In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 01-565V

(Filed: December 20, 2012)

MAKENA SHAYE BAST, by her mother and natural guardian, TIFFANY BAST, **Petitioner,** **v.** **SECRETARY OF HEALTH AND HUMAN SERVICES** **Respondent.**	PUBLISHED Hepatitis B Vaccination; Mitochondrial Disorder; Impact of Oxidative Stress; Seizure Disorder and Developmental Delay; Insufficient Proof of Causation

Clifford Shoemaker, Petitioner, Vienna, VA

Anne Donohue Martin, Respondent, Washington, DC

DECISION[1]

Petitioner, Tiffany Bast, filed this vaccine claim under the National Vaccine Injury Compensation Program ("the Program"),[2] on behalf of her minor daughter, Makena, on

[1] Because this decision contains a reasoned explanation for the undersigned's action in this case, the undersigned intends to post this decision on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). As provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, "the entire" decision will be available to the public. Id.

October 1, 2001 ("Petition"). Mrs. Bast alleges that as a result of the hepatitis B vaccination administered to Makena on October 23, 1998,[3] she suffered seizures, an encephalopathy, and liver damage. Petition at 1-2.

Petitioner's theories of causation have changed over time. Petitioner initially sought compensation for seizures, an encephalopathy, and liver damage without identifying a causal mechanism of harm. Petition at 2. Later, petitioner unsuccessfully sought to transfer this claim into the omnibus autism proceeding ("OAP") on a theory of mercury toxicity. See Motion to Defer Proceedings and Include in Omnibus Autism Proceedings or, in the Alternative, for Enlargement of Time, October 14, 1998 ("Pet'r's Motion to Defer, Oct. 14, 2008"). Petitioner ultimately proceeded on the alternate theories of vaccine-induced autoimmunity and mitochondrial dysfunction.

As developed, the record does not support a finding of entitlement on the theories that petitioner chose to pursue. A procedural overview follows to provide context for the substantive developments in this case.

I. Procedural Overview

Petitioner filed this vaccine petition on Makena's behalf without medical records, affidavits, or other documentation on October 1, 2001. See Petition. The first medical records were filed in November of 2001, a month after filing the petition. Over the course of the next year, petitioner filed 36 exhibits of medical records. Case development then ceased for four years pending efforts to manage groups of hepatitis B claims involving similar injuries as omnibus-type proceedings. Those efforts ultimately were not successful.

The case was reassigned in February of 2006 to the undersigned for further development. Order of Reassignment, Feb. 8, 2006. In July of 2006, respondent filed a

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[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 et seq. (hereinafter "Vaccine Act" or "the Act"). Hereafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

[3] Petitioner's theory of vaccine-related causation--as developed during the hearing--appeared to implicate, without distinction, all of the vaccines Makena received on December 4, 1998. Petitioner asserted in her Post-Hearing Brief ("Pet'r's Br.") that the multiple vaccines Makena received on December 4, 1998, caused her to develop neurodevelopmental disorders and intractable epilepsy. Pet'r's Br. at 1.

Rule 4 report recommending against vaccine compensation.[4] Thereafter, petitioner filed additional medical records, and in November of 2007, an expert report from Dr. Joseph Bellanti, an immunologist. Petitioner then requested and received a number of extensions of time for filing the expert reports from Dr. Mark Geier,[5] an obstetrician with a doctoral degree in genetics, and Dr. Richard Frye, a pediatric neurologist.

In October of 2008, petitioner moved to defer proceedings and to include this case in the omnibus autism proceedings. Pet'r's Motion to Defer, Oct. 14, 2008. Alternatively, petitioner requested another enlargement of time for the filing of the expert reports from Drs. Geier and Frye. Id. at 2. Noting that one of petitioner's treating

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[4] Respondent's Rule 4 report (Resp't's Report) incorrectly identifies petitioner's filing date as July 26, 1999. Resp't's Report at 1.

