet. Ex. 96 (Pukhalsky 2003). Moreover, the participants were girls aged 11-13 years old and the study noted that "immune response to virus infections and attenuated virus vaccines seems to depend on various factors including genetics, age and sex." Id. at 4. The authors suggest that patients of 1-2 years of age (such as I.R. at the time of his vaccination) are likely to be the least impacted clinically, while adolescents (such as the study population) experience the most severe symptoms. Id. The most recently published of petitioners' submissions is the 2004 paper "Measles: immune suppression and immune responses," by Moss, et al., published in the International Journal of Biochemistry & Cell Biology. Pet. Ex. 95. That paper largely examines the immunosuppressive effect of the wild measles virus. It does, however, discuss two particular measles vaccines that had unintended immunologic consequences. Id. at 1. Specifically, a high-titer measles vaccine resulted in atypical measles among girls only, and a formalin-inactivated, alum-precipitated measles vaccine withdrawn in 1967 also resulted in atypical measles. Id. at 4. Neither of these scenarios is relevant to this case.

In light of the IOM's above-cited conclusion, petitioners' argument is unpersuasive. The IOM concluded following a survey of relevant studies not merely that there is insufficient evidence of clinically significant immunosuppression among healthy individuals, but that the laboratory and skin test results are insufficient to constitute persuasive evidence indicating any in vivo immunosuppression at all. Absent preponderant evidence of any immunosuppressive effect among the general population, the notion that there is such an effect among a vulnerable subset of the population remains speculative.

To support their claim that the presence of a mitochondrial disorder would result in clinically significant findings different than the above-discussed literature, petitioners present the testimony of Drs. Zimmerman and Niyazov. However, as noted above, neither Dr. Zimmerman nor Dr. Niyazov is an immunologist. The undersigned thus gives less weight to their opinions that – with or without the presence of a mitochondrial disorder – the ProQuad vaccine at issue in this case would have had a clinically significant immunosuppressive effect. Moreover, those opinions remain challenged as respondent's mitochondrial expert, Dr. Cohen, disputes that a mitochondrial disorder creates additional immune insufficiency or susceptibility to infection. Tr. 487-88.

Additionally, subsequent to the OAP, the question of whether the MMR vaccine has an immunosuppressive effect in the context of a mitochondrial disorder has already been examined. In at least one case, evidence of such an effect was found to be lacking. Anderson v. Sec'y Health & Human Servs., No. 02-1314, 2016 WL 8256278, at *26 (Fed. Cl. Spec. Mstr. Nov. 1, 2016) (characterizing the concept of the MMR vaccine's alleged immunosuppressive capacity as "discredited"), mot. for rev. denied, 131 Fed. Cl. 735 (2017), aff'd, 717 F. App'x 1009 (Fed. Cir. 2018).

Finally, the undersigned observes that it is not necessary to reach the question of whether Dr. Griffin's testimony is prejudicial. In light of the above, the undersigned does not find that Dr. Griffin's testimony is necessary to rebut any aspect of petitioners' theory, and there is no need to reintroduce Dr. Griffin's previously-struck testimony.[81] Petitioners bear the burden of

[81] Of note, petitioners argue that "[t]he OAP ceased to exist when none of the causation theories offered were successful. Only if there had been a successful test case, and subsequent proceedings were held to determine the applicability of those rulings to individual cases, would OAP testimony be admissible in other cases." Pet. Status Report dated June 22, 2015 (ECF No. 121) at 2. That line of reasoning was rejected in Anderson. Upon review of the special master's decision, the Court of Federal Claims held that "[t]he Special Master's citation of a factual finding from the Omnibus Autism Proceeding was not improper, because Petitioners elected to take part in that Proceeding by filing a Short Form Petition. . . . By participating in the Omnibus Autism Proceeding, Petitioners agreed to allow the Office of Special Masters to apply conclusions reached in that test case to Petitioners' claim." Anderson, 131 Fed. Cl. at 753. Like the petitioners in Anderson, the petitioners in this case initiated their case by relying on the "Master Autism Petition for Vaccine Compensation." Nonetheless, the undersigned stresses that she is not relying on the conclusions reached in either the OAP test cases or in the Anderson case. Rather, the undersigned finds that the evidence submitted in this case is inadequate to meet petitioners' burden of proof.

proof on this question and the undersigned is not persuaded by petitioners' prima facie presentation regarding vaccine-caused immunosuppression, regardless of the content of Dr. Griffin's prior testimony. Accordingly, respondent's request to resubmit Dr. Griffin's OAP testimony and petitioners' competing motion to exclude are both denied as moot. Dr. Griffin's testimony is not a factor in the undersigned's analysis of this case.

In sum, petitioners have failed to come forward with preponderant evidence indicating that the ProQuad vaccine administered to I.R., or any other vaccine, would have had an immunosuppressive effect with or without the presence of a mitochondrial defect.

ii. The undersigned finds that I.R. did not suffer immune suppression following his vaccinations and that I.R. did not suffer immune dysfunction.

There is not preponderant evidence in this case that I.R. actually suffered any immune suppression or had any other immune abnormality following his vaccinations.[82] Petitioners point to a period of months following I.R.'s vaccinations, during which he experienced a series of illnesses.[83] See, e.g., Pet. Ex. 197 (petitioners' demonstrative exhibit illustrating dates of illnesses). Although the records suggest that immune deficiency was suspected (and IVIG treatments administered years later), no immune testing was conducted in the period immediately following the vaccinations. None of the experts are immunologists, and thus they cannot reject out of hand any conclusions regarding I.R.'s immune status based on his period of illnesses alone. Moreover, respondent points out that I.R.'s pattern of childhood infections began prior to the administration of the vaccines at issue. Resp. Posthr'g Br. at 29. Specifically, respondent points to I.R.'s medical visits for ongoing cold and viral illness symptoms in October and November of 2005. Id.

I.R. did not have any immunological work-up during the period that petitioners assert he experienced a temporary immune suppression from the MMR vaccine; however, he did subsequently undergo extensive immunological testing in May 2006, approximately five months after his allegedly injury-causing vaccinations. Upon the undersigned's review of the entire record, including all of I.R.'s immunologic testing as well as his clinical course during the

[82] The undersigned draws a distinction between the contention that I.R.'s repeated illnesses following his vaccinations demonstrated an ongoing immune suppression and the fact that I.R. experienced a likely vaccine reaction in the form of fever and rash shortly after vaccination. See Pet. Ex. 15 at 16. Fever and rash are common vaccine reactions, and petitioners' own expert, Dr. Niyazov, agreed that the fever and rash signal that the immune system is functioning. Tr. 307-08. Indeed, I.R.'s later immunologic workup in July 2006 showed that he did develop immunity to measles, mumps, rubella, varicella, tetanus, diphtheria, and polio. Pet. Ex. 11 at 3.

[83] Petitioners argue in their post-hearing brief that, even if the undersigned does not find I.R.'s ASD to be sequela to a vaccine reaction, I.R.'s period of repeated illnesses during the first half of 2006, lasting more than six months, would constitute a compensable vaccine injury in itself. Pet. Posthr'g Br. at 41 n.48. The undersigned's above finding that petitioners have not demonstrated an immunosuppressive effect by the ProQuad vaccine renders that argument moot.

relevant period, the undersigned does not find preponderant evidence that I.R. experienced immune suppression or dysfunction at any time.

a. Initial Immune Testing in May 2006

I.R.'s first immunoglobulin tests were not performed until May 2006. Testing from a blood draw taken on May 23, 2006, showed normal results, with IgA of 25 mg/dL with a reference range of 14-105 mg/dL; IgG of 523 mg/dL with a reference range of 331-1164 mg/dL; and IgM of 131 mg/dL with a reference range of 42-164 mg/dL. Pet. Ex. 9 at 129. Testing from an earlier blood draw taken on May 5, 2006, and performed by a different lab showed low IgA of less than 47 mg/dL against a reference range of 66-436 mg/dL; low IgG of 563 mg/dL against a reference range of 791-1643 mg/dL; and normal IgM of 107 mg/dL with a reference range of 43-279 mg/dL. Id. at 132-33, 137.

However, respondent disputes the accuracy of the reference ranges for the May 5, 2006 testing. Respondent filed literature indicating that age-adjusted IgG reference ranges for one and two year olds are 345-1213 mg/dL and 424-1051 mg/dL, respectively. Resp. Ex. M. at 5 (Agarwal). Significantly, the age-adjusted IgG reference ranges are consistent with the reference ranges used for the May 23, 2006 testing, which showed normal results. The undersigned determines that the reference range reflected on the May 23, 2006 lab results, further supported at least in part by the literature filed by respondent, is more persuasive, since neither lab disclosed the basis for the reported reference range. This would suggest that I.R. had consistently normal IgG. And indeed, I.R.'s "low" May 5 IgG of 563 mg/dL is higher than his later "normal" May 23 IgG of 523 mg/dL. Moreover, I.R.'s results were later reviewed by an immunologist, Dr. Koterba, who recommended interpreting these results against an age-adjusted reference range.[84] Pet. Ex. 29 at 55; Pet. Ex. 28 at 61.

Petitioners stress that respondent's literature does not address the low IgA from May 5, 2006. Pet. Posthr'g Br. at 35 n.44. The undersigned notes, however, that the May 5 IgA test result (less than 47 mg/dL) is not inconsistent with the May 23 IgA result of 25 mg/dL, which was considered normal. In his May 12, 2006 follow up, I.R.'s ENT specialist characterized the IgG and IgA results as "slightly reduced," but assigned no clinical significance to the findings, instructing follow up with I.R.'s pediatrician instead. Pet. Ex. 6 at 10. On May 8, 2006, the pediatrician recommended repeating the labs, which resulted in the May 23 test results, all within normal ranges. Pet. Ex. 15 at 37. Taking the May 5 and May 23 results together, the undersigned concludes that I.R.'s May 2006 immunologic test results were normal.

[84] Dr. Koterba's suggestion that an age-adjusted reference range would be more appropriate further supports the conclusion that the May 23, 2006 results should be interpreted as normal, though Dr. Koterba did suggest a higher reference range which still left I.R.'s result slightly below the reference range. Significantly, however, subsequent immunoglobulin testing at Children's Memorial Hospital used a lower reference range of 445-1187 mg/dL for IgG. See supra note 92. Additional testing by Dr. Gupta, the immunologist upon whose diagnosis petitioners primarily rely, reflected a reference range of 444-1187 mg/dL. Pet. Ex. 35 at 8.

b. Immune Evaluation at Loyola Pediatric Clinic for Asthma, Allergy, and Clinical Immunology

Subsequently, I.R. was seen at 18 months of age by Dr. Amy Sanghavi at the Loyola Pediatric Clinic for Asthma, Allergy, and Clinical Immunology. Pet. Ex. 11 at 7-10. I.R. was seen for his history of multiple infections and an evaluation of a possible immunodeficiency disorder. Id. at 9. A history of multiple viral infections and recurrent acute otitis media were recorded. Id. However, Dr. Sanghavi noted that "[I.R.] is able to mount an immune response as when [I.R.] with illnesses lymph nodes palpable and fever response mounted." Id. Dr. Sanghavi ordered testing of T and B cell subsets, IgE, IgA, IgG, and IgM levels, as well as titers to previously received childhood vaccines. Id.

I.R. was re-seen at the Loyola clinic on August 3, 2006, after his immune testing was complete. Pet. Ex. 11 at 6. I.R.'s T&B cell count and distribution were normal. Id. His IgG, IgA, and IgM were all normal.[85] Id. His IgE was slightly elevated. Id. at 7. I.R.'s IgG2 subclass was below normal, but this was described as "a frequent delay in immunity seen in young boys." Id. Regarding his IgG to previously administered vaccines, I.R. was noted as immune to measles, mumps, rubella, varicella, tetanus, diphtheria, polio, Haemophilus influenza, and to the subtypes given via Prevnar. Id.

On behalf of the Loyola clinic, Dr. Annick Gaye wrote that I.R.'s "vaccine have all taken well" and that "[o]ur conclusion is that [I.R.]'s immune system is responding normally to the environmental challenges related to age and location at this time." Pet. Ex. 11 at 7. I.R.'s record further indicates "unspecific disorder of immune mechanism B cell type – ruled out." Id. at 6. Dr. Gaye indicated: "A repeat of IgG2 level could be obtained in 2 years to confirm [I.R.]'s immunity progress. There is no need to repeat the other tests unless there is a suspicion of regression in his health status." Id. at 7.

c. Dr. Gupta and Children's Memorial Hospital

On October 15, 2009, additional immunologic tests were run. Pet. Ex. 29 at 71. Although IgA, IgG, and IgM were all within normal limits, IgG2 was low. Id. at 71-72. Based on this result, I.R. was referred to Dr. Sudhir Gupta for an IgG deficiency. Id. at 77.

I.R. was seen by Dr. Gupta on December 16, 2009. Pet. Ex. 35 at 2-5. Dr. Gupta appears to have recorded I.R.'s prior history of low IgA and IgG from May of 2006. Id. at 3 (noting "Igs A and G low" and "[r]epeat Igs normal"). However, no notation in his records suggests that he reviewed or was aware of the Loyola evaluation and Dr. Gaye's conclusion. Id. at 2-5. Dr. Gupta concluded:

> [I.R.] has a very impressive history of recurrent acute and chronic otitis media treated with several courses of antibiotic. His immunological work-up shows decreased levels of IgG and further fractionation shows low IgG2. In addition, he

[85] IgG was measured at 490 mg/dL against a reference range of 265-1680 mg/dL. Pet. Ex. 11 at 12.

> does not have positive antibodies to polio even though he was immunized with polio,[86] suggesting a specific antibody deficiency as well, suggesting a diagnosis of hypogammaglobulinemia with specific antibody deficiency (ICD 279.00). . . . [T]aking into consideration his clinical history, low IgG, and failure to make protective antibodies against polio, I recommend that he received IVIG 20gm every 4 weeks.

Pet. Ex. 29 at 103. However, contemporaneous to his report, Dr. Gupta ordered additional immunoglobulin testing. On December 16, 2009, I.R. had IgG of 566 mg/dL against a reference range of 444-1197 mg/dL. Pet. Ex. 35 at 8. Additionally, each of I.R.'s IgG subclasses was normal.[87] Id. at 9.

Subsequently, on February 15, 2010, I.R. was seen by Dr. Alan Koterba in the Division of Allergy & Immunology at Children's Memorial Hospital. Pet. Ex. 29 at 55; Pet. Ex. 28 at 61. Dr. Koterba disagreed with Dr. Gupta's assessment. Pet. Ex. 28 at 61. He noted that using an age adjusted reference range of 592-1723 mg/dL, I.R.'s degree of hypogammaglobulinemia was "minimal" with his result of 564 mg/dL.[88] Id. Given that I.R. had only "limited infectious complications in the past year," he considered the significance of the finding to be "unclear." Id. He also recommended repeating immunoglobulin testing, noting that I.R. had been on a prolonged steroid taper that could cause relative hypogammaglobulinemia. Id.

Additionally, Dr. Koterba indicated that "[t]he marginally low IgG2 subclass level and abs B cell numbers are also of questionable significance given the current clinical picture." Pet. Ex. 28 at 61. Regarding the polio titer, he observed that "[t]he sub-optimal polio titers are difficult to evaluate and not always reliable." Id. He noted that response to pneumococcus would provide a more accurate assessment of specific antibody function, but that Mrs. Reed did not want Pneumovax administered.[89] Id. Dr. Koterba discussed IVIG with Mrs. Reed, but noted that "it is unclear what our endpoint would be."[90] Id.

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[86] On December 13, 2008, I.R. had bloodwork to test for antibodies to a number of viruses, including polio. Pet. Ex. 29 at 129-34. Antibodies were later measured again on August 13, 2010, though polio was not repeated. Pet. Ex. 28 at 195. I.R.'s prior testing in 2006 had shown that he did develop antibodies to polio. Pet Ex. 11 at 6.

[87] Specifically, IgG subclass 1 measured 418 mg/dL with a reference range of 290-1065 mg/dL; subclass 2 measured 41 mg/dL with a reference range of 28-315 mg/dL; subclass 3 measured 24 mg/dL with a reference range of 4-71 mg/dL; and subclass 4 measured 1 mg/dL with a reference range of 0-90 mg/dL. Pet. Ex. 35 at 9.

[88] This refers to I.R.'s May 5, 2006 low IgG of 563 mg/dL against a reported reference range of 791-1643 mg/dL. Pet Ex. 9 at 132.

[89] Dr. Gupta similarly noted that I.R.'s parents did not want Pneumovax administered. Pet. Ex. 29 at 103.

[90] Dr. Koterba was a Fellow in Allergy and Immunology. Pet. Ex. 29 at 55. After the

Subsequently, Dr. Fuleihan ordered immunoglobulin testing for IgG on twelve occasions from March 2010 through September 2011. It was normal on all twelve occasions.[91] Additionally, IgM and IgA were found to be within normal range on March 5, 2010, September 10, 2010, and April 21, 2011. Pet. Ex. 28 at 149, 190-91, 226. IgE was low on September 10, 2010, and April 22, 2011. Id. at 149, 190-91.

d. Subsequent Immunodeficiency Care

On April 3, 2013, I.R. had a new patient consult with Dr. Duane Wong at Arizona Allergy Associates in Scottsdale, Arizona. Pet. Ex. 84 at 8-10. He was referred by Dr. Fuliehan. Id. at 8. Dr. Wong performed a physical exam and took a history. Id. at 8. The history provided indicates, inter alia, that "3-1/2 years ago, [I.R.] was started on IVIG; his IgG was in the 400 mg/dL range. His last dose was 20 gm of Gamunex every 4 weeks and his last IgG level was 945 mg/dL. He has been infection-free since starting IVIG." Id. Based on this evaluation, Dr. Wong recommended continuing the IVIG treatments. Id. at 10. Subsequently, on April 22, 2013, test results showed that I.R. had normal IgA, IgG, and IgM. Pet. Ex. 11 at 7. I.R. returned to Dr. Wong on August 20, 2013, and November 19, 2013. Pet. Ex. 84 at 2-5. On August 20, 2013, Dr. Wong noted I.R.'s normal hematology screen, but did not change his recommendation. Id. at 4-5.

After moving to Austin, Texas, I.R. began seeing Dr. Jackee Kayser in January 2014. Pet. Ex. 98 at 53-55. Dr. Kayser ordered immunoglobulin G testing on three occasions, and all results came back within normal limits. Id. at 43. On January 29, 2014, IgG was 769 mg/dL. Id. On February 26, 2014, IgG was 1090 mg/dL. Id. On March 25, 2014, IgG was 1144 mg/dL. Id. All three results were presented against a reference range of 633-1280 mg/dL. Id.

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evaluation, Dr. Ramsay Fuleihan, an attending in the same division, signed off on Dr. Koterba's assessment and subsequently co-signed Dr. Koterba's report. Id.; Pet. Ex. 28 at 61. Dr. Fuleihan agreed with Dr. Koterba's assessment and communicated the assessment to Dr. Gupta on March 6, 2010. Pet. Ex. 28 at 61. Dr. Fuleihan noted that Dr. Gupta continued to recommend IVIG as a "trial" to assess whether I.R.'s autism would improve. Id. Subsequently, I.R. returned to Dr. Fuleihan on August 29, 2011. Id. at 72. Mrs. Reed reported that he was doing well on IVIG treatments and Dr. Fuleihan recommended continued IVIG. Id.

[91] On March 5, 2010, IgG was 522 mg/dL. Pet Ex. 28 at 226. On April 2, 2010, IgG was 754 mg/dL. Id. at 225. On April 30, 2010, IgG was 904 mg/dL. Id. On June 18, 2010, IgG was 937 mg/dL. Id. at 220. On July 16, 2010, IgG was 879 mg/dL. Id. at 217. On August 13, 2010, IgG was 974 mg/dL. Id. at 196. On September 10, 2010, IgG was 927 mg/dL. Id. at 190. On October 8, 2010, IgG was 891 mg/dL. Id. at 190. On November 5, 2010, IgG was 913 mg/dL. Id. at 168. The reference range for these tests was 445-1187 mg/dL. Id. On April 21, 2011, IgG was 785 mg/dL. Id. at 149. On July 15, 2011, IgG was 812 mg/dL. Id. at 113. On September 9, 2011, IgG was 859 mg/dL. Id. at 101. The reference range for these later tests was 608-1229 mg/dL. Id.

e. Resolving the Conflicting Immune Evaluations

Upon the undersigned's review of the complete medical records, there is not preponderant evidence that I.R. had an immunoglobulin G deficiency. Notwithstanding that I.R. was found to have low IgG2 on two occasions, the undersigned finds that no test results in I.R.'s records suggest that he ever had low IgG overall. The records reflect that I.R. was tested for IgG more than twenty times between 2006 and 2014. In only one instance, on May 5, 2006, did I.R.'s IgG test below the reported reference range. Moreover, at least one of I.R.'s immunologists, Dr. Koterba, suggested that the one below normal result was not clinically significant when viewed against an age-adjusted reference range.

Nor is the undersigned persuaded that I.R.'s medical records contain preponderant evidence of any immune dysfunction at all. The most detailed and significant evaluations of I.R.'s immune status were by the Loyola Clinic and by Dr. Koterba at Children's Memorial Hospital. Pet. Ex. 11; Pet. Ex. 29 at 55; Pet. Ex. 28 at 61. In both instances, the immunologists evaluating I.R. found that the available medical evidence did not support a diagnosis of immune deficiency. Loyola stressed that "[I.R.]'s immune system is responding normally to the environmental challenges related to age and location at this time." Pet. Ex. 11 at 7. Dr. Koterba subsequently opined that the later results were equivocal or unclear. Pet. Ex. 29 at 55; Pet. Ex. 28 at 61.

The undersigned notes that Dr. Gupta's evaluation and report appear to have been less detailed or precise.[92] Moreover, Dr. Gupta relied at least in part on his finding of low IgG. However, by the time of Dr. Gupta's evaluation, I.R.'s IgG had been measured four times. Even accepting arguendo that the initial May 5 result had been below normal, I.R.'s IgG tested within normal limits on three subsequent tests – May 23, 2006, August 3, 2006, and October 15, 2009. Additionally, Dr. Gupta's own testing conducted on December 16, 2009, confirmed normal IgG. Further, Dr. Koterba's subsequent assessment casts significant doubt on Dr. Gupta's reliance on low polio titers and low IgG2. Dr. Koterba characterized those results as being of "questionable significance" in light of I.R.'s overall clinical picture. Moreover, I.R.'s test results were conflicting, with 2006 measures finding that I.R. had developed antibodies to polio.

The records of Drs. Wong or Kayser do not provide any significant support for Dr. Gupta's immunodeficiency diagnosis. There is no evidence of any significant re-evaluation of I.R.'s condition from either physician. Moreover, both physicians ordered additional IgG testing, which showed normal IgG. Additionally, Dr. Wong appears to have relied on a mistaken history. Dr. Wong appears to have assumed I.R. had abnormal IgG of about 400 mg/dL when he began IVIG treatment. However, the above records reflect that I.R.'s IgG was never that low and that it was at 566 on December 16, 2009, when Dr. Gupta recommended IVIG. Drs. Wong and Kayser additionally appeared to rely on the fact that I.R. had no infections since starting IVIG. However, Dr. Koterba had already observed that I.R. had only limited infections in the

[92] This is not the first time a special master has questioned the probative value of Dr. Gupta's evaluations. See Kreizenbeck v. Sec'y of Health & Human Servs., No. 08-209, 2018 WL 3679843, at *30 (Fed. Cl. Spec. Mstr. June 22, 2018) (noting the "conclusory" nature of one of Dr. Gupta's diagnoses), mot. for rev. denied, No. 08-209 (Fed. Cl. Nov. 7, 2018).

year prior to starting IVIG. Additionally, I.R.'s medical records suggest that there may have been motivations for pursuing IVIG other than hyperglobulinemia. Dr. Frye recommended IVIG as an anti-inflammatory treatment. Pet Ex. 29 at 17; Pet. Ex. 25 at 85.

C. I.R.'s POLG Mutation and Alleged Mitochondrial Disorder or Dysfunction

Perhaps the most significant factual predicate requiring resolution is the allegation that I.R. suffered a mitochondrial disorder or dysfunction. Petitioners' expert in pediatric neurology, Dr. Zimmerman, testified that he could not opine that I.R.'s autism was vaccine-caused without an underlying mitochondrial dysfunction. Tr. 771. Dr. Niyazov indicated that he would still maintain his opinion absent a mitochondrial disorder, but acknowledged that "I would have a harder time making that link [to vaccine causation]." Tr. 276.

Petitioners allege that I.R. has a genetic mutation known to result in mitochondrial disease. Additionally, with or without that genetic mutation, petitioners allege that I.R. meets the criteria for a mitochondrial disease based on clinical evaluation. Respondent acknowledges that I.R. has a deleterious genetic mutation, but disputes that the mutation is sufficient in itself to be disease-causing. Respondent further disputes that I.R. meets the clinical criteria for a mitochondrial disorder. For the reasons described below, the undersigned finds no preponderant evidence that I.R. suffered a mitochondrial disorder or any clinically significant mitochondrial dysfunction.

i. Mitochondrial Disorders

Mitochondria are small organelles (structures inside cells) that convert food and oxygen into the body's supply of chemical energy. According to the experts in this case, mitochondria's role within a cell can be analogized to the internal combustion engine that drives a car. Tr. 119-120, 452-54. In addition to energy production, mitochondria play an important role in other cellular functions, such as adaptive thermogenesis, ion homeostasis, innate immune responses, production of reactive oxygen species ("ROS"), and programmed cell death (apoptosis). Resp. Ex. H, Tab 6 (Koopman) at 1.