[5] On April 27, 2011, the Maryland State Board of Physicians (Board) summarily suspended Dr. Geier's license to practice medicine in Maryland on the ground that the public health, safety, and welfare required such action. See In re Geier, Order for Summary Suspension of License to Practice Medicine, Md. State Board of Physicians, Case Nos. 2007-0083, 2008-0454, 2009-0308 (April 27, 2011), available at http://www.mbp.state.md.us/pages/recent_alerts.html. Six other states--California, Indiana, Kentucky, New Jersey, Virginia and Washington--subsequently suspended Dr. Geier's license to practice medicine pending the outcome of the disciplinary proceeding in Maryland. See Medical Board of California, License Look-up System, http://www2.mbc.ca.gov/LicenseLookupSystem/PhysicianSurgeon/Lookup.aspx?licenseType=G&licenseNumber=88736 (last visited December 13, 2012). The State Medical Board of Ohio initiated similar action with Dr. Geier's pending licensure application based on Maryland's licensing board suspension, concluding:

> that the public health, safety, and welfare imperatively required emergency action based on the determination that doctor's treatment for autistic children included exposing children to needless risk of harm resulting from misdiagnoses, failing to conduct adequate physical examinations prior to starting treatment, and treating with therapies not supported by evidence-based studies.

See State Medical Board of Ohio, Monthly Formal Actions July 2011, available at http://med.ohio.gov/professionals-mfal.htm.

On March 22, 2012, following an appeals process, the Board upheld the suspension of Dr. Geier's license to practice medicine. See, In re Geier, Final Decision & Order, Md. State Board of Physicians, Case Nos. 2007-0083, 2008-0454, 2009-0308 (March 22, 2012), available at http://www.mbp.state.md.us/pages/disciplinary.html.

doctors, Dr. DeOrio, believed Makena had extremely high heavy metal levels that negatively affected her brain, counsel requested that the case-specific proceedings be deferred during the pendency of the OAP test cases because the mercury toxicity question in this case might be informed by the hearings in the autism cases. Id. at 1.

The undersigned denied petitioner's request to transfer the case into the OAP because Makena's records did not establish that she had an autism spectrum disorder, one of the prerequisites for inclusion in the OAP. See Order Denying Transfer April 2, 2009 at 7; (See also Autism General Order #1, 2002 WL 31696785 (Fed. Cl. Spec. Mstr., Jul. 3, 2002)). Petitioner subsequently filed expert reports from Drs. Geier and Frye.

In this decision, the undersigned focuses chiefly on the opinion offered by Dr. Frye--even though petitioner filed the opinions of Drs. Bellanti and Geier, see Petitioner's Exhibits (Pet'r's Exs.) 46, 48--because petitioner relied solely on the expert opinion of, and the supporting literature supplied by, Dr. Frye at hearing and in the later prosecution of her claim. See Vaccine Rule 8.

Dr. Frye is a pediatric neurologist specializing in the treatment of such conditions as autism and developmental delay, learning disabilities, and epileptic encephalopathy. Petitioner filed the first of her two expert reports in September of 2009. Pet'r's Ex. 51. In the first expert report, Dr. Frye stated:

> Genetic studies [have] identified that Makena manifests a mutation in the [(SCN1A)] sodium channel gene. . . . In the current case, it is clear that both an environmental (i.e., vaccine) and metabolic factor (i.e., mitochondrial dysfunction), interacted with the [(SCN1A)] mutation to unmask a severe refractory epilepsy. In my medical opinion, to a reasonable degree of medical certainty, Makena's developmental regression, brain injury and seizure disorder is a result of childhood vaccines triggering an underlying susceptibility to manifest severe clinical symptoms.

Id. at 6.[6] Dr. Frye did not mention the earlier received hepatitis B vaccine on October 28, 1998, but he did advert to Makena's "extremely high heavy metal toxicity." Pet'r's Ex. 51 at 4. Dr. Frye implicated the inactivated polio (IPV), diphtheria-tetanus-acellular pertussis (DTaP), Haemophilus influenza type B (Hib), and hepatitis B vaccines that Makena received more than one month later, on December 4, 1998. Id. at 1. Because the SCN1A testing referenced by Dr. Frye was not part of the record, the undersigned

[6] In his expert report, Dr. Frye inadvertently inverted the "1A" in SCN1A. Pet'r's Ex. 51 at 6.

directed petitioner to file the results of Makena's genetic studies and all of her updated neurologic records. Order, Dec. 8, 2009.