Mitochondria use oxygen and food to produce adenosine triphosphate ("ATP"), the primary source of energy for all bodily functions, through a process labeled "the respiratory chain" or "electron transport chain" ("ETC"). Resp. Ex. H, Tab 6 at 2. The activity of the ETC, which takes place largely on the inner of the two membranes comprising the outer part of the mitochondria, consists of five protein complexes (Complexes I-V). Id. A different biochemical step in the conversion of nicotinamide adenine dehydrogenase to ATP takes place in each complex. Id. This conversion process is referred to as "oxidative phosphorylation" or "OXPHOS." Id. at 4.

Mitochondrial disease is not a single entity, but rather a heterogeneous group of disorders characterized by impaired energy production due to genetically based oxidative phosphorylation dysfunction. Resp. Ex. H, Tab 8 at 1 (Haas 2008). Problems with energy production in the ETC

can occur as the result of genetic defects in either the mitochondria's own DNA ("mtDNA")[93] or in the DNA found in the nucleus of cells themselves ("nuclear DNA" or "nDNA"). Pet. Ex. 42 at 1; Tr. 122. When a DNA defect results in clinical symptoms, a person is said to have a "primary" mitochondrial disease or defect. Tr. 121. Other bodily processes or environmental factors may also impact ATP production, producing what is known as "secondary mitochondrial disease."[94] Tr. 121-22; Pet. Ex. 42 at 3.

Mutations in the POLG gene (DNA polymerase gamma) are one of the most common causes of inherited mitochondrial disease. Pet. Ex. 63 (Wong) at 2. POLG is a gene contained in the nuclear DNA that produces polymerase gamma, an enzyme required for the replication of mtDNA. Tr. 355-56. POLG mutations that result in a decrease in production of mtDNA in turn cause a decrease in mitochondrial performance. Tr. 367-68; Pet. Ex. 63 at 2-3. POLG mutations have been identified in several known mtDNA depletion syndromes. Pet. Ex. 63 at 3.

However, not all mitochondrial disorder patients will have genetic confirmation of their disorder. Tr. 133-34; see generally Pet. Ex. 52 (Parikh). In the absence of an identified genetic defect or symptoms fitting a known mitochondrial syndrome, diagnosing a mitochondrial disorder is difficult. Tr. 128-30; Pet. Ex. 52 (Parikh) at 3-7. No definitive biomarker characterizes mitochondrial disease in all patients. Pet. Ex. 52 at 2 (Parikh). Mitochondrial diseases are usually progressive and multisystemic, typically affecting organs with a high energy demand such as skeletal and cardiac muscle, endocrine organs, kidney, retina, and the central nervous system. Tr. 138-40; Pet. Ex. 100 at 2 (Scaglia); Pet. Ex. 62 at 1 (Wolf).

Mitochondrial medicine is "relatively young," and there is not yet a consensus regarding diagnostic criteria for mitochondrial disorders for which there is no genetic confirmation. Pet. Ex. 52 (Parikh) at 1, 7. There are several well-known sets of diagnostic criteria that seek to establish a diagnosis by weighing various biochemical tests, clinical signs and symptoms, and muscle biopsy results, including the Walker Criteria, Modified Walker Criteria, Nijmegen or Wolf Criteria, and Morava Criteria. See Pet. Ex. 60 (Walker); Pet. Ex. 100 (Scaglia citing Modified Walker); Pet. Ex. 62 (Wolf); Pet. Ex. 71 (Morava).

The "Walker Criteria" were laid out in an article published in 1996. See Pet. Ex. 60. The authors of that paper set out to provide a system that pulls together the various diagnostic considerations that impact a clinical assessment of respiratory chain defect disorders. Id. at 1-2. In doing so, they proposed criteria that would allow a suspected mitochondrial disorder to be characterized as either possible, probable, or definite. Id. at 1. The "Modified Walker Criteria," also known as the "Bernier Criteria," refers to a further paper published in 2002 by Bernier, et al., which sought to refine the original Walker Criteria for use in pediatric cases.[95] See generally

[93] The function of the mtDNA is to make proteins that are components of the ETC. Tr. 122.

[94] In addition to mitochondrial disease and disorder (used interchangeably), the experts also mentioned mitochondrial "dysfunction." These distinctions are further discussed in Section VI.C.iii.f.8, below.

[95] Petitioners did not actually file the original publication of the Modified Walker Criteria. When

Pet. Ex. 100. The Walker Criteria and Modified Walker Criteria each consist of a set of "major" criteria and a separate set of "minor" criteria.[96] Pet. Ex. 60 at 5; Pet. Ex. 100 at 3.

"Nijmegen Criteria" refers to a 2002 publication by the Nijmegen Center for Mitochondrial Disorders located in the Netherlands. See Pet. Ex. 62 at 1. It is also sometimes referred to as the "Wolf Criteria" after its lead author, Nicole Wolf. See id. The Nijmegen authors sought to further refine the Modified Walker Criteria for diagnosis of respiratory chain disorders in children. Id. A scoring system based on "points" is used to rate a resulting diagnosis as unlikely, possible, probable, or definite. Id. at 2. Muscular signs and symptoms may add up to two points; signs and symptoms related to the central nervous system may add up to two additional points; evidence of multisystemic involvement may account for up to three points; and metabolic and morphology investigations may contribute up to four points each.[97] Pet. Ex. 62 at 1-2; Pet. Ex. 129.

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referencing the Modified Walker Criteria during the hearing, counsel cited to Exhibit 100, a paper entitled "Clinical Spectrum, Morbidity, and Mortality in 113 Pediatric Patients with Mitochondrial Disease," by Scaglia, et al. See Tr. 145-48; Pet. Ex. 100. The Scaglia study used the Modified Walker Criteria to screen suspected mitochondrial patients for inclusion in a retrospective review seeking to understand the frequency of major clinical manifestations of mitochondrial disease among children. Pet. Ex. 100 at 2. As such, that paper includes a chart listing the Modified Walker Criteria. Pet. Ex. 100 at 3. Petitioners also cited a marked copy of this chart during the hearing, pulled directly from the Scaglia paper and filed as Exhibit 137. That chart marked three of the Modified Walker Criteria within red boxes to denote which of the criteria petitioners' expert believed were met in I.R.'s case. Tr. 148. However, Dr. Niyazov, in his original report, despite using a heading labeled "Modified Walker Criteria," cited the 1996 Walker paper. Pet. Ex. 39 at 3-4. This is the article petitioners filed with Dr. Niyazov's report. Pet. Ex. 60.

[96] A definite diagnosis is made by satisfying either two major criteria or one major criterion and two minor criteria. Pet. Ex. 60 at 6. A probable diagnosis is made when one major criterion and one minor criterion or three minor criteria are satisfied. Id. A possible diagnosis is made when one major criterion is satisfied or one minor criterion is satisfied, along with the clinical criterion listed among the minor criteria. Id. According to petitioners, I.R. meets one major and two minor criteria under the Modified Walker Criteria. Pet. Posthr'g Br. at 99-100.

[97] The scoring system predicts a mitochondrial disorder diagnosis as follows: one point means a mitochondrial disorder is unlikely; two to four points represents a possible disorder; five to seven points represents a probable disorder; and eight to twelve points signals a definite disorder. Pet. Ex. 62 at 1-2. Petitioners allege that I.R. scores 11 out of a maximum 12 points under this system. Pet. Posthr'g Br. at 101. Specifically, they assert that I.R. scores two points for muscular signs and symptoms based on exercise intolerance and muscle weakness; two points for central nervous system signs and symptoms based on developmental delay and loss of acquired skills; one point for multisystemic involvement (of the gastrointestinal tract) based on chronic unexplained diarrhea; and four points for metabolic and other investigations based on elevated blood lactate (two points), elevated lactate/pyruvate ratio (one point), and elevated alanine (one point). Id. at 100-01. If accurate, this would constitute a "definite" mitochondrial

The Morava Criteria refers to a 2006 publication that applied the Nijmegen Criteria to a group of 61 subjects with suspected respiratory chain disorder. Pet. Ex. 71 at 1. The Morava authors developed their own version of the Nijmegen Criteria, which is largely the same as Nijmegen, but assigns the points differently.[98] Pet. Ex. 130; Tr. 194-95.

Respondent's experts are critical of these types of clinical assessments. Dr. Cohen explained that they were designed to help assign probability to a mitochondrial disorder diagnosis because early mitochondrial medicine was unable to prove (or disprove) the presence of a disorder. Tr. 477-78. He himself stopped using such criteria around 2010. Tr. 546-47. Dr. McCandless similarly stressed no agreed-upon "gold standard" for mitochondrial disorder diagnosis exists, and that the published diagnostic criteria are known to have poor predictive ability.[99] Resp. Ex. F at 5. Dr. Cohen also opined that the published diagnostic criteria, though useful for preliminary evaluation, are open to error and misinterpretation. Tr. 526-27. He noted that many mitochondrial disorder specialists have moved away from using these types of diagnostic checklists and predicts that they will be fully obsolete within a few years. Tr. 477-78. Nonetheless, as of 2013, these types of diagnostic criteria were still relied upon to some extent by approximately 63% of specialists in the field.[100] Pet. Ex. 52 at 7, Table 3 (Parikh).

Petitioners' expert, Dr. Niyazov, acknowledged that the diagnostic criteria can be too subjective, but stressed that it is the best available analysis in cases that are not genetically confirmed. Tr. 136-38. He indicated that many cases still lack genetic confirmation and that in his practice he will rely on the diagnostic criteria to make a diagnosis even in the absence of genetic confirmation. Tr. 133-34. Although there is not one single approach to diagnosis, Dr. Niayzov stressed that the Walker, Nijmegen, and Morava papers were all peer reviewed. Tr.

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disorder diagnosis under the Nijmegen criteria. Id. at 101; Pet. Ex. 129 at 4.

[98] Citing the same records and findings as scored under Nijmegen, petitioners allege that under the Morava Criteria, I.R. scores nine points out of twelve, still in the "definite" range. Pet. Posthr'g Br. at 101-02.

[99] Dr. McCandless stated: "The use of various mitochondrial checklists/scoring algorithms is also concerning for several reasons. First, there is no 'gold standard' diagnostic test against which to check the algorithm, therefore, these scoring approaches cannot be well validated. Also, they are well recognized to be sensitive for diagnosing mitochondrial disease (e.g., they do a reasonably good job of identifying patients that experts agree have mitochondrial disease), but most experts recognized that they do not have good specificity (e.g., they are not good at ruling out primary mitochondrial disease), therefore the positive predictive value (the probability that a person with a positive test or score will actually have the disease) is relatively low. This explains why the bulk of the medical literature regarding diagnosis of primary mitochondrial disease ends up relying on expert opinion." Resp. Ex. F at 5.

[100] Dr. Cohen stressed that the survey was broadly phrased, asking the specialists if the criteria "aid in" diagnosis. Tr. 497-98. He suggested that the 63% figure captures at least some specialists who consult the criteria but would not necessarily rely on them for a firm diagnosis. Id.

128-30, 138.

In this case, it is undisputed that genetic testing has revealed that I.R. has inherited a heterozygous POLG mutation from his mother. However, the significance of that mutation and whether or not a single heterozygous mutation can be considered disease-causing is extensively debated. Also disputed is whether I.R. meets the criteria for a clinical diagnosis of mitochondrial disorder. These two issues will be addressed in turn.

ii. I.R.'s POLG Mutation

I.R.'s 2011 genetic test indicated that he has a heterozygous mutation in his POLG gene. Pet. Ex. 30 at 1. That mutation, inherited from his mother, was characterized as "predicted deleterious." Id. The test summary indicated that "[p]atient is a carrier for a predicted deleterious variant in the POLG, a gene with autosomal recessive and autosomal dominant disease inheritance."[101] Id. In 2013, further genetic testing reported that "[w]hole exome sequencing did not identify any definitive mutations that relate to this patient's reported phenotype." Pet. Ex. 89 at 1. However, a heterozygous mutation at M466T was identified as "a good candidate for a disease-causing mutation, which is possibly consistent with some aspects of this patient's reported phenotype." Id. at 2. The report also noted that his mutation "has not been published as a mutation, nor has it been reported as a benign polymorphism to our knowledge. . . . [It] was not observed at any significant frequency . . . in the NHLBI Exome Sequencing Project. . . . [T]he possibility it may be a rare benign variant cannot be excluded." Id. Both labs recommended clinical correlation in order to determine the significance of these findings. Id. at 4; Pet. Ex. 30 at 2.

Based on these results, petitioners' experts opine that I.R. has a mitochondrial disorder caused by his POLG mutation. Tr. 929-30. Upon the undersigned's review of the record as a whole, however, the undersigned does not find that petitioners have provided preponderant evidence that I.R.'s mutation is necessarily a disease-causing mutation. Rather, the undersigned agrees with the interpretation expressed by both genetic laboratories that the significance of I.R.'s mutation cannot be assessed in the absence of clinical correlation.

Respondent's experts agree that the mutation identified by these genetic tests represents a "stop codon," which almost certainly causes problems in POLG protein production.[102] Tr. 360-

[101] An amended report from the lab later indicated reduced likelihood of the variant being pathogenic in an autosomal dominant fashion, based on the finding that I.R. inherited the mutation from his apparently healthy mother rather than the mutation having occurred de novo. Pet. Ex. 31 at 2. However, citing a report of fatigue, Dr. Niyazov suggested that I.R.'s mother might not be asymptomatic. Tr. 208. Dr. Niyazov also suggested that Mrs. Reed may demonstrate mosaicism, meaning that if the mutation first occurred in her, she may not have the mutation in all of her cells, potentially explaining why she is less impacted. Tr. 217.

[102] A codon is "a set of three adjacent bases on an mRNA that specifies an amino acid to be added to the growing polypeptide chain or directs chain initiation or termination." Dorland's at 380. A stop codon is one that causes termination of the synthesis of a growing polypeptide

61. Thus, although the variant is not identified in medical literature, respondent's experts agree that the mutation (or variant) is deleterious. Tr. 363-64, 485. However, respondent's experts note that genetic tests show I.R.'s mutation to be autosomal recessive.[103] Tr. 359-60; Pet. Ex. 89 at 1. Dr. McCandless explained that very reduced – well below 50% of POLG activity – would be expected in an autosomal recessive order in the context of two mutations. Tr. 367. Absent an additional mutation, respondent's experts concede only that I.R.'s POLG protein production capacity would be reduced by half, which they believe is insufficient to cause disease.[104] Tr. 356-58, 362-63, 367, 418-20, 422-23, 485-87.

Dr. McCandless explained that POLG activity is very difficult to measure and is not something that is routinely measured clinically. Tr. 367-68. However, he also noted that skeletal muscle testing of I.R. conducted in 2011 found that he had normalized mtDNA content similar to healthy controls. Tr. 368-69 (citing Pet. Ex. 27 at 7). Since POLG mutations cause disease by depleting mtDNA, this suggests that I.R.'s mutation did not cause disease. Id. Specifically, the report concluded:

> The mitochondrial DNA content in this individual's specimen is approximately 102% of the mean value of the age and tissue matched controls. In patients with mitochondrial depletion syndrome, 2-18% and 6-50% of control mtDNA content have been observed in liver and muscle, respectively. The mtDNA content of this individual is not within the range observed in patients with proven mutations in genes responsible for mtDNA depletion syndrome. We cannot confirm the

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chain. Id. Dr. Niyazov explained that in I.R.'s case, his mutation causes the production of POLG proteins to be stopped in a truncated fashion. Tr. 149-53. This is what is known as a "nonsense" mutation, because it results in a protein that cannot perform its function. Id.

[103] In fact, the Gene DX report at Exhibit 89 identifies the POLG mutation as autosomal recessive, whereas the Transgenomic report at Exhibit 30 initially did not identify whether I.R.'s specific mutation is dominant or recessive, but noted that the POLG variant at issue can have dominant or recessive inheritance. Compare Pet. Ex. 89 at 1, with Pet. Ex. 30 at 1. In a later amended report, Transgenomic indicated that autosomal dominance was of reduced likelihood based on testing of I.R.'s parents. Pet. Ex. 31 at 1. Autosomal refers to any of the 22 pairs of chromosomes (autosomes) other than the pair of sex chromosomes. See Dorland's at 183. In genetics, an autosome is dominant if it is capable of expression when carried by only one of the pair of homologous chromosomes. Id. at 562. A recessive autosome refers to one which is expressed only when it is carried by both members of homologous pair of chromosomes. Id. at 1606. "[T]here are two alleles, identical or differing, for each specific locus of an autosomal chromosome, one on each chromosome of a homologous pair." Id. at 50. When one possesses pairs of different alleles at the same locus, it is described as "heterozygous." Id. at 857. I.R.'s mutation is heterozygous. Pet. Ex. 30 at 1; Pet. Ex. 89 at 1.

[104] Thus, if I.R. had two copies of the mutation at issue, the experts would agree that it is disease-causing. Tr. 361.

presence of mtDNA depletion syndrome in this patient. Clinical correlation and genetic counseling are recommended.[105]

Pet. Ex. 27 at 7.

Dr. Cohen also stressed that approximately two percent of the population are carriers for these types of mutations and are not expected to become symptomatic. Tr. 485-87, 1041-43, 1046. Dr. McCandless similarly estimated that about 70 million people in the world are carriers of recessive deleterious POLG mutations, but that there are far fewer individuals with resulting diseases.[106] Tr. 362-63.

Dr. Niyazov offered inconsistent testimony regarding whether I.R.'s mutation was likely autosomal dominant or recessive. Compare Tr. 206-08 (stating that I.R.'s mutation is likely recessive due to childhood onset), with Tr. 932 (stating that I.R.'s mutation should be considered dominant because no second mutation was found), and Tr. 217 (opining that it is unknown whether I.R.'s mutation is dominant or recessive). Nonetheless, he did testify that autosomal-dominant mutations "are typically associated" with adult onset. Tr. 206. He also acknowledged that it is possible to "get by" with reduced ATP production and that someone with a recessive mutation may never become symptomatic. Tr. 267-68, 297-98. Thus, he conceded that "the finding of a single mutation is not expected to establish a diagnosis in this patient." Tr. 207. However, he also testified that he disagrees that 50% POLG capacity is necessarily sufficient for normal mitochondrial function in all instances. Tr. 267-68, 297-98. Rather, Dr. Niyazov opined that a single heterozygous recessive POLG mutation can manifest as a POLG disorder given sufficient stress. Tr. 206-08, 246. In that regard, petitioners argue that evidence exists to suggest that heterozygous POLG mutations cause disease.

Citing testimony by Dr. McCandless, petitioners begin from the undisputed proposition

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[105] Of note, this test was conducted in 2011, long after I.R.'s alleged vaccine reaction. Dr. McCandless opined that if I.R.'s injury were as severe as alleged, his skeletal muscle results would not likely have returned to normal in that period. Tr. 369-70. Additionally, Dr. McCandless opined that if a child had so much dysfunction of the POLG protein that they had a resulting ATP deficiency severe enough to cause nerve cell dysfunction, that child would probably be unable to produce enough mtDNA in the future to correct the defect. Tr. 382-83. Dr. Niyazov did not dispute that a pathologic POLG mutation should result in lower mtDNA; however, he opined that this finding does not rule out a pathogenic POLG mutation impacting other tissues. Tr. 301-02. Additionally, Dr. Frye posited in a 2016 report that adjusting for mitochondrial content, I.R.'s biopsy sample shows a "modest decrease" in mtDNA content, which he contended is consistent with a POLG-associated mtDNA depletion syndrome. Pet. Ex. 174 at 18. Dr. Frye did not explain what calculations were made to reach that conclusion, or disclose what the resulting mtDNA content would be. Id.

[106] Dr. Niyazov challenged these references to the general population. Tr. 298-99. He contended that the extent of these mutations among the general population is unknowable. Id.

that single POLG mutations can cause adult onset progressive external ophthalmoplegia.[107] Pet. Posthr'g Br. at 45 n.58 (citing Tr. 359) (emphasis in original). Dr. McCandless testified that the mechanism or cause of progressive external ophthalmoplegia is not known, but that the adult onset is believed to result from a slow accumulation of mitochondrial abnormalities over time. Tr. 416-17. Taking adult onset as a conceded point, petitioners then note that "[p]erhaps the single most hotly-contested issue at hearing was whether single (heterozygous) mutations of the POLG gene can cause disease or otherwise have any clinical significance in children." Pet. Posthr'g Br. at 44-45 (emphasis in original).

Petitioners argue that there is no evidence that other POLG phenotypes could not occur during childhood. Pet. Posthr'g Br. at 45-46. Specifically, petitioners assert that "Dr. McCandless conceded that it is only presumed that mitochondrial depletion occurs (only) slowly in single mutation patients, delaying clinical manifestation until adulthood. What he did not say is that childhood-onset of disease could never happen in single POLG mutation carriers, particularly if environmental exposures hastened the mitochondrial depletion in a particular individual."[108] Id. at 46 (emphasis in original).

However, petitioners overlook Dr. McCandless's testimony that autosomal dominant progressive external ophthalmoplegia occurs "in individuals that have mutations in a very specific part of the gene, in a very limited part of the gene." Tr. 359. In contrast, I.R.'s mutation "has not been published as a mutation" and "[w]hole exome sequencing did not identify any definitive mutations that relate to this patient's reported phenotype." Pet. Ex. 89 at 1. Moreover, one of the laboratories consulted in I.R.'s case has, in fact, indicated that I.R.'s mutation was autosomal recessive. Pet. Ex. 89 at 1. Whether or not progressive external ophthalmoplegia results from slow depletion of mitochondria, the fact that a different, known genetic mutation operates in an autosomal dominant expression to cause a different, late-in-life disease provides little support for petitioners' claim.

Petitioners also cite Dr. Cohen's statement that "50 percent activity in 2 percent of the population is enough activity to get you through late adult life, very late adult life, without any neurologic issues." Tr. 1068-69. Petitioners argue that this statement "seemingly conceded that a single POLG mutation will eventually cause neurologic sequelae, just not in childhood." Pet. Posthr'g Br. at 45 (emphasis in original). However, the undersigned does not conclude that Dr. Cohen's quoted statement is a significant concession, as petitioners contend. Dr. Cohen's statement was vague at best. He did not explain under what circumstances a single POLG mutation would result in late-in-life neurologic issues and the thrust of his statement was intended to convey, to the contrary, that early manifestation was unlikely. In earlier testimony, he was very clear in stating his opinion that a single POLG mutation will not produce clinical symptoms. Tr. 1042-43. Specifically, Dr. Cohen testified as follows:

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[107] Ophthalmoplegia is "paralysis of the eye muscles." Dorland's at 1329. I.R. did not receive this diagnosis.

[108] Petitioners' expert, Dr. Niyazov, agreed with Dr. McCandless that mitochondrial disease symptoms follow a build-up of mitochondrial depletion over time. Tr. 944-45. He disagreed regarding whether acute events can expedite onset. Id.

> Q: Under what conditions could you expect [a single POLG mutation] to become pathogenic?
> A: I wouldn't.
> Q: You wouldn't?
> A: You mean the normal – the POLG mutation is pathogenic. The POLG mutation is pathogenic. We've – you know, we've determined that.
> Q: Okay. And under what –
> A: The – the other allele is functioning, period.
> Q: Okay. And are you saying that despite its expected pathogenicity, that you would never expect the POLG to cause any clinical symptoms?
> A: Correct.

Id.

Apart from citing the existence of adult-onset progressive external ophthalmoplegia, petitioners rely most heavily on a 2008 paper by Wong, et al. Pet. Posthr'g Br. at 47. Respondent's expert, Dr. Cohen, participated as an author on that paper. Pet. Ex. 63; Tr. 473-75. Petitioners assert that the Wong paper contradicts Dr. Cohen's testimony, because it identified 28 patients (out of a study population of 350 patients displaying a phenotype consistent with POLG-related mitochondrial disorder) with different phenotypes that had a single identified POLG mutation. Pet. Posthr'g Br. at 47-48; see generally Pet. Ex. 63. However, Dr. Cohen expressed that the Wong paper may be dated, indicating that although it relied on the state-of-the-art gene sequencing of the time (Tr. 518-20), "[i]t represents the 2008 view of what we ought to be publishing." Tr. 1038.

Petitioners argue at length that Dr. Cohen's testimony is contradictory, misleading, and discrediting. Pet. Posthr'g Br. at 47-50. Drawing from a number of statements, petitioners argue in effect that Dr. Cohen has disavowed the Wong paper for the purposes of this case, but otherwise continues to rely on the idea that a single POLG mutation can cause disease.[109] Id.

[109] In his rebuttal, Dr. Niyazov cited an updated 2014 online paper by Dr. Cohen, et al., which he claimed contradicts Dr. Cohen's testimony and supports petitioners' position. Pet. Ex. 206 at 2. Dr. Niyazov stated:

> Dr. Cohen's testimony clearly indicated that single POLG mutations are no longer relevant in human disease and this is why his online Gene Reviews paper was updated to reflect this in recent years. However, the most recent version of the paper published in 2014 still includes the same reference to single POLG mutations as being sufficient to predispose individuals to disease and still recommends that individuals who are heterozygous be reevaluated every few years for symptoms and signs of POLG-related disorders. The significance of single pathogenic POLG mutations like [I.R.]'s is still regarded as sufficient to predispose to disease and has not be usurped by more recent genetic understanding in the past few years.

Id. (citing Resp. Ex. H, Tab 11 at 25). In fact, the statement cited by Dr. Niyazov states in its entirety: "Heterozygotes (carriers) are generally believed to be asymptomatic. However, some

However, in stressing Dr. Cohen's alleged disavowal of the Wong paper, petitioners overstate the forcefulness and significance of the Wong paper itself.

The Wong authors indicated that "[s]everal cases in our cohort with early onset of severe disease were found to harbor only one definitive pathogenic mutation. However, the presence of a second mutant allele located in the promotor region or deep in an intron cannot be excluded. Since POLG is a large gene containing 23 exons, intragenic deletions and/or duplications may be present, which would escape detection by standard sequencing approaches." Pet. Ex. 63 at 12. Ultimately, the authors concluded that "[b]ecause of the contribution of observed allelic heterogeneity, the correlation to phenotypes in terms of severity, age of onset, and spectrum of organ system involvement, much further study will be required to fully understand the genetics underlying the POLG diseases." Id. at 13. Thus, contrary to petitioners' intimation, the Wong paper never asserted in the first instance that disease-causing single POLG mutations must exist.

The Wong paper demonstrates only that some minority of mitochondrial disorder patients have only one identified mutation. The paper explicitly disclaims any finding that these single mutations are necessarily pathogenic by themselves, apart from those involving progressive external ophthalmoplegia. Specifically, the authors state that "[t]wenty eight patients were identified with one altered POLG allele and/or a single nucleotide polymorphism. With the exception of three mutations in the [progressive external ophthalmoplegia], the pathogenicity of these single POLG mutations are unclear and should be considered as uncharacterized variants until other supporting data is available." Pet Ex. 63 at 9. Thus, in light of its equivocal conclusion, the Wong paper does not provide significant support for petitioners' claim that I.R.'s single mutation can be considered disease-causing. Petitioners' characterization of Dr. Cohen's testimony as disingenuous is therefore not persuasive.

Moreover, the undersigned notes that the 28 single-POLG patients discussed in Wong were all reported as having disparate phenotypes. By petitioners' own admission, only one individual out of the 28 – which in turn represents one individual out of a total study population of 350 – demonstrated single-POLG mutation with a phenotype similar to I.R.'s alleged phenotype. Pet. Ex. 206 at 1 (Dr. Niyazov describing Wong as having one patient with a phenotype of autism and hypotonia); Pet. Posthr'g Br. at 47 (same). While that one example does not completely lack evidentiary value, a single case is not significant evidence to support

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individuals with a heterozygous POLG pathogenic variant are reported to have manifestations of POLG-related disorders. Because knowledge of these disorders is changing quickly individuals who are heterozygous should be reevaluated by history and physical examination every few years for symptoms and signs of POLG-related disorders." Resp. Ex. H, Tab 11 at 25. This is not a strong statement in favor of disease-causing single-POLG mutations, particularly not as it would relate to disorders having childhood onset. Moreover, elsewhere in the paper, the authors state with regard to diagnosis and testing that "[e]stablishing the diagnosis of a POLG-related disorder relies on clinical findings and identification of two (biallelic) POLG pathogenic variants for all phenotypes except adPEP, for which identification of one POLG pathogenic variant is diagnostic." Resp. Ex. H at 2. Taken as a whole, the undersigned does not find that this article contradicts Dr. Cohen's testimony.

petitioners' claim.[110] See Paluck v. Sec'y of Health & Human Servs., 104 Fed. Cl. 457, 475 (2012) ("[T]he fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.") (quoting Campbell v. Sec'y of Health & Human Servs., 97 Fed. Cl. 650, 668 (2011).

Related to Dr. Cohen's testimony regarding the Wong paper, the parties also argued extensively about the significance of a database of POLG mutations maintained by Dr. Copeland, another of the Wong paper's authors. Petitioners filed a copy of the database as Exhibit 205 and Dr. Niyazov wrote a supplemental report, which petitioners filed as Exhibit 206, describing the database's significance.[111]

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[110] The undersigned does note Dr. Niyazov's argument that due to variable expressivity, POLG disorders manifest differently and to different degrees in different people. Tr. 126-27. Dr. McCandless stressed, however, that variable expressivity would not be applicable in I.R.'s case, because I.R.'s variant is previously undescribed. Tr. 366. Variable expressivity would address expression of the same variant across many cases. Id.

[111] This also gave rise to a motion to strike a supplemental report by Dr. Cohen. See Pet. Mot. to Strike dated Oct. 31, 2018 (ECF No. 187). Following the hearing held June 22-24, 2016, the undersigned ordered respondent to file the data and tables maintained by Dr. Copeland that were referenced in Dr. Cohen's testimony. Order dated June 10, 2016 (ECF No. 158). Petitioners were also provided the opportunity to file a status report identifying any necessary rebuttal testimony. Id. On July 27, 2016, respondent filed a graphical representation of POLG mutations, purportedly from Dr. Copeland's database. Resp. Ex. R. On August 16, 2016, petitioners filed updated data and tables referenced in Dr. Cohen's testimony. Pet. Ex. 205. On September 15, 2016, petitioner filed rebuttal testimony from Dr. Niyazov and supporting literature. Pet. Ex. 206-09. In response, on October 31, 2016, respondent filed a second supplemental report by Dr. Cohen, along with supporting literature. Resp. Ex. T, Tabs 1-4. Petitioners in turn filed a motion to strike respondent's October 31, 2016 filing – including Exhibit T and Exhibits T, Tabs 1-4. Pet. Mot. to Strike. Petitioners argue:

> Dr. Cohen's supplemental report (Exhibits T-T4) is completely outside the scope of the rebuttal materials filed post-hearing and is largely irrelevant to the supplemental report of Dr. Niyazov, to which it is supposed to be responsive. Specifically, the majority of Dr. Cohen's report is essentially a summary argument about the relationship of the POLG gene generally to autism phenotypes, including opinions and arguments not previously made at hearing or disclosed in pre-hearing reports.

Id. at 1.

The undersigned disagrees with petitioners' characterization of the post-hearing filings. Dr. Niyazov's rebuttal identified additional single-POLG mutations contained in the Copeland database. What petitioners characterize as an irrelevant summary argument regarding POLG and autism phenotypes, the undersigned understands as a contextual explanation by Dr. Cohen for his competing opinion that the database examples cited by Dr. Niyazov are not significant. It is,

Review of the database and of Dr. Niyazov's supplemental report expands the discussion beyond the specific subjects included in the Wong paper, but does not shed any additional light on the questions at issue. Dr. Niyazov indicates that upon his review, there are 41 single POLG mutations listed in the database, including the 28 discussed in the Wong paper. However, upon the undersigned's review, nothing in the database suggests that any greater significance should be given to these instances of single-mutation POLG cases than was stated in the Wong paper. Significantly, Dr. Niyazov did not identify any of these additional single-POLG mutations as resulting in a phenotype similar to I.R.'s alleged phenotype. Nor did Dr. Niyazov suggest that the database reflects any additional genetic testing performed upon the original Wong subjects, meaning that their presence in the database continues to rely on the same 2008 genetics testing that Dr. Cohen referenced during his testimony.

Thus, although petitioners may have cast doubt on Dr. Cohen's assertion that the relevant science has effectively ruled out disease-causing single-POLG mutations following Wong, they have failed themselves to persuasively demonstrate that scientific understanding has advanced to a point where disease-causing single-POLG mutations are any closer to being ruled in.[112] That is, even if petitioners have established that the Wong paper continues to reflect relevant state-of-the-art POLG genetics as they claim, its equivocal conclusion remains insufficient to meet petitioners' burden of proof.

Moreover, even if the undersigned credited petitioners' argument and assumed that Dr. Cohen accepts the possibility of disease-causing single POLG mutations, this still does not establish that all single POLG mutations are necessarily disease-causing. Nor does it establish that I.R.'s mutation in particular is either autosomal dominant or recessive and disease-causing. Again, the genetic reports addressing I.R.'s mutation noted that "[w]hole exome sequencing did not identify any definitive mutations that relate to this patient's reported phenotype." Pet Ex. 89 at 1. Moreover, the report observed that his mutation "has not been published as a mutation, nor has it been reported as a benign polymorphism to our knowledge. . . . [It] was not observed at any significant frequency . . . in the NHLBI Exome Sequencing Project. . . . [T]he possibility it may be a rare benign variant cannot be excluded." Id. Additionally, Dr. McCandless cited test results suggesting that I.R. had mtDNA content similar to healthy controls. Tr. 368-69. Thus, even if the undersigned rejected Dr. Cohen's testimony entirely and accepted petitioners' argument that heterozygous POLG mutations in some instances cause disease, whether by autosomal dominance or in a recessive context, the only way to know whether I.R.'s own mutation was operating in that manner would be if he were symptomatic. Therefore, this case

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therefore, not beyond the scope of rebuttal. Moreover, to the extent petitioners argue that Dr. Cohen's statements are arguments not previously made at hearing or disclosed in pre-hearing reports, the undersigned finds the opposite to be true. Except for his statements directly addressing the literature later filed as Exhibits 207-09, Dr. Cohen's report is cumulative of his and Dr. McCandless's prior hearing testimony. Thus, petitioners' motion is DENIED. However, the undersigned notes that, as cumulative evidence, Dr. Cohen's second supplemental report is not a significant factor in her analysis.

[112] Apart from progressive external ophthalmoplegia.

would still turn on the question of I.R.'s clinical presentation.[113]

The undersigned is not persuaded that I.R.'s single heterozygous mutation is disease-causing. Petitioners have, at best, established that it is possible in a general sense that such mutations could be disease-causing. Again, the laboratory reports remain persuasive in suggesting that I.R.'s particular genetic mutation does not provide any explanation for I.R.'s condition in the absence of clinical correlation.

iii. The undersigned finds that I.R. does not have a mitochondrial disorder or dysfunction.

Notwithstanding the above, clinical evidence demonstrating the presence of a mitochondrial disorder could corroborate petitioners' allegation that I.R.'s POLG mutation is disease-causing. And in any event, the lack of genetic confirmation is not necessarily dispositive of whether I.R. has a mitochondrial disorder. As noted above, some patients are diagnosed based on a host of other clinical symptoms and objective findings without genetic confirmation. In that regard, I.R.'s medical records including a number of findings and reports related to his metabolic function. I.R. was separately evaluated by Drs. Natowicz and Frye, practitioners in the mitochondrial medicine community. In addition to those findings, petitioners' experts, Drs. Niyazov and Zimmerman, both evaluated I.R. for a potential mitochondrial disorder or dysfunction.

In his expert report, Dr. Niyazov scored I.R. using both the Walker Criteria and the Nijmegen Criteria. Pet. Ex. 39 at 3-4. Later, during the hearing, he additionally discussed the Modified Walker Criteria and the Morava Criteria. Tr. 145-49, 192-95. In reaching a diagnosis under these standards, Dr. Niyazov relied on the following: (1) I.R.'s POLG mutation; (2) biochemical findings, including high plasma glycine, high ratio of alanine as compared to either lysine or the combination of tyrosine and phenylalanine, high plasma lactic and pyruvic acids with abnormally high lactate/pyruvate, and ketone 3-OH-butyrate/acetoacetate ratios; (3) a clinical phenotype consistent with a mitochondrial disorder, including fatigue, waxing and waning energy, exercise intolerance, muscle weakness, hypotonia, neurodegeneration, and immunodeficiency; and (4) abnormal mitochondria as seen by electron microscopy. Pet Ex. 39 at 3-4.

In addition to citing some of the same points as Dr. Niyazov, Dr. Zimmerman opined that a test run by Dr. Frye on April 1, 2013, known as a "seahorse assay," provided evidence of a mitochondrial disorder. Tr. 742-45, 773-74. Dr. Zimmerman also cited muscle biopsy results of

[113] To the extent that this leaves open the question of whether I.R.'s heterozygous mutation may be a cause of his mitochondrial disorder in an autosomal recessive manner by operating in conjunction with another undiscovered mutation, such an argument is inherently speculative. Even though respondent's experts cannot say that the entirety of I.R.'s gene has been tested, failing to definitively rule out the presence of an additional mutation is not sufficient to meet petitioners' burden. Without clinical manifestations of a mitochondrial disorder, this theory remains speculative. Thus, even if I.R. had a hidden second mutation, the question of whether I.R. had a mitochondrial disorder must still be answered by relying on his clinical presentation.

an accumulation of enlarged mitochondria and increased citrate synthase as diagnostic of a mitochondrial disorder. Tr. 693-94, 696-97. He further pointed to folate-blocking antibodies as evidence of mitochondrial dysfunction. Tr. 693.

Nonetheless, for the reasons described below, the undersigned is not persuaded that there is preponderant evidence either supporting petitioners' contention that I.R.'s POLG mutation is disease-causing or independently demonstrating that I.R. has or had a mitochondrial disorder or dysfunction in the absence of genetic confirmation.

a. Pathogenic Genetic Alteration (POLG Mutation)

As noted above, the undersigned has concluded that I.R.'s POLG mutation does not provide an independent basis for concluding that I.R. suffers a mitochondrial disorder. However, petitioners also argue that I.R.'s POLG mutation is consistent with the major criteria of "a nDNA or mtDNA alteration of undisputed pathogenicity" under the Walker/Modified Walker Criteria. Pet. Posthr'g Br. at 99-100; see also Pet. Ex. 60 at 5; Pet. Ex. 137. This assertion in part underlies Dr. Niyazov's contention that I.R. scores a "definite" diagnosis under the Walker/Modified Walker Criteria. Pet. Ex. 39 at 3. In his report, Dr. Niyazov also cited I.R.'s POLG mutation as evidence of a mitochondrial disorder under the Nijmegen Criteria. Pet Ex. 39 at 4.

According to the Walker Criteria, an alteration of "undisputed pathogenicity" in either nDNA or mtDNA constitutes a major diagnostic finding. Pet Ex. 60 at 5, Table 3. The Walker authors further provide, by way of example, six criteria that represented undisputed pathogenicity: (1) heteroplasmy (except for LHOH-associated mutations); (2) significant levels; (3) linkage of the particular mutation to the same phenotype in at least two unrelated individuals; (4) absence of the mutation in normal individuals (excluding asymptomatic relatives); (5) transferability of the RC defect with mtDNA in cybrid experiments; and (6) point mutations that alter an evolutionary conserved rRNA, tRHA, or amino acid residue.[114] Pet. Ex. 60 at 6; see also Pet. Ex. 137.

Petitioners have not demonstrated these requirements. In particular, they have not demonstrated that other unrelated individuals with the same mutation display the same phenotype. In fact, the genetic reports suggest the opposite, noting that I.R.'s mutation "has not been published as a mutation, nor has it been reported as a benign polymorphism to our knowledge. . . . [It] was not observed at any significant frequency . . . in the NHLBI Exome Sequencing Project." Pet. Ex. 89 at 2. Thus, for all the reasons discussed in the previous section, the undersigned finds that I.R. does not have a genetic mutation of "undisputed"

[114] The Modified Walker Criteria do not cite the same six criteria for determining whether a mutation is of undisputed or probable pathogenicity, but the factors are also not disclaimed. See Pet. Ex. 137. The six factors are cited in reference to mtDNA. Pet Ex. 60 at 6. The Walker paper notes that at that time, "[o]nly one mutation of nDNA has been associated with RC defects on the molecular level." Id. at 5. In his first report, Dr. Niyazov cited the original 1996 Walker criteria when characterizing I.R.'s mutation as a major diagnostic criterion. Pet. Ex. 39 at 3-4.

pathogenicity and therefore does not satisfy any of the major diagnostic criteria under the Modified Walker Criteria.

A mutation may constitute a minor diagnostic criterion if it is a mutation of "probable pathogenicity." Pet. Ex. 137; see also Pet. Ex. 60 at 5, Table 4. A mutation of probable pathogenicity is one "not previously recognized as being associated with the presenting syndrome and fulfilling some, but not all, of the [above] six criteria . . . ." Pet. Ex. 60 at 5, Table 4. Under Nijmegen, "[m]utations in mtDNA and in nuclear DNA that affect respiratory chain function are not taken into account as a distinct item. We consider the diagnosis of a respiratory chain disorder as definite if in addition to clinical signs and symptoms a pathogenic mutation is found in a given patient." Pet Ex. 62 at 2. In this context, nuclear DNA mutations are described as pathogenic when they affect complexes in the respiratory chain or the maintenance of mtDNA. Pet. Ex. 62 at 1.

However, even in this context, petitioners have not persuasively addressed how I.R.'s actual mutation fits these specific criteria. Although respondent's experts have agreed that I.R.'s mutation is likely deleterious, they have stressed that recessive mutations are not pathogenic in the absence of a second mutation and therefore do not satisfy diagnostic criteria. See, e.g., Resp. Ex. F at 6. Moreover, Dr. McCandless highlighted skeletal muscle test results indicating that I.R. had mtDNA content similar to healthy controls. Tr. 368-69 (citing Pet. Ex. 27 at 7). Dr. Cohen also stressed that I.R.'s POLG mutation is not supportive of a mitochondrial disease diagnosis, because his phenotype is not consistent with the six main categories of known POLG disorders.[115] Tr. 469-72. The undersigned concluded that it was at best possible, not probable or likely, that I.R.'s mutation could be disease-causing. Accordingly, the undersigned is not persuaded that I.R.'s POLG mutation warrants consideration as a factor contributing to a mitochondrial disorder diagnosis under the published diagnostic criteria.

b. Biochemical Evidence

In addition to the genetic mutation, Dr. Niayzov cited a number of biochemical findings as evidence supporting a mitochondrial diagnosis. For the reasons described below, the undersigned is not persuaded that these findings represent significant evidence supporting a mitochondrial disorder or dysfunction diagnosis.

1. High Plasma Glycine and High Ratio of Alanine as Compared to Either Lysine or the Combination of Tyrosine and Phenylalanine

On May 28, 2009, I.R. underwent testing for plasma amino acid analysis. Pet. Ex. 81 at 72.[116] It showed high glycine of 420 um/L against a reference range of 127-341 um/L. Id. The same analysis showed alanine elevated compared to some other amino acids, but within normal

[115] To the extent petitioners argue that I.R. had a non-classic presentation, see Section C.iii.f.6, below.

[116] Exhibit 38 at pages 5-7 and Exhibit 29 at page 179 appear to reflect additional copies of the same laboratory findings.

reference range, and normal lysine levels. Id. Alanine was recorded as 455 um/L and lysine was 136 um/L. Id. Additionally, tyrosine was measured within normal limits at 47 um/L and phenylalanine was within normal limits at 48 um/L. Id. In November 2009, and upon review of these results, Dr. Natowicz opined that I.R.'s prior lab work was not strongly supportive of a metabolic etiology for I.R.'s condition. Pet. Ex. 25 at 114-15. In particular, he stressed that these results were accompanied by unremarkable lactate, pyruvate, and plasma acylcarnitine levels, and that increased plasma glycine, which he characterized as mild, was "unlikely to be of clinical significance." Id.

Dr. Niyazov opined, however, that these results were suggestive of a mitochondrial disorder. Tr. 166-68. Specifically, he cited the high glycine, the ratio of alanine to lysine (more than three to one), and the ratio between the alanine and the combined total of both tyrosine and phenylalanine (more than four to one). Tr. 166-69. Dr. Niyazov indicated that the ratio between elevated alanine and insufficiently elevated lysine, or combined tyrosine and phenylalanine, were indirect measures of mitochondrial dysfunction. Tr. 167.

Respondent's experts did not dispute that these measures could, in theory, be potential evidence of a mitochondrial disorder. Dr. McCandless, however, interpreted these results as showing "mildly" elevated glycine. Tr. 395. He explained that a mild elevation of glycine can have a variety of causes, often including dietary causes. Id. Dr. McCandless opined that in the context of this complete lab report, in which the remaining results are all normal, this glycine finding would not necessarily be concerning without evidence of a chronically elevated glycine level. Id.

Dr. Cohen agreed. Tr. 479. Dr. Cohen also stressed that the ratio of alanine to lysine does not rise to the level of suspicion based on the remainder of the analysis and the fact that it wasn't repeated. Tr. 479-80. He explained that a ratio under three is normal and above four is abnormal, but that a finding of a ratio of 3.31, as in I.R.'s case, would be a grey area. Tr. 1010-13. He stressed, for instance, that an abnormal alanine to lysine ratio can be the result of dietary factors. Id. As the lab noted, "[t]his result is not diagnostic of a specific disorder." Pet. Ex. 81 at 72.

2. High Plasma Lactic and Pyruvic Acids with Abnormally High Lactate/Pyruvate and Ketone 3-OH Butyrate/Acetoacetate Ratios.

On October 25, 2013, I.R. had lactic acid measured at 3,494 umol/L against a reference range of 600-2600 umol/L. Pet Ex. 111 at 15. Pyruvic acid was measured at 145 umol/L against a reference range of 20-140 umol/L. Id. Additionally, hydroxybutric acid (3-OH Butyric Acid) was measured at 34 umol/L against a reference range of 0-30 umol/L and acetoacetic acid was measured at 3 umol/L against a reference range of 0-66 umol/L. Id. On April 16, 2014, I.R. had lactic acid measured at 1.7 MMOL/L against a reference range of 0.3-1.3 MMOL/L and pyruvate measured at 0.17 MMOL/L against a reference range of 0.03-0.08 MMOL/L. Pet. Ex. 98 at 225. On May 26, 2014, I.R.'s lactic acid was measured at 2976 umol/L against a reference range of 600-2600 umol/L. Pet. Ex. 111 at 16. His pyruvic acid was measured at 118 umol/L against a reference range of 20-140 umol/L. Id. Three hydroxybutric acid (3-OH Butyric Acid) was

measured at 41 umol/L against a reference range of 0-30 umol/L and acetoacetate was measured at 16 umol/L against a reference range of 0-66 umol/L. Id.

According to Dr. Niyazov, these findings support a mitochondrial disorder diagnosis. Tr. 163-70; Pet. Ex. 39 at 3-4. In particular, Dr. Niyazov cites as significant: the fact that these results reflect elevated lactic acid on three occasions (October 2013, April 2014, and May 2014); the fact that I.R. demonstrated elevated pyruvic acid (October 2013 and April 2014); the fact that he had a 20-1 ratio of lactic acid to pyruvic acid (October 2013 and May 2014); and the fact that I.R. demonstrated a high ratio of hydroxybutric acid to acetoacetic acid (October 25 and May 2014). Id.

Dr. McCandless, however, indicated that the October 25, 2013 and May 26, 2014 lactic acid and pyruvate results should not be relied upon. He explained that the April 16, 2014 results were a direct measure of lactic acid and pyruvic acid using a quantitated assay. Tr. 389. The other two measures, however, were derived from gas chromatography-mass spectrometry, which is not a quantified test. Id. Dr. McCandless indicated that the latter method is not intended to produce a specific, reproducible number. Tr. 390. Rather, that method is only viable for determining if something is "massively" increased.[117] Tr. 390-91. Dr. McCandless further indicated that the familiar diagnostic criteria for mitochondrial disorders are designed to rely on the quantitated assay. Tr. 390.

Dr. Niyazov did not challenge or address Dr. McCandless's point regarding the distinction between the different testing methods. Additionally, to the extent Dr. Niyazov also cited the ratio of hydroxybutric acid to acetoacetic acid from the same laboratory reports, he did not explained how these results were indicative of a mitochondrial disorder. Nor did he cite any literature or other authority supporting his contention that these findings point to a mitochondrial disorder. Moreover, to the extent these results are part of the same mass spectrometry panels challenged by Dr. McCandless, he did not indicate that these results were free of the same methodological limitation.

With regard to the remaining April 2014 results, Dr. McCandless noted that the ratio of lactic acid to pyruvate was ten, which is normal. Tr. 386-87. Accounting for the fact that lactate was measured as elevated, he explained that in the context of elevated lactic acid, a 10-1 ratio of lactic acid to pyruvate is suggestive of an issue with pyruvate metabolism, which would be evidence against a respiratory chain defect. Id. Dr. Cohen likewise stressed that the ten to one ratio indicates a normal redox state. Tr. 1020-21. Dr. Cohen questioned whether the lactate finding of 1.7 MMOL/L was truly elevated, since the listed reference range was lower than he typically sees. Tr. 1019-20. He indicated that the upper limit for the reference range is typically over 2.0, which would leave this result in the normal range. Id. Under the Nijmegen Criteria, a lactate measure is only considered elevated if it is over 2.0 mmol/L. Pet Ex. 129 at 3.

[117] Of note, the April 2014 results were provided in millimoles per liter, while the other two reports from October 2013 and May 2014 used micromoles per liter. Tr. 391. Dr. McCandless noted that if the October 2013 finding of 3494 micromoles per liter was converted to millimoles per liter, it would be 3.49 MMOL/L against a top reference range of 2.6 MMOL/L. Id. Dr. McCandless characterized this level as moderately elevated. Id.

Dr. McCandless similarly noted that, notwithstanding the reference range provided by the laboratory, lactic acid of 1.7 mmol/L would not constitute an elevated reading consistent with his clinical experience. He indicated that patients with diagnosed mitochondrial disorders typically have lactic acid elevated above 3.5 mmol/L. Tr. 392. Dr. McCandless also noted that on May 28, 2009, I.R. had an additional direct measure of his lactate and pyruvate, and on that occasion both values were within normal limits. Tr. 391-92 (citing Pet. Ex. 29 at 177). On that occasion, I.R. had lactate of 0.9 mmol/L against a reference range of 0.9-20.0 mmol/L, and pyruvate of 0.06 mmol/L against a reference range of 0.03-0.08 mmol/L. Pet. Ex. 29 at 177.

Thus, Dr. McCandless summarized the lactate findings as including two direct measures that were "reasonable values" that should be considered normal, and two "mildly" increased findings on a semi-quantitative plasma organic acid analysis. Tr. 392-93. Dr. McCandless opined that these lactate and pyruvate findings should, at best, spur further testing rather than forming the basis for a diagnosis. Tr. 393. Dr. McCandless cautioned against over-interpreting lactic acid measurements. Tr. 392-93.

Furthermore, although lactate and pyruvate findings can contribute to a mitochondrial disorder diagnosis, there is disagreement within the mitochondrial medicine community regarding the reliability of these tests. For example, Parikh, et al., an article which petitioners have cited as an authoritative consensus statement in mitochondrial medicine, states:

> Elevated lactate levels have long been associated with mitochondrial disease . . . . False elevations of lactate are also common, primarily due to difficulties with specimen collection, improper specimen handling or delays in processing. Specimens should be collected with patients at rest, without the use of a tourniquet and samples should be transported on ice and processed immediately. . . . For some, elevated lactate-to-pyruvate ratios provide a useful tool to indicate respiratory chain dysfunction, especially in spinal fluid and skin fibroblasts. However, for others, a concern of improper specimen collection or processing of pyruvate samples limits the test's routine use.