Petitioner filed additional medical records on January 22, January 28, and March 5, 2010. See Pet'r's Exs. 53-55 and 58. She also filed a statement of unavailability asserting that neither she nor her counsel could find where the testing for the SCN1A sodium channel gene had ever been performed. Pet'r's Ex. 57 at 3. Nor did she or her counsel know "where the information regarding these tests ha[d] come from." Id. During a status conference held on March 18, 2010, petitioner's counsel asserted again that there is no evidence that Makena ever had the SCN1A testing to which Dr. Frye referred in his original report.[7] See Order, Mar. 18, 2010. Nevertheless, petitioner intended to "rely on Dr. Frye" and "proposed filing an amended report from Dr. Frye." Id.

Petitioner filed Dr. Frye's amended report on April 30, 2010, with all references to a SCN1A mutation removed.[8] Pet'r's Ex. 59. Other than the omitted references, Dr.

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[7] At hearing, Dr. Frye acknowledged that Makena has never been tested for the SCN1A gene mutation, known to be causally associated with serious seizure disorders. Tr. at 85 (incorrect transcription of the gene as "FCN1A," as opposed to "SCN1A"). After the hearing, Dr. Frye published a paper in which he presented two case reports of children with clinical features of severe myoclonic epilepsy of infancy but no mutations in the SCN1A gene. Richard E. Frye, Leber's Hereditary Optic Neuropathy Mutations Associated with Infantile-Onset Myoclonic Epilepsy, 26 J. Child Neurology 782 (2011) (attached hereto and referenced as Court Exhibit 1). Instead, the two children were discovered to have mitochondrial DNA mutations associated with Leber's hereditary optic neuropathy ("LHON"). One of the reported cases (pertaining to patient 2) contains facts that are strikingly similar to Makena's, including her clinical history, her recorded blood and serum lactate levels, and her identified 15257G>A point mutation in the CytB gene. Of note, Dr. Frye reports an association between patient 2's point mutation for Leber's hereditary optic neuropathy and her severe myoclonic epilepsy in infancy, noting her SCN1A negative status. Court Ex. 1 at 783. In the published paper, Dr. Frye makes no mention of any association between a LHON mutation, severe myoclonic epilepsy, and vaccines. Court Ex. 1 at 782-85.

[8] Because testing has not shown that Makena has a SCN1A mutation and because Dr. Frye abandoned his earliest theory of causation implicating the SCN1A mutation, the undersigned finds the filed literature associating the SCN1A mutation with seizure activity, specifically Petitioner's Exhibit 83, to be irrelevant in this case. See Pet'r's Ex. 83 (R.H. Wallace et al., Sodium Channel α1-Subunit Mutations in Severe Myoclonic Epilepsy of Infancy and Infantile Spasms, 61 Neurology 765 (2003). Nor did petitioner ultimately rely on this article.

Frye's opinion remained substantially the same. He maintained that Makena's vaccines triggered an underlying susceptibility--created by a mitochondrial abnormality--to cause her "developmental regression, brain injury[,] and seizure disorder." Id. at 6. Petitioner appeared to abandon completely the mercury toxicity theory of causation, which had been suggested by her treater, Dr. DeOrio.[9]

In July of 2010, respondent filed responsive expert reports from Gerald Raymond, M.D., an expert in pediatric neurology and neurogenetics, and Dean Jones, Ph.D., an expert in mitochondrial oxidative stress. Respondent's Exhibits (Resp't's Exs.) A-D. Respondent also filed 19 articles in support of her experts' opinions. Resp't's Exs. E-W. Respondent challenged the vaccine-relatedness of Makena's injury.

An entitlement hearing was conducted on December 6, 2010, in Washington, D.C. Dr. Frye testified for petitioner. Petitioner offered, and the undersigned accepted, Dr. Frye as an expert in child neurology and pediatrics. See Tr. at 11.