Pet. Ex. 52 at 3 (internal citations omitted).

Dr. McCandless explained that a blood sample will continue to produce lactic acid after it has been drawn, raising concerns about processing delays. Tr. 391. Additionally, lactate measurements can be effected by diet and exercise, as well as the blood drawing procedure itself. Tr. 170. For these reasons, Dr. Niyazov acknowledged that it is significant that I.R. had elevated lactic acid on three occasions and not just a single elevated result. Id.

Dr. Cohen took a stronger view, arguing in effect that, given the difficulties in properly drawing and handling the samples, a test result for an autistic patient drawn from an unfamiliar lab should be presumed invalid. Tr. 480, 531-33, 1020. Dr. Cohen explained that in his experience, the blood draw process routinely causes anxiety and struggle among children with ASD and that the resulting laboratory results often must be discarded. Tr. 531-33. He also indicated that it is impossible to know the significance of lactate and pyruvate findings without knowing if the patient was fasting or fed. Tr. 1017-18. With regard to elevated lactate findings,

it has been observed that "spurious elevation of plasma lactate is indeed the most common cause . . . ." Resp. Ex. H, Tab 8 (Haas) at 2.

c. Muscle Biopsy

On February 18, 2011, I.R. underwent a right quadriceps muscle biopsy. Pet. Ex. 21 at 1. Multiple tests were run from this skeletal muscle biopsy, including mitochondrial respiratory chain enzyme analysis, mitochondrial DNA content analysis, skin fibroblast respiratory chain enzyme analysis, electron microscopy, and histochemical staining. Pet. Ex. 27 at 5-11; Pet. Ex. 21 at 1-3. From these results, petitioners' experts cited elevated citrate synthase and accumulations of enlarged mitochondria as evidence of mitochondrial dysfunction. However, the undersigned finds that when viewed as a whole, I.R.'s skeletal muscle biopsy results, which were largely within normal parameters, work against a finding that I.R. has any mitochondrial disorder or dysfunction.

Absent genetic confirmation, tissue biopsy "has often been thought of as the gold standard for mitochondrial diagnosis." Pet. Ex. 105 at 5. The consensus recommendation among mitochondrial specialists is that it should be routinely used when DNA testing cannot confirm a diagnosis. Id. Skeletal muscle in particular is favored for such biopsies. "Skeletal muscle is commonly affected in primary mitochondrial disease." Resp. Ex. H, Tab 8 at 8. This has made skeletal muscle the most widely used tissue for respiratory chain enzyme studies. Id.

Most notable are the results of I.R.'s Mitochondrial Respiratory Chain Enzyme Analysis. See Pet. Ex. 27 at 5. Specifically, the following enzyme activity was measured: Complex I; Complexes I and III together; Complex II; Complex II and III together; Complex IV; and citrate synthase. Id. The following results were normalized against citrate synthase:[118]

Complex I:	99% of mean
Complex I + III:	69% of mean
Complex II:	88% of mean
Complex II + III	94% of mean
Complex IV:	143% of mean

Id. Both Drs. McCandless and Cohen opined that these muscle enzymology results are normal and not indicative of a mitochondrial disorder. Resp. Ex. A at 5; Resp. Ex. F at 5. That opinion accords with the laboratory's report, which noted that "[t]here were no deficiencies of respiratory chain activities detected before or after correction for increased [citrate synthase] activity." Pet. Ex. 27 at 5.

[118] Citrate synthase is not a part of the respiratory chain but is used as a marker for mitochondrial content within the sample. Tr. 461-62; Pet. Ex. 27 at 5. Thus, for I.R.'s biopsy, the laboratory indicated that if citrate synthase activity is greater than 1 standard deviation above or below controls, they recommend normalizing the reported enzyme activity against the citrate synthase. Pet. Ex. 27 at 5. In I.R.'s skeletal muscle biopsy, citrate synthase was reported at 521nm, with a control listed at 280nm and a standard deviation of plus or minus 95nm. Id.

Dr. Frye opined that Complex I + III was "relatively low," but acknowledged that it was not low enough to be evidence of dysfunction pursuant to the diagnostic criteria.[119] Pet. Ex. 174 at 18. Enzyme assays of muscle tissue are an important diagnostic tool for mitochondrial medicine, since they measure mitochondrial function. Pet. Ex. 105 at 5-6. Although such testing has limitations and is subject to differing interpretive views, these results provide some affirmative evidence that I.R.'s mitochondria are functioning normally. See id. (noting that "[f]unctional in vitro assays in tissue (typically muscle) have been a mainstay of diagnosis of mitochondrial disorders," but also noting that "ETC findings should not be used as the sole criterion for excluding mitochondrial dysfunction").

Notwithstanding that the enzyme assay shows normal functioning for the respiratory chain complexes, petitioners' experts cite the finding of increased citrate synthase as suggestive of mitochondrial proliferation. Tr. 300, 696-97. They portray it as evidence of a compensatory mechanism that points to mitochondrial deficiency. Id. For its part, the laboratory stated that "[c]itrate synthase activity was increased, suggesting mitochondrial proliferation. This may be an adaptive response to mitochondrial dysfunction." Pet. Ex. 27 at 5. Dr. Frye likewise cited this finding. Pet. Ex. 174 at 18. In essence, petitioners' experts assert that this evidence of additional mitochondria suggests that I.R.'s body required additional mitochondria to compensate for the reduced mitochondrial activity, i.e. to maintain adequate enzyme activity. Tr. 300, 696-97. Dr. Frye, in particular, stressed that the mitochondrial proliferation must be accounted for by using the citrate synthase-adjusted test results. Pet. Ex. 174 at 18.

The undersigned notes, however, that even when evaluating I.R.'s results using the citrate synthase adjusted figures cited above, none of the respiratory complex enzyme activity results are reduced by enough to suggest mitochondrial dysfunction. For example, under the Modified Walker Criteria, respiratory chain activity represents a major criteria if it is less than 20% in a tissue and a minor criteria if it is 20-30% in a tissue. Pet. Ex. 137. According to Parikh, et al., respiratory complex enzyme activity should be interpreted using published diagnostic criteria and "one should cautiously interpret the relevance of ETC enzyme activity above 20% of the control mean." Pet. Ex. 105 at 6.

Respondent's experts acknowledged the elevated citrate synthase. Resp. Ex. F at 5; Tr. 461. Dr. McCandless, however, noted that the elevation was mild and further opined that the

[119] In fact, two figures were provided by the laboratory regarding Complex I + III enzyme activity. The undersigned has cited the "total" Complex I + III activity, which was reported on a citrate synthase normalized basis as 69% of mean. Dr. Frye cited the "rotenone sensitive" finding of 46% of mean. Pet. Ex. 174 at 18; Pet. Ex. 27 at 5. For his part, Dr. Cohen disputed that these results should be normalized against citrate synthase. Resp. Ex. A at 6. Refraining from normalizing the results, total Complex I + III activity would be 128% of mean and rotenone sensitive Complex I + III activity would be 69% of mean. Pet. Ex. 27 at 5. Whether to normalize citrate synthase is a matter of professional disagreement in the mitochondrial medicine community; however, Dr. Cohen is in a small minority. According to Parikh, et al., 97% of mitochondrial specialists prefer to normalize electron transport values to marker enzymes. Pet. Ex. 52 at 6. Dr. Frye did not explain why he chose to cite the rotenone sensitive finding rather than the total.

interpretation is not otherwise supported by the data. Resp. Ex. F at 5. Specifically, he noted that skin fibroblasts tested at the same time showed no abnormality in citrate synthase.[120] Id.; Pet. Ex. 27 at 10. Dr. Cohen also agreed that citrate synthase is used as a proxy to measure how many mitochondria are in the sample and that it could be evidence of mitochondrial proliferation. Tr. 462, 1022. He opined, however, that the finding is not indicative of mitochondrial disease in this case, because the muscle biopsy did not show other findings suggestive of a pathological elevation. For this reason, Dr. Cohen was critical of the laboratory report for stating not simply that the elevated citrate synthase was evidence of mitochondrial proliferation, but that it may be an adaptive response. Tr. 1006-07. He explained that someone with a pathological elevation in citrate synthase will also have findings on histology such as ragged red fibers, ragged blue fibers, or COX-negative fibers.[121] Tr. 463. In I.R.'s case, these findings were lacking. Id.; Pet. Ex. 21 at 2.

During the hearing, petitioners' counsel questioned Dr. Cohen regarding a paper titled "The in-depth evaluation of suspected mitochondrial disease," of which Dr. Cohen was a co-author. See Resp. Ex. H, Tab 8 (Haas). Counsel suggested that the paper contradicted Dr. Cohen's testimony because it stated that "[t]he presence of mitochondrial proliferation within myofibers is highly suggestive of a mitochondrial OXPHOS disorder." Tr. 1023; Resp. Ex. H, Tab 8 at 8. Consistent with Dr. Cohen's testimony, however, the very next sentence in the paper states that "[t]raditionally, this has been demonstrated as ragged-red fibers (RRF) seen on modified Gomori trichrome staining as red granular deposits of mitochondria in the subsarcolemmal space on the background of a varying degree of muscle fiber atrophy." Resp. Ex. H, Tab 8 at 8. Although ragged-red fibers are not expected in pediatric cases, Dr. Cohen opined that this type of finding would be expected in an individual with a mitochondrial DNA depletion disorder or a POLG disorder. Tr. 1026. In that regard, Dr. Cohen also stressed that the mtDNA depletion study conducted in I.R.'s case did not show any mtDNA depletion.[122] Resp. Ex. A at 7; Pet. Ex. 27 at 7.

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[120] Skin fibroblasts are a commonly used diagnostic tool, relied on for ETC analysis by 59% of specialists. Pet. Ex. 52 at 6. Nonetheless, there are concerns of low sensitivity in such testing. Id.

[121] Histology is "that department of anatomy which deals with the minute structure, composition, and function of the tissues." Dorland's at 863. Dr. Cohen explained the process as follows: "Well, you look at what the muscle looks like under the microscope. So, when they put it under the microscope, they cut the muscle in cross-section, they take thin sections, and they stain it. They stain it with stains like NADH stain. They stain it for ATP. They have three different pHs. They will stain it for Oil Red O, looking for oil droplets. They will do stains looking for glycogen. They will use something called a modified Gomori stain, looking for ragged red fibers; SDH stain, looking for ragged blue fibers; NADH stain; and something called cytochrome c oxidase, or COX stain." Tr. 462-63.

[122] Specifically, the report concluded that "[t]he mitochondrial DNA content in this individual's specimen is approximately 102% of the mean value of the age and tissue matched controls. In patients with mitochondrial depletion syndrome, 2-18% and 6-50% of control mtDNA content have been observed in liver and muscle, respectively. The mtDNA content of this individual is

In addition to elevated citrate synthase, Dr. Zimmerman also cited a finding of accumulations of enlarged mitochondria as evidence of a mitochondrial disorder. Tr. 693-94. Specifically, the laboratory noted that "[e]lectron microscopy showed several accumulations of intermyofibrillar enlarged mitochondria. However, there were no crystalloid inclusions." Pet. Ex. 21 at 2. Like the elevated citrate synthase, Dr. Zimmerman opined that this is evidence of a compensatory response.[123] Tr. 695.

Dr. Cohen explained, however, that the significance of the finding is unknown. Tr. 983-85. Dr. Cohen noted that enlarged mitochondria is an abnormal finding, but not necessarily a finding indicative of a mitochondrial disorder. Tr. 1029. Additionally, Dr. Cohen explained that in mitochondrial diseases, accumulations of abnormal mitochondria are seen in the subsarcolemmal region and have crystalloid inclusions. Tr. 984; Resp. Ex. A at 6. This is not consistent with the findings in I.R.'s case. See Pet. Ex. 21 at 2. Dr. Cohen indicated that muscle biopsies sometimes show large or abnormal mitochondria in the intermuscular fiber, such as in this case, but that the significance of such findings is unknown and of less concern than findings related to the subsarcolemmal region. Tr. 985. Given the location and nature of the accumulations seen in I.R.'s biopsy, he disagreed that the results provided evidence of mitochondrial proliferation or that the result accords with the finding of elevated citrate synthase. Tr. 1008-09. He also stressed that the biopsy results overall are normal. Id.

d. Seahorse Assay

On April 1, 2013, and April 15, 2014, Dr. Frye ran stress tests and mitochondrial stress tests on I.R. Pet. Ex. 90 at 3-4, 7-8. The results were presented to Mrs. Reed in letter format and include reference ranges for both typical and autistic subjects. Id. at 3-6. Dr. Frye indicated in summary of the April 1, 2013 results that the results "may show a reduction in reserve capacity when exposed to oxidative stress." Id. at 6. For the April 15, 2014 results, Dr. Frye indicated that the mitochondrial stress results show "a normal or compensatory mitochondrial response," but opined in conclusion that the results indicate a potential adaptive response. Id. at 8, 10. However, no numerical test result was provided for either test, only Dr. Frye's finding of results that were "high," "low," or "within range," with a corresponding bar graph.

These reports contain no explanation of the methodology used in these tests, or of how the reference ranges were established. Dr. Frye included disclaimers in his letters indicating that the results were for a research study that "has not been validated in the clinical population." Pet. Ex. 90 at 8. He warned that the results "are based on limited and unpublished data." Id. Dr.

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not within the range observed in patients with proven mutations in genes responsible for mtDNA depletion syndrome. We cannot confirm the presence of mtDNA depletion syndrome in this patient. Clinical correlation and genetic counseling are recommended." Pet. Ex. 27 at 7.

[123] Dr. Zimmerman referenced his own currently unpublished studies. Tr. 694-95. He indicated that he hopes to replicate the study to demonstrate that mitochondrial dysfunction stimulates the replication and proliferation of mitochondria. Id. These studies did not analyze the mitochondria under a microscope to determine the size of mitochondria, but precipitated the mitochondria into a mass, stained them, and analyzed them for overall numbers. Tr. 695.

Frye also cautioned that "[e]ven though these test batteries were designed carefully, certain limitations involved in their use should be considered. These tests are not meant to diagnose, prevent, or cure any diseases or disorder – mental or physical." Id. at 10. The referenced limitations were not disclosed. Significantly, Dr. Frye himself did not include these seahorse assay results in his own report opining on I.R.'s mitochondrial disorder diagnosis. Pet. Ex. 174 at 14-20.

With regard to the mitochondrial stress tests, Dr. Zimmerman characterized them as a "seahorse assay."[124] Tr. 744-45. Notwithstanding the above, Dr. Zimmerman opined that these results were compelling. Tr. 774. Dr. Zimmerman described such tests as measures of mitochondrial reserve capacity generated by applying mitochondrial poisons. Tr. 744-45. He described the results in I.R.'s case as consistent with what he has seen in other autistic children and demonstrating reduced mitochondrial reserve capacity when I.R.'s mitochondria were challenged. Tr. 745. Dr. Zimmerman indicated that he is familiar with seahorse assays and opined that they are accepted in the metabolic medicine community. Tr. 745. Significantly, however, he acknowledged that he has not used them personally, and that he is neither an expert in mitochondrial disorders nor a metabolic specialist. Tr. 745, 777.

Dr. Cohen testified, however, that the seahorse assay has significant limitations. Tr. 494-95, 1001-03. He indicated that the tests experience oxygen leak, which creates many errors or "data noise," and that the test must be repeated to verify the data. Tr. 494-95, 1001-03. With regard to the specific test run by Dr. Frye on I.R., Dr. Cohen indicated that he could not opine on the results. Tr. 1033. Though he agreed that the test appeared to be a seahorse assay, he could not confirm it. Tr. 989-90. Dr. Cohen indicated that the way in which the results were provided leaves the methodology unclear. Id. He indicated that it is not a type of study typically used among his patients. Tr. 1033.

Particularly in light of Dr. Frye's own disclaimers accompanying the test results, the undersigned does not find sufficient indicia of reliability to credit the seahorse assay results cited by Dr. Zimmerman or any of the stress test results included in Dr. Frye's April 1, 2013 and April 15, 2014 test results. Moreover, even assuming arguendo that such test results are themselves accepted as valid by the relevant scientific community, as Dr. Zimmerman suggested, the undersigned does not find preponderant evidence that these results are utilized in a diagnostic capacity. Significantly, they are not discussed in any of the diagnostic criteria cited in this case or in the mitochondrial medicine consensus statement cited by petitioners.[125]

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[124] A 2014 PLOS One article filed in this case describes the "seahorse assay" as a test using "the state-of-the-art Seahorse Extracellular Flux (XF) 96 Analyzer . . . to measure the oxygen consumption rate (OCR), an indicator of mitochondrial respiration, and the extracellular acidification rate (ECAR), an indicator of glycolysis . . . ." Pet. Ex. 55 (Rose) at 2. Dr. Cohen noted that PLOS One specializes in presenting first pass or more preliminary data. Tr. 496-97, 1001-03.

[125] To the extent the seahorse assay was characterized in 2014 as "state-of-the-art" (see supra note 123), the undersigned recognizes that the published diagnostic criteria discussed in this case were all published in 2006 and earlier.

e. Folate-Blocking Antibodies

During the hearing, Dr. Zimmerman opined that the finding of folate receptor antibodies provides some support for the presence of mitochondrial dysfunction. Tr. 693. The undersigned does not find this assertion persuasive.

When Dr. Zimmerman evaluated I.R., he noted that I.R. "has had a complex history with immune deficiency and possible mitochondrial dysfunction, as well as apparent folate deficiency in the presence of folate receptor blocking antibodies." Pet. Ex. 20 at 1. Describing I.R.'s history, Dr. Zimmerman indicated that "[f]olate receptor blocking antibodies were detected peripherally with folate levels being normal in the presence of folate supplementation." Id. Dr. Zimmerman posited that because folate is essential to mitochondrial function, folate receptor antibodies would be an indicator that increased levels of folate are needed to overcome the antibodies. Tr. 692-93.

However, that opinion is based on speculation. Experts for both parties testified that although folate is involved in mitochondrial function, the causality or significance of a finding of folate receptor blocking antibodies in a mitochondrial disorder patient is unknown. Tr. 692, 989, 1031. In particular, when asked the significance of the folate receptor antibody finding, Dr. Zimmerman himself replied that "[t]his isn't entirely clear yet." Tr. 692. He indicated that "at this point we don't exactly understand the nature of those antibodies, where they come from, when they arise, or why." Id.

f. Clinical Phenotype

In addition to the above biochemical and muscle biopsy results, petitioners also allege a clinical phenotype consistent with a mitochondrial disorder, including fatigue, waxing and waning energy, exercise intolerance, muscle weakness, hypotonia, neurodegeneration (developmental delay and loss of skills), and immunodeficiency. For the reasons described below, the undersigned is not persuaded that these findings support a mitochondrial disorder diagnosis.

1. Fatigue, Waxing and Waning Energy, and Exercise Intolerance

In his expert report and testimony, Dr. Niyazov cited fatigue, waxing and waning energy, and exercise intolerance, as evidence contributing to a mitochondrial disorder diagnosis for I.R. Pet. Ex. 39 at 4. In that regard, petitioners cite several specific medical record notes, which they argue are suggestive of fatigue or exercise intolerance consistent with a mitochondrial disorder. Pet. Posthr'g Br. at 100 (citing Pet. Ex. 80 at 190; Pet. Ex. 79 at 7, 16, 20, 45).

Among the records cited by petitioners, most are reports of I.R. being tired during occupational therapy sessions. Petitioners cite four dates on which such notations were made. Specifically, on October 25, 2011, an occupational therapy progress note states that "[I.R.] expressed being quite tired today. He had a snack with him that he ate/drank and then participated fully in the session." Id. at 20. Close to two months later, on December 13, 2011, the occupational therapist wrote: "[I.R.] appeared to be quite tired today. He did however appear

to attend well to therapy activities." Id. at 16. A further note on January 10, 2012 stated "very tired today." Id. at 45. On August 28, 2012, occupational therapy notes indicated "[reduced][126] endurance noted today. Struggled with organizational skills. [I.R.] displayed frustration when he was unable to use L + R sides of his body efficiently to complete a pinball type activity." Id. at 7.

Upon the undersigned's review, these notations of tiredness appear to be isolated and are not diagnostic. I.R. attended occupational therapy from October 2011 to October 2012. Although he attended 17 sessions, tiredness is only referenced in four entries with spans of up to eight months between reports of tiredness. Pet. Ex. 79 at 1-22. In all but the August 28, 2012 notation, I.R.'s tiredness is not noted to interfere with or limit his therapies.[127] Moreover, there are other instances where I.R. is noted to perform gross motor therapy in a gymnasium and complete obstacle courses without any references to fatigue. Additionally, fatigue is not discussed in either his initial occupational therapy evaluation or his discharge. Id. at 1, 22. Nor is it ever referenced or addressed as an ongoing concern.

Additionally, there are parental reports in the medical records where Mrs. Reed indicates that I.R. experienced fatigue. For example, in 2009, Mrs. Reed provided a history to Dr. Natowicz which indicated that I.R. was "irritable and fatigued" at about 18 months following his period of illnesses between 12 and 15 months of age. Pet. Ex. 25 at 110. In 2013, Mrs. Reed reported to Dr. Frye that I.R. "fatigues easily." Pet. Ex. 80 at 190. In the same record, Dr. Frye records "exercise intolerance." Id. There is no indication, however, that this notation was inspired by anything other than Mrs. Reed's report. I.R.'s medical records do not suggest that any type of exercise intolerance evaluation was completed. Moreover, other medical records include notations indicating normal energy levels. For example, in November 2012, Mrs. Reed provided a history which indicated that "[I.R.] has a normal energy level and will play until he is exhausted and his mother makes him take a break. He participates in multiple sports including basketball and football." Pet. Ex. 85 at 41-42. Dr. McCandless testified that this is not consistent with the trajectory of a mitochondrial disorder. Tr. 397-98.

Dr. Cohen challenged the idea that what is described in I.R.'s medical records constitutes exercise intolerance in a mitochondrial disorder context. Tr. 480-81. He explained that the diagnostic criteria discuss exercise intolerance in the context of an overall mitochondrial disorder phenotype. Id. To be considered exercise intolerance, fatigue should be reported in conjunction with other related symptoms such as myopathy or neuropathy. Id. In that regard, the undersigned notes that the Walker Criteria lists exercise intolerance only in connection with

[126] The record includes a downward pointing arrow before the word endurance. The undersigned interprets that arrow as indicating low or reduced endurance.

[127] The undersigned notes that the word "tired" is ambiguous insofar as it is sometimes used in reference to physical fatigue and sometimes used in reference to drowsiness or sleepiness, which would not necessarily be relevant. Given the specific reference to endurance on August 28, 2012, it may be more likely that the therapist's references to being "tired" refer to sleepiness. In at least one instance it is explicit in the note that the observation of tiredness came before I.R. engaged in his therapy session and that he nonetheless participated fully. Pet. Ex. 79 at 20.

"weakness, wasting." Pet. Ex. 60 at 4, Table 2. The Nijmegen criteria cited by petitioners describes exercise intolerance as "a symptom characterized by abnormal, premature fatigue/weakness/muscle aches or cramps after normal play or activities of daily living." Pet. Ex. 129 at 1. No evidence suggests that I.R. was having muscle aches or cramps in conjunction with reported tiredness or fatigue. Nor is there any evidence that he suffered weakness and wasting.[128] In 2014, an autism evaluation noted that I.R. was at that time in the 99th percentile for height and weight. Pet. Ex. 80 at 13.

To the extent Dr. Niyazov suggested that I.R.'s energy might have waxed and waned, he discussed this in the context of mitochondrial disorder patients responding to stress events, such as illness or overexertion. Tr. 256-57. For his part, Dr. Cohen indicated that waxing and waning typically refers to the expected downward course for a mitochondrial disorder patient whereby periods of decline will be punctuated by periods of stability or improvement. Tr. 507. He opined that this is not demonstrated in I.R.'s medical records. Id. Even accepting Dr. Niyazov's interpretation, the reports of fatigue in I.R.'s medical records are not sufficiently linked to stress events to conclude that the reports are explained by waxing and waning energy. In that regard, Dr. McCandless additionally stressed that, without more, fatigue is a non-specific finding. Tr. 380. Fatigue is found quite commonly in the general population, and the vast majority of people who are fatigued do not have a mitochondrial disorder. Id.

2. Muscle Weakness and Hypotonia

Dr. Niyazov also cited muscle weakness and hypotonia in support of his opinion. Pet. Ex. 39 at 4. Although the medical records do not reference muscle weakness, they do mention hypotonia.[129] In 2009, Dr. Natowicz noted "mild diffuse hypotonia." Pet. Ex. 25 at 114. In 2010, Dr. Zimmerman noted "mild proximal hypotonia with prominent lumbar lordosis." Pet. Ex. 20 at 2. In 2014, an autism evaluation noted "mild appendicular hypotonia and slightly decreased but symmetric reflexes." Pet. Ex. 80 at 13.

In prior cases, experts have been careful to distinguish hypotonia from muscle weakness. See, e.g., Miller v. Sec'y of Health & Human Servs., No. 02-235, 2015 WL 5456093, at *32-33 (Spec. Mstr. Fed. Cl. Aug. 18, 2015) (describing muscle tone as the state of an engine at idle and muscle strength as a measure of a car's horsepower). Prior cases have also distinguished between brain-based and muscle-based hypotonia, asserting that only the latter is associated with mitochondrial disorders. See Holt v. Sec'y of Health & Human Servs., No. 05-236, 2015 WL 4381588, at *68 (Fed. Cl. Spec. Mstr. June 24, 2015), mot. for rev. denied, 132 Fed. Cl. 194.

[128] Wasting is defined as "gradual loss" or "emaciation." Dorland's at 2075.

[129] In their post-hearing brief, petitioners cited two medical records that they indicate reflect muscle weakness. Pet. Posthr'g Br. at 100. These are a page from a neuropsychological evaluation that referenced "a very weak grip" on a pencil (Pet. Ex. 24 at 19), and an occupational therapy progress note that notes that I.R. "continues to struggle with grading the speed, timing, and force of many motor movements" (Pet. Ex. 79 at 19). Upon the undersigned's review, neither of these records reflect an assessment of I.R.'s muscle strength.

In this case, however, although Dr. Niyazov included hypotonia among the findings supporting his conclusion, he never described the nature of I.R.'s reported hypotonia or the basis for his assertion that it supports a mitochondrial disorder diagnosis. Dr. McCandless opined in his expert report that there is no convincing documentation in I.R.'s medical records of "cardinal" signs of mitochondrial disorder, including "significant hypotonia," but did not further explain under what circumstances, if any, hypotonia could be considered diagnostic. Resp. Ex. F at 4. None of the experts in this case discussed hypotonia in any detail.

Hypotonia is a common feature among patients with mitochondrial disorders. See, e.g., Pet. Ex. 100 at 4 (noting that 79% of patients in one clinical group exhibited hypotonia). Nonetheless, it is not included among clinical features described as diagnostic under the Walker Criteria.[130] Pet. Ex. 60 at 4, Table 2. Hypotonia was added to the Modified Walker Criteria as a symptom compatible with a respiratory chain defect, but only in a neonatal context. Pet. Ex. 137. Similarly, the Nijmegen Criteria includes hypotonia as a diagnostic sign only up to age 6 months. Pet. Ex. 129. In this case, I.R.'s medical records do not reference hypotonia until 2009, when I.R. was five years old.

3. Neurodegeneration, including Ataxia, Developmental Delay, and Loss of Skills

Dr. Niyazov opined that I.R. demonstrated a pattern of regression (and then progression following treatment) that is more consistent with a mitochondrial disorder than with autism. Pet. Ex. 39 at 5; Tr. 223-24. Citing Wiggins, et al., Dr. Niyazov describes regression as "a documented loss of previously acquired skills in social, communication, play or motor areas." Pet. Ex. 39 at 5. He contrasted regression with plateau, which he described as "a flattening or leveling off of skills in the same developmental domains." Id. He cited ataxia and language deterioration as indicators of regression in I.R. Id. Dr. Zimmerman likewise opined that I.R. experienced an autistic regression following his immunizations, evidenced by postural unsteadiness and ataxia at 17 months followed by loss of language and social skills at 24 months of age.[131] Pet. Ex. 32 at 1.

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[130] Notably, Dr. Niyazov specifically cited hypotonia as supportive of a diagnosis using the Walker Criteria. Pet. Ex. 39 at 4.

[131] Another potential symptom of central nervous system involvement is seizures. See, e.g., Pet. Ex. 71 at 2. Although I.R. had an abnormal MRI, neither petitioners nor their experts have contended that I.R. had any seizure activity supportive of a mitochondrial disorder. Notwithstanding the abnormal EEG, Dr. Cohen disputed that I.R. had seizures. Tr. 476. This is consistent with a 2009 evaluation at the Cleveland Clinic, which concluded following a 72 hour EEG study that I.R. "does not have clinical seizures. His staring spells are most likely nonepileptic behavioral spells." Pet. Ex. 38 at 14. I.R.'s study including findings "typical for benign focal epileptiform discharges of childhood." Id. It was further noted that "'[t]his finding has known association with neurocognitive and developmental behavior difficulties in some children, however in case of [I.R.], the discharges are not pervasive enough in sleep to clearly suggest cause and effect relationship at this time." Id. Of note, seizures are also common among individuals with autism. Tr. 867-68. Twenty to thirty percent of individuals with autism will

i. The undersigned finds no preponderant evidence of language regression.

There is not preponderant evidence that I.R. experienced a language regression or that his autism can be characterized as regressive autism. Thus, to the extent Drs. Niyazov and Zimmerman base their opinion that I.R. suffered a mitochondrial disorder on the fact that I.R. had regressive autism or a language regression, those opinions are not supported by the record evidence. Dr. Niyazov, in particular, testified that I.R.'s condition is set apart from a typical autism presentation because his first year of life was neuro-typical, followed by a post-vaccination regression. Tr. 276. For all the reasons discussed in Section VI.A, the undersigned finds that this assertion is not supported by the record. In Section VI.A.i, the undersigned found that I.R.'s autism manifested prior to one year of age, and in Section VI.A.iii, the undersigned found that I.R. did not experience an autistic regression.

ii. The undersigned finds no preponderant evidence of ataxia.

Ataxia is a symptom consistent with mitochondrial disorders. See Pet. Ex. 60 at 4, Table 2. Moreover, I.R.'s medical records refer to instances of I.R. showing signs of unsteadiness in conjunction with illnesses. See, e.g., Pet. Ex. 15 at 17 (noting fever and unsteadiness at 10 months of age); Pet. Ex. 15 at 41 (noting "falling down- 'floppy today'" in context of fever, diarrhea, and vomiting at 17.5 months of age); Pet. Ex. 9 at 23 (noting at healthy 18 month well visit that I.R. is "less wobbly"); Pet. Ex. 25 at 114 (noting that I.R.'s "history is potentially notable for excessive clumsiness when ill"). However, respondent's experts persuasively opined that these notations are not representative of neurologic ataxia consistent with a mitochondrial disorder. Tr. 828-29; 459-60; 400-01.

Dr. Wiznitzer opined that I.R. did not have the ataxia claimed. With regard to videos from 2006 when I.R. was 1-2 years old, Dr. Wiznitzer noted that I.R. demonstrated good balance. Tr. 828-29. Significantly, these videos reflect the period of time during which I.R.'s ataxia was alleged to have occurred. See, e.g., Pet. Ex. 25 at 110 (report of noticeable decline in balance at 18 months of age). Dr. Wizntizer indicated that true ataxia for that age would include wobbliness even when sitting. Tr. 828-29. Dr. Wiznitzer opined that there is no evidence of I.R. having persistent ataxia as opposed to temporary ataxia related to fever or illness. Tr. 840-42. To the extent that I.R. had documented problems with motor coordination, Dr. Wiznitzer opined that I.R. had developmental coordination disorder, a condition associated with autism. Tr. 841-42; see also Pet. Ex. 154 (Blank) at 8 (stating that developmental coordination disorder is "so strongly associated" with autism that separate diagnoses of ASD and DCD are not allowed under DSM-IV).

In contrast, Dr. Cohen explained that ataxia in a mitochondrial disorder is persistent and worsens progressively over time, even if it includes periods of stabilization. Tr. 459-60. Like

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develop epilepsy by the time they reach adulthood. Id. Dr. Frye included seizures in his assessment. Pet. Ex. 174 at 19. He interpreted I.R.'s 2009 EEG from the Cleveland Clinic as being consistent with a subclinical seizure disorder. Pet. Ex. 25 at 134.

Dr. Wiznitzer, Dr. Cohen opined that I.R. did not have ataxia. He stressed that ataxia is a neurological term and that it is distinct from the type of wobbliness or stumbling that may occur when someone is ill. Tr. 506-07. Dr. McCandless offered similar testimony and further opined that I.R.'s contemporaneous records, including his baby book, demonstrate only temporary intermittent wobbliness consistent with the effects of being ill, rather than a permanent neurological condition. Tr. 400-01. In that regard, Dr. McCandless also stressed that I.R.'s pattern of illnesses included ear infections requiring the placement of ear tubes. Tr. 402. He noted that such significant ear infections can affect balance. Id.

Petitioners' own expert, Dr. Zimmerman, also agreed that true ataxia would persist. Tr. 776. He acknowledged that a child learning to walk may be unsteady during illness and that this would not be ataxia. Id. Dr. Zimmerman also acknowledged that toe walking, such as I.R. demonstrated, is common in autism and can cause an unsteady gait. Tr. 776-77.

Also of note, I.R. was seen by Dr. Natowicz in 2009 for an evaluation of a potential metabolic basis for I.R.'s ASD. Pet. Ex. 25 at 109-115. At that time, Dr. Natowicz recorded a history that included a report of a noticeable decline in I.R.'s balance at 18 months of age. Id. at 110. Additionally, Dr. Natowicz observed possible gross motor clumsiness during the physical exam. Id. at 113. However, he concluded that no ataxia was present. Id. Dr. Natowicz described the history of clumsiness as occurring in conjunction with illness and he characterized that history as "modest." Id. at 114. Though he noted that the history of increased clumsiness and fasting intolerance raised the possibility of a metabolic basis for I.R.'s condition, he also expressed significant doubt, cautioning that "these historical features are not certainties" and noting the lack of corroboration history or laboratory data to firmly support a metabolic etiology. Id. Dr. Frye likewise noted ataxia in I.R.'s history, but found no evidence of ataxia during the physical exam. Pet. Ex. 80 at 190-91.

iii. The undersigned finds no preponderant evidence of neurodegeneration.

Developmental delay is listed among the diagnostic criteria for both the Nijmegen and Morava Criteria. Pet. Ex. 129 at 1; Pet. Ex. 71 at 2. Moreover, to the extent autism is a syndrome describing a pattern of behaviors, Dr. McCandless indicated that it could be theoretically possible for a mitochondrial disorder to include autism-like symptoms. Tr. 351-52. He noted, however, that this would be controversial in the field of mitochondrial medicine. Id. Dr. Cohen likewise testified that a neurodegenerative injury could theoretically result in symptoms fitting the definition of autism. Tr. 510-11. Nonetheless, both experts opined that this is not what happened in I.R.'s case. Tr. 346-47, 510-11. The undersigned agrees.

Dr. McCandless opined he is not aware of typical autism by itself as the presenting feature in a patient with a mitochondrial disorder. Tr. 351-52. He further indicated that speech and language delay, particularly in isolation, would not be a typical presentation for a mitochondrial disorder. Tr. 352-53. Additionally, Dr. Cohen disputed that I.R. experienced a regression. Tr. 459. He noted that I.R.'s contemporaneous medical records show no language deterioration and that he continued to develop language, albeit with delay. Tr. 508-09. He also opined that the medical records do not show any evidence of neurological deterioration

following I.R.'s ProQuad vaccination. Tr. 509-10. Dr. McCandless likewise agreed that I.R. showed no signs of a true loss of previously achieved neurological development. Tr. 408-09.

Dr. Cohen further explained that I.R.'s history is not consistent with neurodegeneration. Tr. 476-77. He indicated that neurodegeneration in a mitochondrial disorder context would look like "a stepwise loss of cognitive function and skills over a period of time." Tr. 503. In that regard, Dr. McCandless similarly indicated that if a child had enough mitochondrial insufficiency to cause nerve cell dysfunction of the type alleged in this case, it is unlikely that they would be able to correct that defect in the future. Tr. 382-83.

Dr. Cohen explained that the type of neurodegeneration associated with mitochondrial disorders – mitochondrial encephalopathy – includes abrupt deterioration following a period of normal development. Tr. 466-67. Such degeneration typically is severe enough to include emergency hospitalization and is not of insidious onset. Tr. 467. Dr. Zimmerman acknowledged that I.R. did not experience any precipitous or abrupt regression. Tr. 753.

4. Immunodeficiency

Dr. Niyazov cited immunodeficiency among the factors he considered in opining that I.R. has a phenotype consistent with a mitochondrial disorder. Pet. Ex. 39 at 4. However, for the reasons described in Section VI.B.ii, the undersigned concluded that I.R. does not have an immunodeficiency. Moreover, notwithstanding Dr. Niyazov's and Dr. Zimmerman's discussions of the interplay between mitochondria and the immune system (Tr. 955-58, 688), no evidence supports the use of immune function as a diagnostic consideration for mitochondrial disorders.

Dr. Niyazov cited a review article titled "Powering the Immune System: Mitochondria in Immune Function and Deficiency." Pet. Ex. 191 (Walker). He summarized the article as demonstrating that mitochondrial dysfunction creates immune deficiency that increases susceptibility to infection. Tr. 957. That same article, however, characterized the available "data regarding immune dysfunction predisposition to infect in patients with diagnosed primary mitochondrial disorders" as "limited." Pet. Ex. 191 at 4-5. The article further noted that "immune dysfunction is not currently included in clinical diagnostic criteria for primary mitochondrial disorders" and concluded: "Current laboratory studies and clinical observations are expanding our understanding of mitochondrial function in both the innate and adaptive immune systems, as well as documenting immune dysfunction in disorders affecting the mitochondrion. Further investigation – both bench and clinical – is required to further our understanding of the role of this critical organelle in immunity." Pet. Ex. 191 at 3, 6. Dr. Zimmerman likewise acknowledged that "[t]he relationship of immune dysfunction to mitochondrial abnormalities . . . is not known . . . ." Pet. Ex. 34 at 1.

5. Gastrointestinal Symptoms

Petitioners cite chronic unexplained diarrhea as an indicator of a mitochondrial disorder. Pet. Posthr'g Br. at 100 (citing Pet. Ex. 25 at 138; Pet. Ex. 81 at 3-7; Pet. Ex. 80 at 190). This was not initially included in Dr. Niyazov's report; however, during the hearing he testified that

I.R.'s history of gastrointestinal concerns was diagnostic under the Nijmegen Criteria. Tr. 183-84; Pet. Ex. 129. Respondent's experts countered with their opinion that unexplained diarrhea is not sufficient to support a mitochondrial disorder diagnosis. Dr. Cohen indicated that the diagnostic criteria are not intended to include general gastrointestinal complaints. Tr. 464-65. Rather, the GI symptoms must be severe pseudo-obstructions that demonstrate improperly functioning bowels. Id.

In addition to acute or chronic hepatic dysfunction, failure to thrive, exocrine pancreatic dysfunction, and intestinal pseudo-obstruction, the Nijmegen Criteria checklist includes a line for "otherwise unexplained chronic diarrhea (>3 weeks)." Pet. Ex. 129 at 2. In contrast, the Walker and Modified Walker Criteria list only "gastro-intestinal dysmotility and/or malabsorption." Pet. Ex. 60 at 4, Table 2; Pet. Ex. 137. The Morava Criteria lists only gastrointestinal involvement without description. Pet. Ex. 71 at 2.

6. Classic Phenotypes

An additional significant point of contention is how much consideration to give the many clinical signs and symptoms of a mitochondrial disorder that I.R. does not meet. Petitioners argue, at least in part, that respondent's experts require too much confirmation. Specifically, citing testimony by Dr. Cohen, petitioners stated that they are "not contending that [I.R.] has a classic mitochondrial disease, thus it would not be expected that he fit the clinical phenotype of one." Pet. Posthr'g Br. at 107.

In that regard, Dr. Niyazov testified in reference to the Nijmegen Criteria: "Can I now point out that there is all these other things here, endocrine, heart, kidney, ears, nerve – that we don't have to satisfy all of them, because that's one of the criticism that, you know, people had, is that, oh, well, he doesn't have this system, he doesn't have that system and this system and that system, and the reason why we have these scoring systems is because precisely you cannot have – you don't have to have all those other things to be involved . . . ." Tr. 184-85. Dr. Niyazov opined that mitochondrial disorder can have a preferential impact on different tissues, including the brain. Tr. 253-54, 258-60.

Dr. McCandless and Dr. Cohen likewise testified that the symptoms of a mitochondrial disorder can be highly varied and can affect any tissue. Tr. 349-50, 1036-37. However, in contrast to petitioners' contention, they each opined that a mitochondrial disorder still occurs within a defined context, with multiple symptoms and certain cardinal findings. Tr. 349-50, 1036-37. Dr. McCandless identified those cardinal findings as central nervous system dysfunction, often with changes visible on MRI; sensory neural hearing loss; retinal disease; skeletal muscle myopathy; autonomic and peripheral nervous system involvement; cardiomyopathy; diabetes; and pancreatic dysfunction. Tr. 350. This is supported by literature filed in this case by petitioners. See, e.g., Pet. Ex. 42 (Chinnery) at 3 (noting that "[c]ommon clinical features of mitochondrial disease . . . include ptosis, external ophthalmoplegia, proximal myopathy and exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, and diabetes mellitus," and further noting that "[c]ommon central nervous system findings are fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity").

Dr. McCandless also opined that mitochondrial disorders have a clinical course characterized by a downward trajectory. Tr. 398-99. Noting that I.R. has seen improvement, he indicated that a marked clinical improvement would not be consistent with having a primary mitochondrial disorder. Id. To the extent that I.R. later received treatments for a mitochondrial disorder, Dr. McCandless testified that there is not sufficient literature to support the idea that antioxidant treatments are effective. Tr. 421-22. He opined that I.R.'s clinical improvement is more likely the result of speech and occupational therapies. Id. Indeed, I.R.'s medical records reflect that his autism symptoms had improved by the time of his March 2009 evaluation at four years and two months of age, at which point his diagnosis was changed from the more severe autistic disorder to PPD-NOS.[132] Pet. Ex. 24 at 13. Dr. Zimmerman additionally acknowledged that there is no good data available regarding outcomes for autism patients treated with mitochondrial disorder treatments. Tr. 697-98.

Dr. Cohen likewise opined that Dr. Niyazov misapplied the clinical phenotype criteria. Tr. 480-81. Although Dr. Cohen acknowledged that there can be heterogeneity in presentation, he indicated that the findings cited by Dr. Niyazov need to be present in the context of an overall mitochondrial disease phenotype. Id.; Tr. 1034-37. Such a phenotype would include other symptoms such as myopathy or neuropathy. Tr. 480-81. In I.R.'s case, his symptoms are more compatible with autism. Dr. Cohen opined that to conclude I.R. had a mitochondrial disorder, he would need to see a concordance of data, including biochemical data indicative of an electron transport chain abnormality, genetic data, and a pattern of symptoms consistent with a described clinical phenotype. Tr. 1034-37. He suggested that even a perfectly healthy person would demonstrate some abnormal findings if enough tests were run. Tr. 1035-36.

While it is true that mitochondrial disorders have high variability in presentation, and not all diagnoses will fit neatly into an established phenotype, petitioners' argument that I.R.'s phenotype presentation is effectively "non-classic" is not persuasive. Although I.R. seemingly has some mild clinical features potentially consistent with a mitochondrial disorder, the various diagnostic criteria cited by petitioners are designed to limit the diagnostic significance of such features in the absence of other factors. Significant in that regard, Dr. Niyazov testified that he views a probable or definite diagnosis pursuant to the established diagnostic criteria as a threshold for pursuing treatment of a suspected mitochondrial disorder. Tr. 196-97. Yet, based on the above analysis, the undersigned does not find that I.R. meets that threshold.

Under the Walker and Modified Walker Criteria, symptoms falling short of complete respiratory chain encephalomyopathy or mitochondrial cytopathy but compatible with a respiratory chain defect are counted only as a minor diagnostic criteria. Pet. Ex. 60 at 5, Table 4; Pet. Ex. 137. Thus, under that scoring system, these symptoms must be accompanied, as Dr. Cohen alluded, by additional criteria such as a mutation of probable pathogenicity or one or more metabolic indicators of impaired metabolic function. However, for the reasons described above, the undersigned finds these factors lacking. Similarly, the Nijmegen Criteria limits the categories related to clinical symptoms (i.e., muscular signs and symptoms, CNS signs and symptoms, and multisystemic involvement) to a total of seven out of twelve points. Pet. Ex. 129.

[132] Dr. Niyazov conceded as a factual matter that I.R. began to improve even before he began treatment for his alleged mitochondrial disorder. Tr. 283.

This means that even in a case with far more severe clinical signs, a clinical diagnosis limited to the clinical categories can be "probable" at best. Id. In this case, however, petitioners only allege five points for clinical features, the minimum for a probable diagnosis, and respondent's experts have cast significant doubt on many of the features petitioners include in their scoring. Id. Thus, I.R. can only be considered to have at best a "possible" diagnosis under the Nijmegen Criteria. Id.

As open-ended and subjective as these diagnostic criteria are, they are still intended in force and effect to reflect parameters for what can and cannot be considered a valid mitochondrial disorder diagnosis.[133] To the extent that petitioners would seek to circumvent those types of parameters by claiming they are alleging something other than a "classic" phenotype, such a claim would be based on the ipse dixit of their experts alone and would therefore not be persuasive. A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." Moberly, 592 F.3d at 1324.

The undersigned notes that several references in the literature filed in this case suggest that clinical diagnosis of a mitochondrial disorder is extremely difficult and often rests in the judgment of the individual clinician. The attempted consensus statement for mitochondrial medicine by Parikh, et al., makes particularly clear that the weight afforded to different test results and different published diagnostic criteria varies greatly from clinician to clinician and that at this juncture, the mitochondrial medicine community lacks either the will or the ability to achieve greater consensus. See Pet. Ex. 52 at 7 ("Similarities exist in diagnostic approaches used. However determination of a primary mitochondrial disease diagnosis without genetic confirmation, extent of testing sent in muscle and interpretation of biochemical results remain disparate."). Dr. McCandless has noted there is no "gold standard" for diagnosis. Resp. Ex. F at 5.

However, as has been noted in a prior case, "the lack of an agreed upon 'gold standard' is not the same as having no standard at all." R.K., 2015 WL 10936124, at *43. In R.K., petitioner's mitochondrial expert initially opined that her diagnostic opinion was based on the Bernier Criteria, before later criticizing the diagnostic criteria and admitting that mitochondrial disorder diagnosis "is as much an art as it is a science." Id. at 42. The special master in that case rejected that approach as suggesting "that there are no credible or limiting diagnostic standards whatsoever" and held that the credibility and persuasiveness of the expert's diagnosis must be assessed in the context of her application of diagnostic criteria such as the Bernier criteria,

[133] Notably, the experts on both sides, as well as the literature filed in this case, all indicate that clinical diagnosis of a mitochondrial disorder is subjective to a significant degree. Tr. 189-90, 526-27. In that regard, each party's experts charge the other party's experts with a biased interpretation of the data. See, e.g., Pet. Ex. 39 at 6 (Dr. Niyazov suggesting that Dr. Cohen "relies on his own experience" in preference to "the diagnostic criteria accepted by the vast majority of mitochondrial experts"); Resp. Ex. F at 6 (Dr. McCandless asserting that Dr. Niyazov relies "on a biased interpretation of the clinical history"). The undersigned finds Drs. McCandless and Cohen's testimony and opinions more persuasive regarding the correct interpretation of the biochemical results and clinical symptoms.

which, while not rising to the level of "gold standard," are nonetheless generally recognized as valid tools in the relevant scientific community. Id. at 43.

The undersigned notes that diagnosis of a mitochondrial disorder is not as simple as rigidly applying one or more of the published diagnostic criteria. But where, as here, application of the diagnostic criteria leaves suspicion of a mitochondrial disorder very low and consensus in the relevant field is otherwise lacking, it is unclear on what basis petitioners' experts could reliably or credibly opine that a mitochondrial disorder is present.

7. Opinions of Treating Physicians

In addition to the expert analysis addressed above, I.R. was evaluated for a potential mitochondrial disorder by multiple treating physicians. Often, treating physician opinions are given considerable weight. See, e.g., Capizzano v. HHS, 440 F.3d 1317, 1326 (Fed. Cir. 2006) (noting that "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'"). In this case, however, they do not provide additional support for petitioners' claim.

I.R. was first evaluated for a possible mitochondrial disorder on November 16, 2009, by Dr. Marvin Natowicz, a geneticist at the Cleveland Clinic. Pet. Ex. 25 at 109-115. Based on a complete review of I.R.'s history, Dr. Natowicz concluded that "[I.R.]'s clinical history and exam do not immediately suggest an underlying etiological basis for his ASD." Id. at 114. Dr. Natowicz noted a reported history of increased clumsiness and possible fasting intolerance, but stressed that "there is no other history information or lab test data that strongly support the possibility of an underlying metabolic etiology." Id.

Dr. Natowicz indicated that blood lactate, pyruvate, and plasma acylcarnitine profiles were all unremarkable. Pet. Ex. 25 at 114-15. He further noted unremarkable results on urinalysis and observed that "a plasma amino acid analysis showed a mildly increased plasma glycine level and a relative increase of plasma alanine, although the absolute level of alanine was normal." Id. at 115. He further indicated that the increased plasma glycine is unlikely to be of clinical significance, since I.R. had been receiving dimethyl glycine. Id.

Dr. Natowicz indicated that these results "make unlikely a number of considerations," including "many organic acidemias and mitochondrial cytopathies . . . ." Pet. Ex. 25 at 115. Nonetheless, despite concluding there was not sufficient medical evidence to support a mitochondrial disorder diagnosis, he recommended "casting a relatively wide 'diagnostic net' to screen for a number of potentially relevant metabolic etiologies or risk factors for ASD . . . ." Id. at 114.

Subsequently, I.R. was evaluated by Dr. Richard Frye. I.R. was first seen by Dr. Frye in September of 2009. Pet. Ex. 25 at 132. Initially, Dr. Frye noted that a mitochondrial disorder had been ruled out by the Cleveland Clinic. Id. However, he subsequently re-evaluted I.R. after additional tests had been performed. Pet. Ex. 174 at 14-20. Based on many of the same considerations as discussed by the testifying experts in this case, including lactate, pyruvate, and alanine/lysine measures, as well as accumulation of enlarged mitochondria, POLG mutation, and

clinical signs including ataxia and exercise intolerance, Dr. Frye diagnosed I.R. as having a mitochondrial disorder by applying the Morava and Modified Walker criteria. Id.