Dr. Frye received his medical and doctoral degrees from Georgetown University. Pet'r's Ex. 52 at 1; Tr. at 9. His Doctor of Philosophy degree was awarded in the areas of physiology and biophysics. Pet'r's Ex. 52 at 1; Tr. at 9. He completed residencies in both pediatrics and neurology, a clinical fellowship in behavioral neurology, and a research fellowship in psychology. Id. He is board certified in both pediatrics and neurology. Pet'r's Ex. 52 at 1; Tr. at 11. He has special competency in pediatric neurology. Id. Dr. Frye began his practice at the University of Florida. Pet'r's Ex. 52 at 1; Tr. at 9. Employed as an assistant professor at the University of Texas Medical School at the time of hearing, he teaches, conducts research, and treats children with neurodevelopmental disorders. Tr. at 10. As defined in the leading textbook on pediatrics, neurodevelopmental disorders involve "disruptions of neuroanatomic structure or psychophysiologic function that may be associated with problems related to cognition, academics, and/or behavioral, emotional, social, and adaptive functioning." Robert M. Kliegman et al., Nelson Textbook of Pediatrics 108 (19th ed. 2011).

Drs. Raymond and Jones testified for respondent. Respondent offered, and the undersigned accepted, Dr. Raymond as an expert in pediatric neurology and neurogenetics, and Dr. Jones as an expert in mitochondrial function and oxidative stress. See Respondent's Prehearing Submission at 1; Tr. at 129-30, 207-08.

Dr. Raymond received his doctorate from the University of Connecticut Medical School. Resp't's Ex. B at 1; Tr. at 127. He completed a residency in pediatrics at Johns

[9] Although Dr. DeOrio appears to have treated Makena over an extensive period of time, the medical records filed from his office were sparse and very difficult to read. See Pet'r's Ex. 36.

Hopkins Hospital, a fellowship in Brussels in developmental neuropathology (involving the structural features of nervous system disease), and a fellowship at Massachusetts General Hospital in genetics and teratology (involving abnormal development and congenital anomalies). Resp't's Ex. B at 1; Tr. at 127-28. He is board certified in neurology and clinical genetics and has special qualifications in child neurology. Resp't's Ex. B at 10; Tr. at 128.

Earlier in his career, Dr. Raymond practiced at Newton-Wellesley Hospital. Resp't's Ex. B at 2. The last 18 years of his career have been spent at John Hopkins and Kennedy Krieger Institute. Id. There, Dr. Raymond serves as a professor of neurology at Johns Hopkins, teaching medical students at the pre-clinical level as well as medical residents and fellows at the clinical level. Resp't's Ex. B at 2; Tr. at 128. He also serves as the Director of Neurogenetics at Kennedy Krieger. Resp't's Ex. B at 2; Tr. at 128.

In his clinical practice, Dr. Raymond sees patients who have genetic disorders that result in neurologic manifestations, such medical conditions including muscular dystrophy (a group of genetic, degenerative muscle diseases), leukodystrophy (neurodegenerative diseases involving the white matter of the brain), and progressive neurodegenerative disorders. Tr. at 129. Dr. Raymond also treats patients with general neurological issues such as seizure disorders and movement disorders. Id.

Dr. Raymond is the attending physician one month of the year at Johns Hopkins' genetic service, and in his clinical practice, he identifies mitochondrial disorders. Id. He has published extensively on the neurological manifestations of various genetic disorders. See Resp't's Ex. B at 2-6.

Respondent's second testifying witness, Dr. Jones, holds a doctoral degree in biochemistry. Resp't's Ex. D at 2; Tr. at 204. He received postdoctoral training at Cornell University and at the Karolinska Institute in molecular toxicology. Resp't's Ex. D at 2; Tr. at 205. Currently, he is a professor in the Department of Biochemistry at Emory University School of Medicine, teaching biochemistry and nutrition courses as part of the medical school curriculum and teaching pharmacology and toxicology in the graduate school curriculum. Tr. at 204, 206. In addition, Dr. Jones holds adjunct appointments in the Pediatrics and Ophthalmology Departments as well as in the Winship Cancer Institute. Resp't's Ex. D at 2; Tr. at 205. He also serves as the Director of the Clinical Biomarkers Laboratory. Resp't's Ex. D at 2; Tr. at 204. Denoted as a clinical laboratory, the focus of the work in the laboratory is on identifying new biomarkers to aid the work done in clinical settings. See Tr. at 206.