Although a treating physician's opinion is often given significant weight, to the extent that Dr. Frye relied on the same findings and rationales as Drs. Niyazov and Zimmerman, his report suffers the same limitations. "The reasoning underlying the finding that opinions of treating physicians should be given particular weight does not apply when, as here, the treating physician only saw the patient after the injury and based his opinion on the same evidence as relied upon by the retained experts."[134] Nuttall v. Sec'y of Health & Human Servs., 122 Fed Cl. 821, 832 (2015); see also Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 745 n.67 (2009) (emphasizing that a statement of a treating physician is not "sacrosanct" and can be rebutted).

Additionally, the undersigned notes that Dr. Frye's medical opinions have come before the Office of Special Masters in the past, both as a testifying expert and as treating physician. In both capacities, his judgment has been called into question, and even specifically criticized for misapplying the same mitochondrial disorder criteria he applied to I.R. See, e.g., Bast v. Sec'y of Health & Human Servs., No. 01-565, 2012 WL 6858040, at *25 (Fed. Cl. Spec. Mstr. Dec. 20, 2012) ("Dr. Frye offered a theory of causation that turned on a finding of mitochondrial dysfunction. But he did not properly apply the diagnostic criteria set forth in the 2002 Bernier article . . . ."), mot. for rev. denied, 117 Fed. Cl. 104 (2014); R.V. v. Sec'y of Health & Human Servs., No. 08-504, 2016 WL 3882519, at *8, 33 (Fed. Cl. Spec. Mstr. Feb. 19, 2016) (noting that "[i]n spite of such generally inconclusive data, . . . Dr. Frye diagnosed L.V. . . . with a mitochondrial disorder," and noting further that "[n]either expert accepted Dr. Frye's diagnosis that L.V. had a 'definite' mitochondrial disease under the Morava Criteria"), mot. for rev. denied, 127 Fed. Cl. 136 (2016); T.M. v. Sec'y of Health & Human Servs., No. 08-284, 2016 WL 11087157, at *24 (Fed. Cl. Spec. Mstr. Aug. 9, 2016) ("[T]he evidence does not support Dr. Frye's cerebral folate deficiency diagnosis. A.P.M.'s MTHF levels were unquestionably within a normal range. In addition, and as Dr. Frye himself admitted, other than autism A.P.M. displayed none of the symptoms that would otherwise characterize infant-onset cerebral folate deficiency. Even Dr. Shafrir could not accept Dr. Frye's diagnosis—a telling admission for a testifying expert.").[135]

Some medical records also suggest that other practitioners have reviewed I.R.'s reported history and metabolic status. For example, in a letter report dated June 8, 2011, Dr. Barbara Kirschner, a pediatrician specializing in pediatric inflammatory bowel disease, noted that she had

[134] The undersigned also notes that petitioners' experts, Drs. Niyazov and Zimmerman, did evaluate I.R. in person. Tr. 115, 688-90. However, the undersigned's findings are based in significant part on objective data as well as I.R.'s clinical course prior to those evaluations.

[135] Dr. Zimmerman testified that Dr. Frye is "very reputable" in the fields of autism and metabolic studies. Tr. 743. Dr. Wiznitzer characterized Dr. Frye's views on autism and mitochondrial dysfunction as "outlier" views in the pediatric neurology community. Tr. 868. Dr. Cohen likewise indicated that Dr. Frye's views on autism and mitochondrial dysfunction are not generally accepted in the mitochondrial medicine community. Tr. 1003.

conferred with a colleague in pediatric neurology, Dr. Kenneth Silver, and that he agreed there are sufficient findings "to consider a mitochondrial process." Pet. Ex. 81 at 3-5. Dr. Richard Kelly was consulted in this case and provided at least some test results. Pet. Ex. 33 at 1; Pet. Ex. 74. Additional records show certain practitioners relying on prior reports of I.R. having a mitochondrial disorder without separately confirming the diagnosis. For example, in November 2012, I.R. was seen for an evaluation of "cardiac disease associated with mitochondrial complex 1 deficiency." Pet. Ex. 85 at 41-44. The pediatric cardiology team took a history that included a prior history of mitochondrial encephalopathy but did not independently confirm the diagnosis. They performed an EKG and physical exam and concluded that "[i]t is our impression that [I.R.] has a mitochondrial disorder that increases his risk of developing cardiomyopathy. However, his physical exam, ECG, and echocardiogram today are all normal. As such we see no indication for any medical intervention at this time and we recommend continued surveillance."[136] Id. at 43. An endocrinologist, Dr. Miller, similarly referenced and relied on the prior diagnosis. Pet. Ex. 81 at 21-26.

However, none of these additional providers completed metabolic evaluations comparable in scope to Drs. Natowicz and Frye. Nor have they provided opinions as detailed as those of the relevant experts in this case. In some instances, such as that of Dr. Silver's reported opinion, the result of the assessment is reported only by a third party. Thus, upon review of the complete records, the undersigned does not find significant evidence in I.R.'s medical records further supporting or corroborating the opinions of Drs. Natowicz or Frye.

8. Primary Mitochondrial Disorder versus Secondary Mitochondrial Disorder

Despite the fact that petitioners' experts have opined that I.R. meets the diagnostic criteria for a mitochondrial disease or disorder, petitioners argue that they "are not contending that [I.R.] has a 'well-described,' or classic, mitochondrial disease, thus it would not be expected that [I.R.] would fit the clinical phenotype of one." Pet. Reply Posthr'g Br. at 25. Additionally, petitioners have repeatedly referred to I.R. as having a "mitochondrial disease or dysfunction." Id. (emphasis added). This raises the question of whether a lesser level of evidence might support the presence of mitochondrial dysfunction short of a diagnosed disorder.

Dr. McCandless indicated that no well-established definitions in the mitochondrial medicine community separate mitochondrial disease or disorder on the one hand and mitochondrial dysfunction on the other. Tr. 348-49, 432-33. He indicated that his understanding would be that the term dysfunction is used to refer to abnormal respiratory function as evidenced by laboratory tests measuring respiratory chain function in particular, or in some cases clinical findings attributed to abnormal respiratory chain function. Tr. 349. He noted that disease or disorder is typically reserved for reference to individuals who have a pattern of symptoms that are explained by an underlying dysfunction of the mitochondria. Id. Mitochondrial dysfunction

[136] The undersigned notes that these are examples only. Many of I.R.'s later medical records make mention of I.R.'s reported mitochondrial disorder diagnosis.

itself may or may not be the cause of any symptoms and may or may not ultimately be caused by a respiratory chain defect.[137] Tr. 348-49, 432-35.

Dr. Niyazov similarly indicated that "I personally strongly believe that environmental conditions and the genetic makeup, that is nonmitochondrial genetic makeup, makes a lot of difference when it comes to primary mitochondrial disease, and I am also a firm believer in secondary mitochondrial – and I would call it dysfunction – because mitochondria are intimately tied to so many different other things, that if it's something that is not related to mitochondria, it may affect the mitochondria secondarily." Tr. 113-114.

Although the undersigned does not find preponderant evidence of a mitochondrial disorder, a remaining factual issue is whether the evidence in this case is sufficient to characterize I.R. as having any mitochondrial dysfunction at all. This distinction has been explored in depth in prior cases. See, e.g., Holt, 2015 WL 4381588, at *22-23. In this case, Drs. Cohen and McCandless both opined that I.R.'s medical history does not indicate any mitochondrial dysfunction. Tr. 435-36, 1068. That is, they asserted that based on the sum of evidence, it is more likely than not that I.R.'s mitochondria function normally. Resp. Ex. F at 5; Tr. 1068. The undersigned agrees.

Significantly, the record evidence suggests that there is not any agreed upon threshold for determining when isolated findings consistent with mitochondrial dysfunction rise to the level of demonstrating with any medical probability that such dysfunction actually exists. Indeed, the consensus statement from the Mitochondrial Medicine Society repeatedly warns against taking particular findings in isolation due to the limitations of different testing methods. Pet. Ex. 105 at 3 ("Caution must be taken to not overinterpret small elevations in postprandial lactate."); Pet. Ex. 105 at 4 ("mtDNA proliferation is a nonspecific compensatory finding that can be seen in mitochondrial disease, secondary mitochondrial dysfunction, myopathy, hypotonia, and as a by-product of regular, intense exercise."); Pet. Ex. 105 at 6 ("Biochemical testing in tissue does not always differentiate between primary mitochondrial disease and secondary mitochondrial dysfunction."); Pet. Ex. 105 at 6 ("ETC findings should not be used as the sole criterion for excluding mitochondrial dysfunction.").

Moreover, the Mitochondrial Medicine Society specifically instructs that "[i]nterpretation of mitochondrial biochemical testing results is aided by utilizing established diagnostic criteria to

[137] Dr. McCandless further explained that a mitochondrial disease or disorder would typically be referred to as a primary mitochondrial disorder or disease, because the mitochondrial dysfunction is the primary cause or explanation for the condition. Tr. 432-35. Where mitochondrial dysfunction is the result of some other process, it is referred to as being secondary. Id. For his part, Dr. Cohen agreed with Dr. McCandless's description. Tr. 455-56. In addition, he analogized the distinction between a primary and secondary mitochondrial disorder to the problems one might encounter with a car engine. Tr. 455. By analogy, a primary mitochondrial disorder would be an engine malfunction caused by a problem with the parts of the engine itself – for example, a broken gasket, piston, or spark plug. Id. A secondary mitochondrial disorder would be an external problem resulting in an engine malfunction, such as throwing sugar in the gas tank. Id.

avoid mitochondrial dysfunction being identified in a subjective fashion and interphysician variability in diagnoses provided." Pet. Ex. 105 at 6. In that regard, although mitochondrial disease and mitochondrial dysfunction are not synonymous or coextensive, the record evidence suggests that mitochondrial dysfunction is likewise best assessed within the context of diagnostic criteria for a disease or disorder.

Indeed, while the diagnostic criteria scoring is geared toward identifying disorders, the diagnostic criteria arose precisely due to the difficulty in developing consensus around what evidence suggests mitochondrial dysfunction. For example, the Wolf authors noted that their motivation in developing the Nijmegen Criteria was due in part to the fact that "difficulties arise from the lack of agreement on optimal biochemical assays and cut-off values and from the common occurrence of secondary abnormalities in respiratory chain function. These difficulties complicate the identification of children with respiratory chain disorders, investigations of possible underlying gene defects, and the establishment of correct incidence data." Pet. Ex. 62 at 1.

In that regard, Parikh, et al., explained:

> Diagnosing primary mitochondrial disease remains challenging. Recent advances in genomics have allowed for an increased ability to diagnose primary mitochondrial disease. Despite this recent progress, many patients are still only found to have biochemical abnormalities suggesting mitochondrial dysfunction without a definitive genetic etiology identified. Diagnostic criteria that allow for a diagnostic prioritization of "possible," "probable," or "definite" diagnosis exist (Bernier et al., 2002; Morava et al., 2006; Wolf and Smeitink, 2002), though they are heavily weighted towards mitochondrial biochemical abnormalities being identified in muscle. However, for most patients, and despite extensive testing, a genetic diagnosis is not attained. Most clinicians combine the clinical phenotype, biochemical abnormalities seen on testing and their professional opinion to reach a mitochondrial disease diagnosis.

Pet. Ex. 52 at 7.

Thus, the undersigned is not persuaded that isolated findings in I.R.'s medical history can be selectively cited to indicate the presence of mitochondrial dysfunction. Rather, the undersigned finds that Drs. Cohen and McCandless have more persuasively integrated "the clinical phenotype, biochemical abnormalities seen on testing and their professional opinion" to conclude that I.R. does not have mitochondrial dysfunction. Notwithstanding that some findings may arguably constitute evidence of mitochondrial dysfunction when taken in isolation, the totality of medical evidence suggests that I.R.'s respiratory chain is more likely than not functioning normally.

VII. Petitioners' Medical Theory

Although the undersigned's above fact findings render petitioners' theory inapplicable to this case, the undersigned nonetheless addresses petitioners' theory in the interest of completeness. Petitioners summarize their theory as follows:

> Phenotypic manifestations of mitochondrial defects, like a POLG mutation, only occur when mitochondrial reserve capacity is exceeded. Once this threshold is surpassed, mitochondria can no longer compensate for environmental stressors and ATP becomes depleted. ATP depletion, or a lack of energy for the bodies' cells, tissues and organs, causes disease. In a person with mitochondrial dysfunction attributable to a POLG mutation, the MMR vaccine, fever and continuous infections can cause ATP depletion leading to disease. When this threshold is exceeded during a critical neurodevelopmental period, autism can result from synaptic dysfunction and neuronal cell death.

Pet. Posthr'g Br. at 42.

Some aspects of the theory laid out by petitioners are not disputed. Respondent's experts agree that mitochondrial disorders or dysfunction manifest when a "threshold" of stress is exceeded. Tr. 1056. They also agree that physiological stressors can contribute to ATP depletion, potentially resulting in damage or disease.[138] Tr. 430, 538-39. But significant disagreement still surrounds the question of whether there is sufficient evidence to implicate vaccinations as a trigger to that process and whether it can ultimately lead to autism.

At the most basic level, petitioners' theory is premised on the general assertion that "mitochondrial dysfunction explains a subset of autism cases." Pet. Posthr'g Br. at 68. Accordingly, much of the evidence in this case bearing on petitioners' medical theory relates to the general question of whether there is any causal association between autism and mitochondrial dysfunction. For the reasons described below, the undersigned does not find preponderant evidence of any causal relationship.

Petitioners have filed several studies that suggest an association between mitochondrial dysfunction and a subset of the ASD population. See, e.g., Pet. Ex. 47 (Frye); Pet. Ex. 48 (Ghanizadeh); Pet. Ex. 49 (Giulivi); Pet. Ex. 56 (Rossignol and Frye); Pet. Ex. 61 (Weissman);

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[138] Petitioners cite a statement from the Mitochondrial Medicine Society paper that "[a] catabolic state is induced by physiological stressors such as fasting, fever, illness, trauma, or surgery. Because of a lower cellular reserve, mitochondrial patients may more quickly enter a catabolic state and create more toxic metabolites and reactive oxygen species during catabolism. These cellular stresses may lead to cell injury and associated worsening of baseline symptoms or the onset of new ones." Pet. Posthr'g Br. at 114 (quoting Pet. Ex. 105 at 8-9). Petitioners stress that Dr. Cohen agreed with that statement "in principle." Id. The undersigned notes, however, that it is not clear from the phrasing of counsel's question whether Dr. Cohen agreed with the middle sentence regarding the assertion that mitochondrial patents enter catabolism more quickly. Dr. McCandless disagreed with that specific statement. Tr. 429.

Pet. Ex. 189 (Legido). Some studies have placed the percentage of ASD children with mitochondrial disorders at 5-7%. Pet. Ex. 61 (Weissman) at 1; Pet. Ex. 56 (Rossignol-Frye) at 1; Pet. Ex. 189 (Legido) at 3. Dr. Zimmerman has further stressed post-mortem brain studies, which he has indicated suggest evidence of mitochondrial dysfunction among autistic subjects.[139] Tr. 727-32; Pet. Ex. 171 (Anitha); Pet. Ex. 172 (Chauhan); Pet. Ex. 173 (Tang). None of these studies, however, establish any causal connection between mitochondrial dysfunction and autism. Moreover, the studies that assert a potential relationship between the two admit that this relationship is not well understood. For example, following a review of literature addressing mitochondrial dysfunction in autism, Rossignol and Frye concluded that "[m]any studies suffered from limitations, including small sample sizes, referral or publication biases, and variability in protocols for selecting children for [mitochondrial disease] workup, collecting mitochondrial biomarkers and defining [mitochondrial disease]. Overall, this evidence supports the notion that mitochondrial dysfunction is associated with ASD. Additional studies are needed to further define the role of mitochondrial dysfunction in ASD."[140] Pet. Ex. 56 at 1.

Indeed, the Mitochondrial Medicine Society has identified autism as a condition potentially "associated" with mitochondrial dysfunction, but stressed that "the majority of autism is likely due to a constellation of genetic abnormalities and select environmental factors." Pet. Ex. 52 at 7. They further noted that "[t]here have also been concerns raised that certain traits/symptoms in autism might increase the likelihood of comorbid mitochondrial dysfunction," even suggesting the possibility of a causal relationship inverse to that claimed by petitioners. Id. The authors of Liu, et al., a study cited by Dr. Zimmerman, note that "[m]uch evidence from a variety of specialties has documented that multiple non-central nervous system (CNS) abnormalities are associated with ASD. This strongly suggests that ASD may involve not just organ-specific abnormalities, but systemic abnormalities, at least in some individuals." Pet. Ex. 190 at 1. In that regard, Rossignol and Frye similarly stated that "[a]t this point, it is not clear if

[139] Petitioners argue that "[t]aken together, these papers provide us good evidence that there are clear differences in the brain, statistically significant differences, in the brains of autistics versus controls with respect to mitochondrial function." Pet. Posthr'g Br. at 87-88.

[140] Rossignol and Frye is a literature review paper. From that review, petitioners stress certain of the studies described. Pet. Posthr'g Br. at 69-70. Specifically, petitioners note that Rossignol and Frye described studies in which mitochondrial dysfunction was induced in animal models, leading to ASD. Id. at 69 (citing Pet. Ex. 56 at 12). The undersigned does not find Rossignol and Frye's brief description of these studies to be persuasive evidence. Petitioners have not provided adequate information regarding the study parameters, nor have they separately filed the studies. Notably, another paper cited by petitioners suggests that "there are no animal models that encompass the complete phenotype of autism." Pet. Ex. 55 at 14. Petitioners also stress a reference to a study discussed by Rossignol and Frye, which found that 61% of children with mitochondrial dysfunction and autism regressed with fever or illness. Pet. Posthr'g Br. at 69-70 (citing Pet. Ex. 56 at 15). This reference, however, is to the Shoffner, et al., study discussed in greater depth below. Compare Pet. Ex. 56 n.49, with Pet. Ex. 58.

mitochondrial dysfunction contributes to the development or pathogenesis of ASD or if it is merely an epiphenomenon of ASD."[141] Pet. Ex. 56 at 19.

None of the mitochondrial specialists participating in the Parikh, et al., consensus survey for mitochondrial medicine specialists felt that mitochondrial dysfunction in autism patients represented a primary mitochondrial disease. Only a small minority (4 out of 32, or about 12%) felt that it represented a secondary mitochondrial dysfunction. Pet. Ex. 52 at 7, Table 4. The vast majority of specialists (88%) felt that there was insufficient data available to characterize autism as a secondary mitochondrial dysfunction. Id. Petitioners' own expert in mitochondrial medicine, Dr. Niyazov, testified that he was among that majority and that he does not believe there is sufficient data to characterize autism as a secondary mitochondrial dysfunction. Tr. 311-13.

However, starting from the proposition that energy-dependent tissues such as heart, muscle, liver, kidney, and brain tissue are more vulnerable to defects in energy metabolism, Dr. Niyazov opined that parts of the brain necessary to vital function (such as the brain stem or midbrain) are prioritized over the cerebral hemispheres when there is a lack of energy resources. Tr. 138-40. Therefore, Dr. Niyazov opined, when there is a depletion of mitochondrial energy, the resulting neurodegeneration sacrifices cognitive function and can lead to autism. Id. Dr. Zimmerman additionally asserted that autistic regression may result from the remodeling of synaptic networks within the brain. Tr. 723-25. He contended that the 18-24 month age group is an important time for nervous system development and that this corresponds to the period when autistic regression is often seen. Id.

Dr. McCandless persuasively testified, however, that Dr. Niyazov's explanation does not accurately portray how energy metabolism works. Tr. 383-84. Dr. McCandless explained that the body has the ability to shunt blood from one part of the brain to another, but that respiratory chain function occurs at the cellular level and cannot be prioritized. Id. Each cell either has sufficient ability to produce energy or it does not. Tr. 384. If a cell cannot produce enough energy, it will die or have dysfunction. Id. Energy production does not shift from one cell to another, and this is true for all types of tissue. Id. Nor does the undersigned find Dr. Zimmerman's testimony regarding synaptic remodeling to be persuasive. Dr. Zimmerman acknowledged that the etiology of autistic regression is not known. Tr. 723-24; see also Pet. Ex. 58 (Shoffner) at 3-4 (estimating that regression occurs in 25% of autism cases and that the etiology is unknown). Dr. Wiznitzer additionally opined that no link between mitochondrial disorders and autism has been established. Tr. 864-65.

[141] Subsequently, the same authors conducted a further literature review of studies finding post-mortem evidence of oxidative stress in autistic brains. Pet. Ex. 97 (Rossignol 2014). The authors felt that the presence of such evidence in the central nervous system potentially strengthened the idea of a causal connection. However, the authors cautioned that "studies of mitochondrial function in the brain of individuals with ASD are mostly based on small numbers of samples, involve a wide variety of methods, and study various regions of the brain without consistency across studies." Pet. Ex. 97 at 6.

Petitioners take issue with Dr. Wiznitzer's suggestion that, notwithstanding studies cited by petitioners, a causal association has not yet been proven. Pet. Posthr'g Br. at 88 n.128. They contend that requiring proof of a causal association is equivalent to improperly requiring scientific certainty and stress that they are entitled to rely on circumstantial evidence. Id. In that regard, the undersigned stresses that she is not requiring that a causal association be proven with scientific certainty. The issue here is that, notwithstanding the variety of ways in which these collected studies examine the association between autism and mitochondrial disorders, they do not speak, even circumstantially, to the question of causation. Rather, they largely establish only the presence of the two conditions. Moreover, the undersigned found petitioners' experts less persuasive than respondent's experts in discussing the interplay between autism and mitochondrial function.

For these reasons, the undersigned finds no preponderant evidence on this record of any causal association between mitochondrial dysfunction and autism. This provides important context, but is not in itself dispositive. Petitioners are not obligated to present epidemiological evidence and, as they stress in their post-hearing brief, they are asserting that a rare event occurred. Moreover, respondent's experts have conceded that it is theoretically possible, though likely controversially so, for a mitochondrial disorder to have sequela resembling autism.[142] Tr. 351-52, 510-11. In addition to asserting as a general matter that mitochondrial disorders or dysfunction explains a subset of autism, petitioners assert they have shown "a plausible, and compelling, medical theory of how a child with disordered mitochondrial function can develop autism, in the face of repeated environmental immune stressors." Pet. Posthr'g Br. at 76.

Dr. Zimmerman opined that environmental causes are strongly suggestive of mitochondrial dysfunction in autism, indicating that mitochondria are very sensitive to environmental factors such as immune stimulation from infection. Tr. 700-01. Dr. Wiznitzer, however, testified that such environmental exposures are limited to pre-natal exposures.[143] Tr. 864. Similarly, a paper cited by petitioners states that "[s]everal studies suggest that pre- or perinatal exposure to certain triggers might imprint a state of both dysregulated immune response and mitochondrial dysfunction in the progeny as a result of the integration of basic mitochondrial functions with the immune response and antioxidant defense mechanisms. Furthermore, maternal immune response (fever, inflammation) has been associated with significant increased risk of autism spectrum disorder (ASD)." Pet. Ex. 51 at 5. Indeed, when testifying that environmental stressors contribute to autism, Dr. Zimmerman specifically cited valproic acid,

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[142] However, to be clear, Drs. Cohen and McCandless dispute that this is what has happened in I.R.'s case. Tr. 351-52, 510-11.

[143] In that regard, the undersigned notes, however, that prior cases have dealt extensively with what is known as the "triple hit hypothesis," a leading theory on autism causation. The triple hit hypothesis suggests that autism is caused by a convergence of three factors: (1) a critical period of brain development, (2) an underlying vulnerability, and (3) exogenous (or environmental) stressors. See, e.g., R.K., 2015 WL 10936124, at *92-93. Consistent with Dr. Wiznitzer's testimony in this case, this hypothesis places the critical period of brain development within the first trimester of pregnancy, meaning that the environmental factors at issue would be in utero exposures. Id. at *93.

which is an epilepsy or mood stabilizing drug to which fetuses are exposed in utero. Tr. 684, 864-65. Dr. Wiznitzer explained that there is no post-natal association between valproic acid and autism. Tr. 865. Little to no evidence supports Dr. Zimmermans' opinion that childhood environmental exposures, even immunological exposures, lead to autism or autistic regression.[144]

Petitioners have cited literature linking mitochondrial dysfunction and immune dysfunction, but that literature does not suggest that such immune dysfunction leads to autism. These articles are Giulivi, et al. (Pet. Ex. 49), Napoli, et al. (Pet. Ex. 51), and Rose, et al. (Pet. Ex. 55). Petitioners assert that "[t]aken together, these three articles provide strong support for Petitioners' medical theory – an alteration in mitochondrial function caused by a POLG mutation creates a vulnerability to oxidative stress which can result in autism caused by continued immune activation and the failure of compensatory mechanisms." Pet. Posthr'g Br. at 82. However, the undersigned does not find that these studies provide preponderant evidence for petitioners' assertion.

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[144] Citing lumbar puncture findings by Dr. Gupta of elevated cytokines and chemokines in I.R.'s cerebral spinal fluid (see Pet. Ex. 68), petitioners assert:

> Dr. Zimmerman testified that the pro-inflammatory cytokines in [I.R.]'s spinal fluid were of personal interest to him because of his focus on cytokines and the immune system. The significance of the proinflammatory cytokines in [I.R.]'s CSF is that there is a disordered state of cytokines in the immune system – an alteration of the immune system and nervous system, as well as peripherally in the body. Dr. Zimmerman explained that in many children with autism, there is an inflammatory-like state in the nervous system and perhaps in the bowel as well that may be indicated by a change in cytokines. Also in autism, the microglia, resident immune cells of the nervous system, are activated. Thus, elevations in cytokines/chemokines in [I.R.]'s CSF are consistent with an inflammatory process in his brain. [I.R.]'s CSF also revealed decreased BH4 consistent with inflammation, according to Dr. Frye. This evidence of brain inflammation is consistent with the Napoli authors' finding that dysregulation in the antioxidant pathway may contribute to a state of chronic inflammation with a diminished capacity to compensation for conditions of increased oxidative stress, including environmental triggers, thereby limiting the mitochondrial switch.

Pet. Posthr'g Br. at 119-20 (internal citations omitted).

The undersigned has considered this argument, but is not persuaded. Notwithstanding Dr. Zimmerman's stated personal interest in cytokines and the immune system, he is not an immunologist. Moreover, the testimony cited by petitioners was equivocal. He testified that "we think that in many children with autism, there is a – an inflammatory-like state in the nervous system and perhaps in the bowel as well that may be indicated by a change in cytokines." Tr. 691 (emphasis added). Dr. Zimmerman continued by characterizing this inflammatory-like state as "presumably inflammatory" before indicating that the above-referenced activation of microglia occurs "for reasons, again, that aren't entirely clear." Tr. 691-92.

The Giulivi study sought to test the hypothesis that "children with full syndrome autism have dysfunctional mitochondria in peripheral blood lymphocytes." Pet. Ex. 49 at 2. To do this, ten children with autism between the ages of two and five were evaluated for oxidative phosphorylation capacity, mtDNA copy number and deletion, mitochondrial rate of hydrogen peroxide production, and plasma lactate and pyruvate. Id. at 1. They were compared to ten control subjects. Using the same cohort, Napoli, et al., evaluated the subjects for OXPHOS capacity from granulocytes. Pet. Ex. 51 at 3. The Napoli study found that "all mitochondrial outcomes tested in lymphocytes correlated statistically with those obtained with granulocytes from the same individual." Id. at 4.

Because the studies found lower oxidative phosphorylation capacity among the autistic children – i.e., reduced ATP or energy – within lymphocytes and granulocytes, Dr. Niyazov characterized the studies as reflecting that mitochondrial dysfunction in autistic children weakens the immune system. Tr. 247-48. He characterized the studies as pertinent because "they see a higher prevalence of mitochondrial dysfunction in autistic kids, and they see that because they have lower oxidative phosphorylation capacity and they contribute to oxidative stress, but by – by having lower ATP, basically, you produce more reactive oxygen species, and that increases oxidative stress." Tr. 249. Dr. Niyazov suggested that the papers went beyond finding an association between autism and mitochondrial dysfunction, agreeing with counsel's suggestion that they proposed a mechanism for the relationship and further asserting that the proposed mechanism was measured. Id. Petitioners emphasize a statement in the Giulivi paper that "[c]ollectively, these results suggest that cumulative damage and oxidative stress over time may (through reduced capacity to generate functional mitochondria) influence the onset or severity of autism and its comorbid symptoms." Pet. Posthr'g Br. at 78 (quoting Pet. Ex. 49 at 7).

Notwithstanding that quoted statement, Dr. Niyazov and petitioners overstate the significance of the results of the Giulivi and Napoli studies. Like the previously-discussed studies, the hypothesis and conclusion of the Giulivi study was limited to the observation that "evidence of mitochondrial dysfunction was observed in children presenting with full syndrome autism." Pet Ex. 49 at 7. Moreover, the authors explicitly disclaimed any reliance on their findings as evidence of a causal association. They wrote that "[t]he high prevalence of mitochondrial dysfunction observed in this preliminary study performed with children presenting with full syndrome autism may or may not indicate an etiological role." Pet Ex. 49 at 6. Napoli expanded upon the scope of Giulivi, but still noted that "we cannot exclude other mechanisms that could account for our findings." Pet. Ex. 51 at 5. Significantly, the other mechanisms which the Napoli authors cannot rule out includes autism itself. [145]

[145] More specifically, the Napoli study authors noted that "[i]n search of a common mechanism that would explain [our] results, we focused on NFE2L2 [i.e., nuclear factor erythroid 2-related factor 2] because this nuclear transcription factor regulates clusters of genes that control cellular antioxidants, modulate both innate and adaptive immune responses, and has a strong association with mitochondrial function . . . ." Pet. Ex. 51 at 4. This led the authors to posit that "it is likely that a dysregulation in the NFE2L2 pathway may contribute to a state of chronic inflammation with a diminished capacity to compensate for conditions of increased oxidative stress, including exposure to environmental triggers . . . ." Id. at 5. However, when discussing the limitations of the study, they noted that "no study has evaluated the gene expression for NFE2L2 in children

The authors further warn that their methodology hinders the type of conclusion petitioners seek to draw. The Napoli paper notes that "[o]ur findings should be interpreted with caution, because this is a case-control study, in which blood samples were collected postdiagnosis in a small number of probands."[146] Pet. Ex. 51 at 5. In Giulivi, the authors similarly note that "inferences about a cause and effect association between mitochondrial dysfunction and typical autism cannot be made in a cross-sectional study." Pet. Ex. 49 at 7. The authors explained that "[s]everal factors influence expression of mitochondrial respiratory insufficiencies in both the affected and general populations (i.e., nuclear genetic backgrounds, mtDNA heteroplasmy in different tissues, different energy thresholds within a given tissue or organ, and environmental factors). Nevertheless, our exploratory study suggests that mitochondrial defects in children with autism may be more common than in controls." Pet. Ex. 49 at 7. Again, as with previously-discussed studies, this conclusion is limited to asserting an association between the two conditions.

Significantly, Dr. Cohen was highly critical of these studies. Dr. Cohen explained that the studies evaluated mitochondrial dysfunction for Complex I by measuring NADH oxidase, which is only a proxy measurement and not a mitochondrial assay. Tr. 490, 492-93. Dr. Cohen indicated that because NADH oxidase can be impacted by enzymes unrelated to mitochondrial function, it is a poor measure of Complex I activity. Tr. 490-91. Citing the electronic supplement to the published Giulivi paper, Dr. Cohen indicated that an assay called NQR, which is a measure of Complex I activity, was also performed; by this measure, the autistic children had Complex I activity higher than did controls. Tr. 491. He also noted that the electronic supplement showed that Complex V activity among the autistic subjects was also higher than controls. Tr. 492. Dr. Cohen opined that this supplemental data throws the authors' entire conclusion into question. Tr. 490-93. That is, Dr. Cohen casts doubt on the very premise that this is actually a study of subjects with mitochondrial insufficiency. Given the opportunity to respond to Dr. Cohen's critique, Dr. Niyazov demurred as to the specifics of the study and stressed the rigor of the review process in general, as well as the number of subsequent papers that have cited the study.[147] Tr. 962-64.

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with autism. Thus, we cannot exclude the possibility that the reported downregulation could be downstream from NFE2L2." Id. This was listed among the factors that led the authors to state that "we cannot exclude other mechanisms that could account for our findings." Id. The undersigned understands these caveats to indicate, in effect, that this study did not establish a causal link to autism. The authors have explicitly warned that their findings could be entirely explained by gene expression related to autism itself, which has not been studied in relevant part. Thus, the undersigned is not persuaded that the Giulivi and Napoli studies significantly diverge from the previously-discussed studies which perceive a co-morbid association between autism and mitochondrial dysfunction, but which do not establish a causal connection between the two conditions.

[146] A proband is "an affected person ascertained independently of relatives in a genetic study." Dorland's at 1515.

[147] To the extent that Dr. Niyazov noted that the findings of Giulivi were replicated by Napoli, this is not persuasive since the studies involved the same research group using the same testing

With regard to petitioners' specific contention that the Giulivi paper addresses how immune stressors may lead to autism, the paper notes that "[w]hether the mitochondrial dysfunction in children with autism is primary or secondary to an as-yet unknown event remains the subject of future work." Pet. Ex. 49 at 6. Furthermore, to the extent that Dr. Niyazov intimated that the Giulivi paper establishes the presence of immune dysfunction in mitochondrial patients, nothing in the paper suggests any clinical evaluation of immune function. Nor do the authors even posit that immune function may be compromised clinically.

The Napoli study did look at immune response by artificially stimulating the granulocytes with phorbol 12-myristate 13-acetate (PMA) to incite a "respiratory burst." Pet. Ex. 51 at 3. The authors concluded that "[t]his report broadens our knowledge because it includes studies of the immune response of granulocytes from probands. These cells presented a lower PMA-mediated oxidative burst with a longer latency to trigger this response. Taken together, these findings are in agreement with those reporting immune dysregulation, mitochondrial dysfunction, increased oxidative stress, and decreased antioxidant repair capacity in some cases of autism." Pet. Ex. 51 at 4-5. Notably, however, this conclusion stops short of asserting a causal relationship. Moreover, nothing in the paper substantiates the idea that the artificial stimulation by PMA is representative of immune response in an in vivo or clinical context.

However, in addition to the Giulivi and Napoli studies, Dr. Niyazov also cited a study by Rose, et al. The Rose study summarized its findings as follows:

> There is increasing recognition that mitochondrial dysfunction is associated with the autism spectrum disorders. However, little attention has been given to the etiology of mitochondrial dysfunction or how mitochondrial abnormalities might interact with other physiological disturbances associated with autism, such as oxidative stress. In the current study we used respirometry to examine reserve capacity, a measure of the mitochondrial ability to respond to physiological stress, in lymphoblastoid cell lines (LCLs) derived from children with autistic disorder (AD) as well as age and gender-matched control LCLs. We demonstrate, for the first time, that LCLs derived from children with AD have an abnormal mitochondrial reserve capacity before and after exposure to increasingly higher concentrations of 2,3-dimethoxy-1,4-naphthoquinone (DMNQ), an agent that increases intracellular reactive oxygen species (ROS). . . . We further demonstrate that these reserve capacity abnormalities are driven by a subgroup of eight (32%) of 25 AD LCLs. . . . This study suggests that a significant subgroup of AD children may have alterations in mitochondrial function which could render them more vulnerable to pro-oxidant microenvironment derived from intrinsic and extrinsic sources of ROS such as immune activation and pro-oxidant environmental toxicants. These findings are consistent with the notion that AD is caused by a combination of genetic and environmental factors.

Pet. Ex. 55 at 1 (Abstract).

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methods on the same subjects. However, Dr. Niyazov did also contend that the conclusions of the Rose study, conducted by an independent group, corroborate the findings. Tr. 965-66.

The Rose study also has significant limitations. Although in vitro studies are considered in the Vaccine Program, the undersigned is not persuaded that this in vitro study models what would happen in an in vivo context. Nor have petitioners offered persuasive expert testimony extrapolating the in vivo implications of the study. Compare Kelley v. Sec'y of Health & Human Servs., 68 Fed. Cl. 84, 92 (2005) (noting that indirect evidence of causation may include "inferential clinical and laboratory studies"), with Mead v. Sec'y of Health & Human Servs., 2010 WL 892248, at *73 (Fed. Cl. Spec Mstr. Mar. 12, 2010) ("An in vitro experiment permits the study of a cell to generate hypotheses about what effects a chemical might have in humans. But no conclusions can be reached from such a study because the laboratory environment is 'radically different' from the environment of the body.")

Here, the Rose study found as an initial matter that reserve respiratory capacity was "overall not different between the AD and control LCL groups." Pet. Ex. 55 at 5. It was only with the artificial introduction of DMNQ that a subset of the AD LCLs demonstrated a greater decrease in reserve capacity. Id. Although the introduction of DMNQ was intended to mimic reactive oxygen species, the study did not explore to what extent the experiment did, or was even intended to, introduce reactive oxygen species in a manner reflective of an in vivo environment.[148] As was previously noted in Mead, "[t]he principal difference between the two environments is that the complex cellular interactions that are present in the body are missing in the in vitro environment. Stated in other words, more of the added reactive material is available to be taken up by the cells in the artificially constructed in vitro environment than would occur in the more carefully balanced in vivo environment." 2010 WL 892248, at *73. Indeed, discussing in vitro studies in a different context, the Federal Circuit noted that there is a "common sense notion that one cannot simply proclaim without proof that he has constructed an apparatus capable of mimicking pertinent environmental variables . . . ." Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1296-97 (Fed. Cir. 2006).

The undersigned is further concerned that the study used a single control LCL line for up to three AD LCL lines. See Pet. Ex. 55 at 2. In total, the study had only thirteen LCL controls

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[148] Of note, Dr. Niyazov asserted that the study results from Giulivi, Napoli, and Rose all reinforce one another. Tr. 962-66. In that regard, the Rose authors state:

> [I]mmune cells may be an ideal surrogate for investigating the consequences of mitochondrial abnormalities when neural tissue cannot be practically studied. It will be important to expand these findings to primary immune cells (PBMCs) with the aim of developing a model of mitochondrial function in an accessible tissue such as immune cells and developing a practical biomarker which could be eventually clinically useful. Finding mitochondrial dysfunction similar to that found in the LCLs in PBMC from a subgroup of individuals with ASD could validate the LCL model and further help to determine the clinical relevance of this type of mitochondrial dysfunction in individuals with ASD.

Pet. Ex. 55 at 14. However, given the above-discussed limitations of the Giulivi and Napoli studies, the undersigned is not persuaded that these studies provide meaningful in vivo corroboration of this study.

for its 25 AD LCLs. Id. Additionally, even in the in vitro context, the study found significant differences in only a minority (32%) of AD LCLs. Id. at 11. In this regard, it is significant that the study relied heavily on a Seahorse Assay. See id. at 2-3. As discussed above in Section VI.C.iii.d, Dr. Cohen called into question the reliability of this technology, raising concerns which petitioners' experts were unable to rebut. Dr. Cohen also noted that the study lacked certain follow up experiments that could have helped account for the difficulties with the Seahorse assay. Tr. 495-97. He opined that such follow up would have been necessary for him to accept the study results.[149] Id. As previously discussed, petitioners' experts had no satisfactory response to Dr. Cohen's criticism of the Seahorse Assay.

Even assuming arguendo that petitioners demonstrated that immune stressors could lead to autism among those with mitochondrial dysfunction, the question of what role, if any, vaccinations play in that process is still left open. Moreover, petitioners also stress that the clinical phenotype for a mitochondrial disorder does not manifest until the critical "threshold" is reached. Pet. Posthr'g Br. at 56 (citing Tr. 245; Pet. Ex. 132 (Saneto)). This raises the question of what evidence, if any, correlates autism or autistic regression to alleged inciting events such as fever and vaccination. This aspect of petitioners' theory is effectively premised on four papers. These papers are Shoffner, et al. (Pet. Ex. 58); Poling, et al. (Pet. Ex. 53); Weissman, et al. (Pet. Ex. 61); and Phillips, et al. (Pet. Ex. 54). Each of these papers has been extensively addressed in prior decisions.[150] However, they have been presented in this case without much discussion by

[149] Dr. Cohen also stressed that the particular journal in which this study was published – PLOS One – is known for publishing preliminary data that might not be ready for publication in other journals. Tr. 496-97.

[150] Although the undersigned discusses several prior decisions addressing these studies, she emphasizes that she is not relying on the conclusions reached in those decisions. Rather, the undersigned bases her decision on her review of the record evidence in this case. In that regard, the undersigned notes that petitioners have argued at length in their post-hearing reply brief that the outcome in Paluck should control in this case. Pet. Reply Posthr'g Br. at 12-14. The undersigned disagrees. Although Paluck reviewed several of the same studies filed in this case, the undersigned reaches her conclusion based on the record as a whole, which in this case includes over two hundred exhibits filed by petitioners alone as well as 1,078 pages of hearing transcript. Moreover, the undersigned is not bound by prior decisions of the Office of Special Masters or the U.S. Court of Federal Claims. See, e.g., Hanlon v. Sec'y of Health & Human Servs., 40 Fed. Cl. 625, 630 (1998) (noting that "[s]pecial masters are neither bound by their own decisions nor by cases from the Court of Federal Claims, except, of course, in the same case on remand"). To the extent that the Federal Circuit addressed the same literature, the undersigned notes that the Circuit's discussion of these articles was limited to the question of whether they established a definitive timeframe for onset in the context of Althen Prong 3. Paluck, 786 F.3d 1373, 1383-84 (Fed. Cir. 2015). The Federal Circuit explicitly did not reach any question regarding Althen Prong 1, as it was noted that petitioners' medical theory had been previously conceded before the special master. Id. at 1377. Notably, subsequent to the Federal Circuit's decision in Paluck, another special master reviewed some of the same literature and concluded that petitioners had not met their burden of establishing a medical theory under Althen Prong 1. In that case, the special master's analysis was validated on review by the Court of Federal

the testifying experts. Upon the undersigned's review in this case, none of these papers alone or in combination provides preponderant evidence for petitioners' theory.

The Shoffner study looked retrospectively at 28 patients with co-morbid diagnoses of autism and mitochondrial disease to discern whether a relationship between autistic regression and fever existed. Pet. Ex. 58 at 3-4. About 61% (17 of 28) of the children studied were said to have experienced an "autistic regression,"[151] which represented a higher percentage of regression than commonly reported in those with ASD, which the authors estimated at 25%. Id. at 5. The authors also reported that 12 of the 17 children experienced an autistic regression within two weeks of a febrile episode. Id. at 4-5. However, vaccination without any associated fever was not associated with regression. Id. The authors of the Shoffner article explicitly stated: "No individual [studied] showed regression with vaccination unless a febrile response was present." Id. at 5. Additionally, two siblings in the study, who regressed frequently with idiopathic fevers, did not regress after vaccination. Id. The authors concluded that "[i]n our patients with mitochondrial disease and autistic spectrum disorders, the vaccines did not appear related to the neurologic regression." Id. at 6.

Petitioners cited this paper for the proposition that the rate of regression among children with mitochondrial disorders is double the rate of regression for ASD patients generally, and that the risk of regression is enhanced by prolonged fever with or without vaccines. Pet. Posthr'g Br. at 70; Tr. 261-62. Dr. Niyazov testified that the Shoffner paper represents the mechanism of injury he proposes in this case.[152] Tr. 262. Dr. Cohen, however, stressed that the Shoffner paper

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Claims and on appeal to the Federal Circuit. See H.L. v. Sec'y of Health & Human Servs., No. 10-197, 2016 WL 3751848 (Fed Cl. Spec. Mstr. Mar. 17, 2016), mot. for rev. denied, 129 Fed. Cl. 165 (Sept. 29, 2016), aff'd, 715 F. App'x 990 (Fed. Cir. 2017). In H.L., the Federal Circuit characterized its Paluck decision as holding only "that the special master erred by imposing a strict time constraint for the onset of the vaccinee's neurodegeneration. We observed that mitochondrial disorders 'are as yet poorly understood by the medical community,' and that the special master therefore 'had no reasonable basis for setting a hard and fast deadline of three weeks for the onset of neurological symptoms.'" 715 F. App'x at 996-97 (quoting Paluck, 786 F.3d at 1384). In any event, petitioners conceded that the Paluck case is factually distinguishable. Pet. Posthr'g Reply Br. at 13 (stating that "[t]he only significant difference between the Paluck facts and the facts of the instant case is that the Paluck child suffered from neurodegeneration, which was NOT an ASD").

[151] As previously discussed, the testifying experts in this case disagreed regarding the definition of regression. The Shoffner study defined regression as "the loss of developmental skills that included speech, receptive skills, eye contact, and social interest in individuals <3 years of age." Pet. Ex. 58 at 4.

[152] Dr. Zimmerman also discussed a paper by Liu, et al. Tr. 736-38. Dr. Zimmerman indicated that the paper shows that "[t]he heat shock response and the redox – the heat shock response and the redox imbalance and oxidative stress are connected to mitochondrial dysfunction and immune dysregulation, and they're all interrelated and probably all are important in the field of autism." Tr. 737-38. He indicated that the paper grew out of his own observation that some

does not implicate vaccinations in autistic regression and that the Shoffner authors recommended vaccination as being safe.[153] Tr. 502. He characterized the Shoffner paper as reflecting fever as "the highest variable" among a number of things potentially contributing to regression. Id.

To the extent that petitioners argue that I.R.'s condition was triggered not merely by a vaccine but by a vaccine-caused fever, the Shoffner paper has several significant limitations on its face. Most notably, the authors caution that "[t]his study did not investigate changes that could be important in the induction of regression such as dehydration, hypoglycemia, decreases in substrate availability to oxidative phosphorylation, and other metabolic abnormalities such as fatty acid oxidation dysfunction." Pet. Ex. 58 at 6. This caveat directly supports Dr. Cohen's interpretation of the study as highlighting fever as only one variable among many, and further warns that these other variables have not be accounted for or addressed. Significant in that regard, nearly 30% of those subjects experiencing regression regressed "without identifiable linkage to fever or vaccinations." Id. at 3. It is also significant then that the study had a very small population size at just 28 patients. The authors themselves noted that the study's data "emphasize the need for larger studies to investigate the role of fever, plus coexisting metabolic abnormalities in patients with mitochondrial disease who experience autistic regression." Id. at 6.

It is also worth noting that the study does not include data regarding the age at which ASD was diagnosed. Nor does it explain how the authors determined that a regression occurred or describe the reported regressions in any detail. The authors did not specify whether the regression marked the first manifestation of ASD or whether symptoms of ASD were already extant in the children studied. As a prior decision has noted, these are "significant omissions" given the study's objective. R.K., 2015 WL 10936124, at *82.

The Poling paper involved a case report of a child who regressed after receiving vaccines at 19 months of age and who was subsequently diagnosed with both ASD and a mitochondrial disorder. Pet. Ex. 53. It also included a retrospective analysis of 159 children with autism

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children with autism seem to improve during fever and illness. Tr. 738. Upon review of this article, the undersigned does not find its discussion of febrile illness and heat shock response to be persuasive. The authors premise their discussion on "[w]idespread anecdotal reports [that] have suggested that fever can dramatically but temporarily ameliorate the disturbed behavior of many autistic patients" but also indicate that "the mechanisms of the fever effects in ASD patients are unclear" and that "[e]lucidation of the fever response might provide insight into the mechanism of ASD and point to new therapeutic approaches." Pet. Ex. 190 at 5. Thus, the authors effectively acknowledged that the proposed mechanism and role of febrile illness in autism is an unsupported hypothesis.

[153] The Shoffner paper states that "[c]hildren with identified mitochondrial diseases are routinely managed carefully by their physicians with aggressive fever control and hydration. In this context, vaccination of children with mitochondrial diseases is recommended. In our experience, the vast majority of patients with mitochondrial diseases receives a full vaccination schedule according to American Academy of Pediatrics guidelines without consequences, particularly when physicians are sensitive to fever control and hydration." Pet. Ex. 58 at 6.

compared to 94 patients with other unspecified neurological disorders. Id. at 3. The study compared results for some of the same tests performed on the Poling child. Id. They found elevated levels of AST[154] in the ASD group as compared to the children with other neurological disorders. Id. They also suggested that the creatine kinase levels were elevated in those with ASD; however, too few results from the "other neurological disorders" group were available to allow for comparison. Id. The specific numbers of children with AST results available in each group were not reported. Id. at 3-4. The authors speculated that, in view of the AST and creatine kinase levels, some of the children with ASD might have a mitochondrial disorder as well.[155] Id. at 4. However, the Poling article presents only a single case report of developmental regression and autism in the context of a mitochondrial disorder. Moreover, as the Poling child also experienced a fever following her immunizations (id. at 2), this case report falls squarely within the parameters of the above-discussed Shoffner study findings, which implicated fever as a trigger for mitochondrial decompensation, not simply vaccination.

Dr. Niyazov portrayed the Poling case report as being "very similar" to I.R.'s case. Pet. Ex. 39 at 5. Dr. Zimmerman likewise relied on the Poling report to support his opinion. Tr. 762-63. He identified the Poling report as the only published literature he could find that sought to link the MMR vaccine to autism via immunosuppression. Id. Dr. Cohen disputed that the two cases are factually similar, but also opined that a single case report is insufficient to draw an association. Tr. 500-02.

Due to an undisclosed conflict of interest, the Poling case study has been harshly criticized in prior decisions.[156] See, e.g., Holt, 2015 WL 4381588, at *27 n.75 (explaining that Dr. Poling's familial relationship to the case report subject was not disclosed as would be

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[154] AST is aspartate transaminase, a measure of liver function. Dorland's at 164.

[155] The undersigned stresses that the authors themselves used the term "might" and expressed that the presence of any abnormal mitochondrial function could not be confirmed based on increased AST and creatine kinase alone. Pet. Ex. 53 at 4.

[156] The father of the Poling subject was an author of the case study and the Poling family had a pending claim in this Program. That claim was ultimately settled without an adjudication on the basis of presenting a Table encephalopathy, which carries a presumption of vaccine causation when onset is within the prescribed timeframe. This history was most fully addressed by former Chief Special Master Vowell in a ruling on a motion for discovery related to the case study in R.K. See 2015 WL 10911950, at *15-30 (Fed. Cl. Spec. Mstr. May 23, 2016). Neither the familial relationship nor the fact of the pending claim for compensation were disclosed. Pet. Ex. 53. Of note, petitioners' expert in this case, Dr. Zimmerman, co-authored the Poling case report. Asked about this criticism, Dr. Zimmerman indicated only that he and the other authors (other than Dr. Poling) were unaware of the pending compensation claim. Tr. 762-63. However, the fact that Dr. Zimmerman was not aware of the claim does not resolve the conflict it created. It remains the case that the paper's lead author had an undisclosed conflict of interest. Additionally, it also remains the case that Dr. Poling's co-authors would have been aware of the undisclosed familial relation. Dr. Zimmerman indicated that he was a treating physician of the Poling child and so would have known Dr. Poling to be her parent. Tr. 762-63.

expected when submitting a medical journal article for publication). In Holt, the special master noted that conflicts of interest should be weighed when applying Daubert, as such considerations go to the question of whether the research has a valid scientific purpose. Id. (citing Daubert v. Merrell Dow Pharm., 43 F.3d 1311 (9th Cir. 1995) and Exxon Shipping Co. v. Baker, 554 U.S. 471 (2008)).

Separate and apart from the potential conflict of interest, prior cases have also extensively addressed the weight the Poling report deserves as a single case study. Prior decisions have concluded that little weight should be given to the Poling case report, because it represents only a single instance of a temporal association between vaccination and regression, leaving significant potential that the association is coincidental. See, e.g., R.K., 2015 WL 10936124, at *88 (noting that a single instance of something happening is by definition not evidence of a pattern); H.L., 2016 WL 3751848, at *15 ("[A]s a single case report, the Poling article's suggestion of a temporal relationship is not in itself strong evidence of a causal connection, since it could easily be the result of pure chance."). The undersigned agrees.

The Weissman study, cited above regarding the general association between autism and mitochondrial disease, does not directly examine vaccine causation. It purports only to examine a possible association between autism and mitochondrial disease. Pet. Ex. 61. The authors conducted "a chart review of the biochemical, genetic and histopathological findings in 25 patients with ASD who had unequivocal evidence of a disorder of oxidative phosphorylation." Id. at 1. Nothing in the study's reported methodology suggests that the authors sought to examine vaccine causation, nor is there any suggestion that they systematically reviewed patient histories for any temporal association between vaccination and onset of symptoms. They did, however, identify one subject out of the 25 as having experienced a regression that "coincided with a recent vaccination." Id. at 3. That one subject was the same subject described in the Poling case report.[157]

Petitioners emphasize a statement in the Weissman article that "there might be no difference between the inflammatory or catabolic stress of vaccinations and that of common childhood diseases, which are known precipitants of mitochondrial regression." Pet Ex. 61 at 4; see also Pet. Posthr'g Br. at 71-72. Viewed in context, however, the undersigned is not persuaded that this statement offers support for petitioners' theory. The full statement reads:

> Recently, there has been increased concern regarding a possible causative role of vaccinations in autistic children with an underlying mitochondrial cytopathy. For one of our 25 patients, the child's autism/neurodevelopmental deterioration appeared to follow vaccination. Although there may have been a temporal relationship of the events in this case, such timing does not prove causation. That said, there might be no difference between the inflammatory or catabolic stress of

[157] The Weissman paper itself cited the Poling case report when discussing this subject. Additionally, Dr. Cohen is listed as an author of the paper. He testified in a prior case that the subject identified in Weissman as regressing following vaccination is the same individual as described by the Poling case report. R.K., 2015 WL 10936124, at *90.

> vaccinations and that of common childhood diseases, which are known precipitants of mitochondrial regression.

Pet. Ex. 61 at 4.

In context, the statement comparing the catabolic stress of vaccines and diseases does not carry significant weight. First, the statement itself is equivocal. Further, the complete statement reveals that the authors are explicitly disclaiming any causal association. Additionally, the statement does not derive from the results of the study. The study looked only at a potential association between mitochondrial disease and autism through a chart review. The catabolic stress of vaccination was not measured in any way, leaving the basis for the statement entirely unclear.[158]

For his part, Dr. Cohen (a co-author) was critical of this study because it does not disclose the denominator relating to the identification of the 25 subjects. Tr. 500. That is, the study does not disclose how many cases were reviewed in order to come up with 25 subjects that met the review parameters. Id. Petitioners protest that this is a "meaningless criticism" of the Weissman paper which, at most, suggests these 25 children are non-representative of the general population. Pet. Posthr'g Br. at 72 n.98. Petitioners also note that vaccine events of the type alleged are rare. Id. The undersigned does not agree that Dr. Cohen's critique is "meaningless." Rather, it goes directly to the question of whether the study results should be assigned statistical significance at all.[159] Moreover, since the study was not even aimed at detecting vaccine reactions, petitioners' rebuttal argument is not relevant.

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[158] In support of the statement, the authors cited a prior study titled "The otolaryngological manifestations of mitochondrial disease and the risk of neurodegeneration with infection," appearing in the Archives of Otolaryngology - Head and Neck Surgery. That paper has not been filed into the record of this case. Petitioners also stress a 2008 statement by Dr. Cohen from U.S. News & World Report, in which he similarly suggested thate "it's proper reasoning to think that vaccine could do what viruses do." Pet. Posthr'g Br. at 72-73 (citing Pet. Ex. 134 at 3). Dr. Cohen testified that he would not say the same thing today. Tr. 536-37. Even before accounting for Dr. Cohen's retraction, the undersigned does not find that Dr. Cohen's press statement adds any weight to the statement presented in the Weissman paper.

[159] The Weissman authors state that "[t]he cohort of 25 patients reported here comprises the largest group of individuals with co-occurrence of ASD and defective oxidative phosphorylation reported to date. While previous case reports implicated an association of ASD and mitochondrial dysfunction, it could be argued that this was a chance occurrence in those individuals." Pet. Ex. 61 at 4. The import of Dr. Cohen's criticism is that, without additional information regarding the number of individuals screened, the notion of chance occurrence persists. The authors further note that "[o]ur results indicate diverse and complete developmental, neurological, and medical phenotypes of persons with mitochondrial autism, nearly all of which differ from those of patents with idiopathic ASD." Id. Again, given that the assembled cohort is both very small and, according to the authors, demonstrating "substantial clinical heterogeneity" (id. at 5), the question of how many screened patients were poor fits for the review parameters goes directly to the strength of the claimed mitochondrial autism

The Phillips study examined 33 healthy subjects who received live attenuated influenza vaccine in nasal spray form. Pet. Ex. 54 at 2-3. Prior to administration, as well as two, seven, and fourteen days after administration, the researchers measured breath volatile organic compounds (VOCs) as biomarkers of oxidative stress using a breath collection apparatus. Id. at 2. The researchers also measured VOCs from the vaccine itself to address any VOCs present in the vaccine. Id. They found none. Id. After running a statistical analysis called a Monte Carlo simulation,[160] the authors found "sustained changes in the abundance of VOCs in breath" following live attenuated influenza vaccination. Id. at 4. The authors hypothesized that the live attenuated vaccine increased oxidative stress by a similar mechanism as influenza virus pneumonia. Id. Dr. Niyazov cited this paper as evidence that "the live flu vaccine serves as an attenuated infection, because it's [an] attenuated influenza virus, but it still can cause attenuated infection, and infection can cause fever, and fever can cause oxidative stress, which results in catabolism." Tr. 954. Dr. Niyazov indicated that this paper refutes those who say vaccines do not cause oxidative stress. Tr. 258, 980-82.

This paper has been presented in several prior cases, and experts in those cases have indicated that it has significant limitations. Specifically, the reliability of breath testing as a whole has been questioned. In Bast, the special master heard testimony from an expert indicating that reactive oxygen species is very difficult to measure, both because the results are easily skewed by competing factors (such as what the subject ate) and because the presence of oxidants is not necessarily dispositive of a disease process. 2012 WL 6858040, at *31-32. In H.L., expert testimony similarly questioned whether the physiological differences observed in the Phillips study were representative of metabolic differences.[161] 2016 WL 3751848, at *17 n.20.

These limitations are likewise demonstrated in the record of this case. Discussing the need for the Monte Carlo simulation, the Phillips authors cautioned that "[a] central problem in a biomarker discovery study is the need to distinguish true from false biomarkers of disease. When a large number of VOCs are assayed in a comparatively small number of subjects, some non-biomarker VOCs may appear to be accurate identifiers of disease solely because of random statistical fluctuations."[162] Pet. Ex. 54 at 4. Dr. Niyazov also testified, in effect, that levels of

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phenotype.

[160] Monte Carlo simulation is an algorithm developed at Los Alamos in the 1940s that uses repeated random sampling to simulate physical and mathematical systems. Pet. Ex. 54 at 5. According to the study authors, the simulation helps distinguish between true and false biomarkers. Id. at 4.

[161] However, the special master in Paluck discounted the evidentiary value of the Phillips paper on the basis that the same researchers had used a different biomarker in a prior study. The special master concluded that F2-isoprostane would be a more reliable measure of oxidative stress. The Court of Federal Claims found that the special master's rationale improperly elevated petitioners' burden of proof under Althen Prong 1. Paluck, 104 Fed. Cl. 457, 473-74 (2012).

[162] Unlike the previously-discussed studies, the Phillips study did not involve individuals with rare co-occurrence of both autism and mitochondrial disorders. Rather, the authors stress that the

oxidative stress are idiosyncratic, dependent on the individual person and their activity at any given time. Tr. 978-80. He acknowledged that quantifying oxidative stress would occur at a molecular or cellular level and that comparing levels of oxidative stress would have to occur in a research laboratory context. Tr. 978-79. He acknowledged that measuring oxidative stress outside of a laboratory setting is difficult and described the Phillips study as an "elaborate" indirect measure of oxidative stress that "could be an indication" of increased post-vaccination oxidative stress. Tr. 981-82 (emphasis added).

Moreover, although the breath VOCs were statistically significant, the study authors note that "the clinical value of this test is not yet known." Pet. Ex. 54 at 6. In that regard, the undersigned notes that the vaccine administered to the subjects was inhaled and the VOCs measured in breath. This leaves open the possibility of a localized oxidative reaction, which would not support petitioners' theory. See, e.g., R.K., 2015 WL 10936124, at *111 n.250 (discussing the "significant distinction" between the live viral vaccine administered into the lungs in the Phillips study and a killed virus administered intramuscularly).

VIII. Ruling on Entitlement

In its ruling in Althen, the U.S. Court of Appeals for the Federal Circuit discussed "causation-in-fact" in Vaccine Act cases. The court stated:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (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. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

Althen, 418 F.3d at 1278 (internal citations omitted). The Althen court noted that a petitioner need not necessarily supply evidence from medical literature supporting their causation contention, so long as the petitioner supplies the medical opinion of an expert. Id. at 1279-80. The court also indicated that, in finding causation, a Program fact-finder may rely upon "circumstantial evidence," which the court found consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." Id. at 1280.

Where a petitioner in a cause-in-fact or "off Table" case seeks to prove that their vaccination aggravated a pre-existing injury, the Court must apply three additional factors

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participants were "normal healthy human subjects." Pet. Ex. 54 at 1. Thus, given the authors' acknowledgement that biomarker studies are subject to false positives in small study populations due to statistical fluctuations, the small study population in this study is concerning. No readily discernable factor limited the availability of a larger study population, nor was any such limitation discussed in the article.

originating from the standard for assessing aggravation claims in "Table" injury cases. See Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 143-44 (Fed. Cl. 2009) (combining the first three Whitecotton factors for claims regarding aggravation of a Table injury with the three Althen factors for off Table injury claims to create a six-part test for off Table aggravation claims); see also W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352, 1357 (Fed. Cir. 2013) (applying the six-part Loving test). The additional Loving factors require petitioners to demonstrate aggravation by showing: (1) the vaccinee's condition prior to the administration of the vaccine, (2) the vaccinee's current condition, and (3) whether the vaccinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. Loving, 86 Fed. Cl. at 144.

Petitioners alleged that I.R.'s ProQuad vaccine significantly aggravated his preexisting mitochondrial disorder, causing him to suffer from immunodeficiency disorder, bowel disease, pathological neuroinflammation, seizure disorder, mitochondrial dysfunction, and autism spectrum disorder. Second Am. Petition at 15. Applying the above standards to this theory, the undersigned finds as follows.

A. Loving Prong 1

Loving Prong 1 requires a finding on I.R.'s condition prior to the administration of his ProQuad vaccine at about one year of age on December 30, 2005. With regard to Loving Prong 1, petitioners assert that I.R. was "developmentally normal" and "generally healthy" during his first year of life. Pet. Posthr'g Br. at 6. They dispute that I.R.'s autism manifested prior to his ProQuad vaccination, arguing that "[a] preponderance of evidence shows that [I.R.] exhibit only typical behaviors through age one." Id. at 31. However, for the reasons described in Section VI.A.i, the undersigned concludes that prior to his ProQuad vaccination on December 30, 2005, I.R. exhibited signs of an autistic spectrum disorder. I.R. also had repeated illnesses prior to his vaccinations on December 30, 2005, including "back to back" colds, followed by fever, cough, and diarrhea in November 2005. By mid-November, I.R. had been "sick on and off for weeks." Pet. Ex. 15 at 13. Although I.R. had repeated illnesses, for the reasons described in Sections VI.B.ii and VI.C.iii, the undersigned finds that prior to his ProQuad vaccination, I.R. had no metabolic or immunologic disorders or dysfunction.

B. Loving Prong 2

Loving Prong 2 requires a finding as to I.R.'s current – or post-vaccination – condition. Petitioners allege that I.R. had an acute vaccine reaction consisting of a high fever and rash. Pet. Posthr'g Br. at 32. Petitioners further allege that I.R. subsequently experienced a prolonged period of repeated illnesses. Id. at 33. Petitioners contend that I.R.'s development concerns and autism arose for the first time during this period. Id. at 33-40.

Although I.R. experienced repeated illnesses, for the reasons described in Sections VI.A.iii, VI.B.ii, and VI.C.iii, the undersigned finds that post-vaccination, I.R. continued to be an immunologically and metabolically normal child who demonstrated a continued trajectory of non-regressive autism that began prior to administration of his ProQuad vaccine. I.R.'s autism

improved (to a subsequent diagnosis of PDD-NOS) prior to and without intervention from metabolic or immunologic treatment.

C. Loving Prong 3

Loving Prong 3 asks whether a vaccinee's current or post-vaccination condition constitutes a significant aggravation of the vaccinee's pre-vaccination condition. The Vaccine Act defines a "significant aggravation" as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration in health." § 300aa-33(4). Petitioners assert that I.R.'s pattern of acute vaccine reaction, period of repeated illnesses, and worsened developmental trajectory constitute a significant aggravation under Loving Prong 3, as this represents "a serious deterioration in health." Pet. Posthr'g Br. at 41.

Although I.R.'s acute vaccine reaction and period of repeated illnesses may represent a "substantial deterioration in health", they do not constitute a significant aggravation, because they are not related to any pre-existing condition. That is, for the reasons described in Sections VI.B.ii and VI.C.iii, the undersigned has concluded that I.R. had no immunological or mitochondrial dysfunction either before or after his vaccination. Thus, neither I.R.'s illnesses nor his autism can be considered manifestations of an aggravation of such conditions.

Significantly, petitioners did not argue that the trajectory of I.R.'s autism constituted a significant aggravation in itself. Indeed, they contend that his autism did not pre-date his vaccination and therefore did not constitute a pre-existing condition. To the extent that the undersigned found that I.R.'s autism manifested prior to vaccination, as discussed in Section VI.A.i, the undersigned did not find preponderant evidence that I.R. experienced a neurological regression or that his autism was regressive.[163]

D. Loving Prong 4/Althen Prong 1

As noted above, Loving Prong 4 is also Althen Prong 1. This prong requires petitioners to establish by preponderant evidence a medical theory causally connecting the vaccinee's injury or significantly aggravated condition to the vaccination at issue. That is, petitioners must present a theory establishing that the vaccination at issue can cause I.R.'s condition. Petitioners summarize their theory as follows:

> Phenotypic manifestations of mitochondrial defects, like a POLG mutation, only occur when mitochondrial reserve capacity is exceeded. Once this threshold is surpassed, mitochondria can no longer compensate for environmental stressors and ATP becomes depleted. ATP depletion, or a lack of energy for the bodies' cells, tissues and organs, causes disease. In a person with mitochondrial dysfunction

[163] As described in Section VI.A.iii, absent a regression, autism typically presents as a stagnation or plateau in social development. The appearance of worsening is attributable to the fact that a child experiencing such a plateau falls farther from the expected developmental trajectory as he ages, relatively speaking.

> attributable to a POLG mutation, the MMR vaccine, fever and continuous infections can cause ATP depletion leading to disease. When this threshold is exceeded during a critical neurodevelopmental period, autism can result from synaptic dysfunction and neuronal cell death.

Pet. Posthr'g Br. at 42.

As a threshold matter, even if the undersigned credited petitioners' theory as a general matter, the undersigned's factual findings in Sections VI.B.ii and VI.C.iii, which find no metabolic or immune abnormality present, render petitioners' theory effectively inoperative in this case. Nevertheless, the undersigned does not find preponderant evidence of a reliable medical theory explaining how I.R.'s ProQuad vaccination could have caused or contributed to his condition.

That is, for the reasons described in Section VI.C, the undersigned does not find preponderant evidence that autism can be causally explained by the presence of a mitochondrial disorder or dysfunction. Although evidence was presented to suggest that mitochondrial disorders may be associated with or comorbid to autism, there is not preponderant evidence of any causal connection. Nor is the undersigned persuaded that there is preponderant evidence, as petitioners suggest, that repeated immune stressors can lead to the development of autism among those with a mitochondrial disease or dysfunction. Moreover, there is not preponderant evidence that vaccinations can be implicated as triggering events, bringing about injurious catabolism. Additionally, as the undersigned found in Section VI.B, that there is not preponderant evidence of clinically significant immune suppression by the MMR vaccine.

To the extent that petitioners argue that I.R. experienced a vaccine-caused fever, which in turn caused catabolism leading to neurological deterioration, they have failed to demonstrate that such a deterioration explains I.R.'s condition given the facts here. Respondent's experts agreed in theory that any brain injury, including neurological deterioration following metabolic decompensation, could appear similar to autism in terms of behavior manifestations, but as described in Section VI.C.iii, they persuasively explained that such an injury would have appeared as part of a constellation of symptoms that are simply not present in this case. There is not preponderant evidence on this record that metabolic decompensation would present as autism or in any other manner consistent with I.R.'s presentation.

E. Loving Prong 5/Althen Prong 2

Under Loving Prong 5 and Althen Prong 2, petitioners must demonstrate by preponderant evidence a logical sequence of cause and effect showing that the vaccination was the reason for the injury. Complementing the prior prong's "can it?" formulation, this prong is sometimes conceptualized as requiring that the vaccine at issue did cause the vaccinee's injury.[164]

[164] See, e.g., Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355-56 (Fed. Cir. 2006).

Following his ProQuad vaccination, I.R. did experience a likely vaccine-reaction consisting of a fever and rash. Petitioners additionally allege, however, that he experienced a prolonged period of illnesses causally-connected and temporally associated to his vaccination by means of immune suppression and immune dysfunction. For the reasons discussed in Section VI.B.ii, the undersigned does not find preponderant evidence supporting this contention. Specifically, the undersigned does not find preponderant evidence that I.R. experienced vaccine-caused immune suppression in the weeks or months following administration of his ProQuad vaccine or that he experienced any other immunological deficiency.

Additionally, petitioners allege that I.R.'s condition is a consequence or aggravation of mitochondrial disorder or dysfunction. However, for the reasons described in Section VI.C.iii, the undersigned does not find preponderant evidence that I.R. had any mitochondrial disease or dysfunction. Petitioners further allege that I.R. was neurologically typical prior to receiving his ProQuad vaccine, and that subsequent to his vaccinations he regressed and became autistic. Yet, for the reasons discussed in Section VI.A.iii, the undersigned does not find preponderant evidence supporting this contention. Rather, the undersigned found preponderant evidence that I.R.'s autism manifested prior to his ProQuad vaccination and did not find preponderant evidence that he subsequently experienced a regression.

F. Loving Prong 6/Althen Prong 3

The final prong requires petitioners to show a proximate temporal relationship between vaccination and injury. In this regard, petitioners assert multiple temporal relationships.

First, petitioners note that I.R. experienced an acute ProQuad reaction consisting of fever and rash eight days after his vaccination. Pet. Posthr'g Br. at 123. Petitioners alleged further that I.R. experienced a period of post-vaccination immune suppression evidenced by rashes, infections, and fevers, beginning with a roseola infection on February 3, 2006. Id. at 124. Petitioners assert that this infection corresponds with the expected nadir for post-vaccination immune suppression, which is five weeks post-vaccination. Id. Petitioners allege that the period of illness concluded within a medically-appropriate 12 weeks of the ProQuad vaccination. Id. Petitioners argue that from that time forward, a process of accumulating catabolism and immune dysfunction led to worsening neurodevelopment. Id. at 125. They argue that clear markers of autism began at around 15 months of age, with I.R. exhibiting "mostly atypical behaviors" by 17 months of age. Id. at 126-27.

However, petitioners' assertion that I.R. experienced a period of illnesses temporally associated with his vaccination does not establish a temporal association between his vaccination and his autism. As noted in Section VI.B.ii, I.R.'s onset began prior to his vaccination and, in any event, this period of illness does not explain the trajectory of his autism. As previously noted, the undersigned found that I.R. more likely than not was autistic prior to receiving his ProQuad vaccine and that he did not subsequently experience a regression. Nor did he ever have any mitochondrial disorder or dysfunction or immune deficiency, whether temporally associated with his vaccination or not. Thus, the petitioners failed to provide preponderant evidence of a temporal association between his vaccinations and ASD.

G. Similar Conclusions from Prior Decisions

The undersigned notes that many prior cases within the Vaccine Program have alleged that one or more vaccines caused or aggravated a mitochondrial disease or dysfunction leading to autism. In no instance has any petitioner prevailed on such a theory.

In their post-hearing briefs, the parties disagreed as to the significance of this context. Respondent characterizes petitioners' causation argument as an attempt to "temper the findings of the OAP by asserting a mitochondrial component." Resp. Posthr'g Br. at 14. He argued that many prior petitioners have made similar attempts. Id. In their reply brief, however, petitioners stressed that the presence of a mitochondrial disorder allegation does in fact make the issues litigated in this case distinct from the issues litigated during the OAP. Pet. Reply Posthr'g Br. at 2. Petitioners correctly note that none of the OAP test cases involved a child with a mitochondrial disorder. Id. Respondent pointed out, however, that many former-OAP cases litigated subsequent to the conclusion of the test cases have specifically addressed autism in the context of a mitochondrial disease or dysfunction.[165] Resp. Posthr'g Br. at 14 n.8.

Respondent is correct that many prior decisions following from the OAP have addressed issues related to autism and mitochondrial disease or dysfunction. In each of these post-OAP cases, petitioners have failed to demonstrate that any vaccination caused or contributed to the vaccinee's autism. Additionally, those that have been challenged have been upheld upon review at the Court of Federal Claims and appeal to the U.S. Court of Appeals for the Federal Circuit. See, e.g. R.K., 2015 WL 10936124; R.V., 2016 WL 3882519; Anderson v. Sec'y of Health & Human Servs., No. 02-1314V, 2016 WL 8256278 (Fed. Cl. Spec. Mstr. Nov. 1, 2016), mot. for rev. denied, 131 Fed Cl. 735, aff'd, 717 F. App'x 1009 (2018); Holt, 2015 WL 4381588; Coombs v. Sec'y of Health & Human Servs., No. 08-818, 2014 WL 1677584 (Fed. Cl. Spec. Mstr. Apr. 8, 2014); Brook v. Sec'y of Health & Human Servs., No. 04-405, 2015 WL 3799646 (Fed Cl. Spec. Mstr. May 14, 2015); Bushnell v. Sec'y of Health & Human Servs., No. 02-1648, 2015 WL 4099824 (Fed. Cl. Spec. Mstr. June 12, 2015); Miller, 2015 WL 5456093; Hardy v. Sec'y of Health & Human Servs., No. 08-108, 2015 WL 7732603 (Fed. Cl. Spec. Mstr. Nov. 3, 2015); Hooker v. Sec'y of Health & Human Servs., No. 02-472, 2016 WL 3456435 (Fed. Cl. Spec. Mstr. May 19, 2016); Dempsey v. Sec'y of Health & Human Servs., No. 04-394, 2017 WL 1058480 (Fed. Cl. Spec. Mstr. Feb. 23, 2017); Pope v. Sec'y of Health & Human Servs., No. 14-78, 2017 WL 2460503 (Fed. Cl. Spec. Mstr. May 1, 2017); Kreizenbeck v. Sec'y of Health & Human Servs., No. 08-209, 2018 WL 3679843 (Fed. Cl. Spec. Mstr. June 22, 2018), mot. for rev. denied, No. 08-209 (Fed. Cl. Nov. 7, 2018).[166]

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[165] Following the conclusion of the OAP test cases, those petitioners that opted not to dismiss their cases were required to present a theory of causation distinct from the theories presented during the test cases. In many instances, petitioners proceeded with a theory that an underlying metabolic abnormality was aggravated by a vaccine, leading to autism. See, e.g. Anderson, 2016 WL 8256278, at *26.

[166] Paluck, previously discussed, alleged neurodegeneration and mitochondrial disorder, but not autism. See 104 Fed. Cl. 457.

Though petitioners acknowledge that at least some of the prior decisions turned in part on the lack of any persuasive theory of causation, they nonetheless argue that the primary failure in most of these prior cases was the inability of petitioners to establish the presence of any mitochondrial disease or dysfunction. Pet. Reply Posthr'g Br. at 2-4. They stress that no prior case involved a POLG mutation and argue that "[t]hese failures cannot be imputed to petitioners in the instant case," noting that "[p]etitioners' case must be judged on its own merits." Id. at 2-3.

Notwithstanding the fact that the undersigned's conclusion in this case accords with the many prior post-OAP decisions rejecting vaccine causation of autism in the context of mitochondrial disease or dysfunction, the undersigned agrees with petitioners' assertion that the findings in those prior cases cannot be imputed to petitioners. The undersigned stresses that she has not done so and that, as the preceding pages reflect, she has judged this case on its own merits and based on the evidence of record. The resulting conclusions are highly fact intensive, but ultimately fail to meaningfully distinguish this case from the previous cases in which compensation has been denied.

IX. Conclusion

I.R. has clearly endured much suffering in his young life. The undersigned feels great sympathy for him, and great admiration for the way his parents have advocated on his behalf. However, she must decide this case not on those emotions, but on the record before her. For all of the reasons discussed above, the undersigned finds that petitioners have not established entitlement to compensation and that their petition must be dismissed. In the absence of a timely filed motion for review filed pursuant to Vaccine Rule 23, the Clerk is directed to enter judgment consistent with this decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Chief Special Master