Dr. Jones described his ongoing research in two main areas, both of which are supported by grants from the National Institutes of Health. Tr. at 206-07. The first area involves "looking at the compartmentalization of oxidative stress, specifically

mitochondria and oxidative stress." Tr. at 207. The second area involves metabolic profiling, particularly for the progressive movement disorder of Parkinson's disease. Id.

Dr. Jones has published between 150-200 papers on oxidative stress. Tr. at 207. He also lectures nationally and internationally on the topic. Id. He has spent the last five years lecturing on the redefinition of oxidative stress that has "occurred as a consequence of the failure of large scale antioxidant trials to actually protect against human disease outcomes." Tr. at 207-08.

After the hearing, the parties filed briefs. The matter is now ripe for decision.

II. Summary Evaluation of the Parties' Testimony

The undersigned has carefully considered the experts' opinions and the filed literature[10] as well as Makena's medical records.[11] While each of the testifying experts was unquestionably competent, respondent's experts possessed superior expertise in the particular medical topics at issue in this case.

The testimony of Drs. Jones and Raymond reflected the highly specialized nature of their expertise. Dr. Jones offered current scientific insights on the concept of oxidative stress, and Dr. Raymond brought to bear his extensive clinical experience in evaluating mitochondrial disorders. Respondent's experts cogently rebutted petitioner's offered medical theory based on the facts of this case.

In contradistinction, the strength of Dr. Frye's expert report and his testimony was greatly diminished by his lack of familiarity with Makena's medical records and her clinical course. Further diminishing the strength of Dr. Frye's opinion was his unflagging reliance on the affidavits of Makena's parents (the Basts) to develop a

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[10] During the hearing, Dr. Frye referenced articles that were not part of the record. These were accepted as evidence during the hearing and designated as petitioner's trial exhibits. Dr. Jones used a white board to illustrate two points during his testimony. His demonstrative illustrations were photographed at the hearing and designated as respondent's trial exhibits. During the preparation of this opinion, the undersigned learned that respondent's trial exhibits were never filed into the record because they were lost before filing.

[11] The record in this case is voluminous and the same medical records can often be found in more than one place in the record. The undersigned does not cite to each of the duplicative records.

timeline of critical events for Makena--even when confronted with the information that the parental affidavits were either unsupported by or contradicted by the contemporaneous medical records.

In his first submitted expert report, Dr. Frye did not mention the earlier administered October 28, 1998, hepatitis B vaccine, implicating instead the inactivated polio, diphtheria-tetanus-acellular pertussis, Haemophilus influenza type B, and hepatitis B vaccines that Makena subsequently received on December 4, 1998. Pet'r's Ex. 51 at 1. Dr. Frye also pointed erroneously to Makena's SCN1A testing until petitioner's counsel indicated during a status conference that the SCN1A testing was never performed. See Order, Dec. 8, 2009, and see also Order, Mar. 18, 2011. Dr. Frye removed references to an SCN1A mutation, in his amended report filed on April 30, 2010, without changing the ultimate conclusion that "Makena's developmental regression, brain injury and seizure disorder" resulted from her childhood vaccines and triggered an "underlying susceptibility to manifest severe clinical symptoms." Pet'r's Ex. 59 at 6.

The general causation theory as presented by Dr. Frye contravenes the contemporary scientific understanding of oxidative stress as distinguished from oxidative damage. In addition, the facts specific to Makena's case offer poor support for Dr. Frye's theory of vaccine-triggered mitochondrial decompensation, and Dr. Frye allowed that he was "just trying to find some evidence in the literature" to explain how the theory he proposed "actually might occur." Tr. at 74, 76-7.

A close review of Makena's medical records does not provide the necessary support for petitioner's offered theory of causation. During her first two years of life, Makena received a number of extensive examinations by diverse specialists to evaluate her seizure disorder and the impact of the treatment she had received on her different organs and body systems. Makena's treating physicians attributed her health issues variously to congenital brain abnormalities, an evolving seizure disorder that may have been caused by a metabolic disorder, and the effects of Makena's anticonvulsant medications. It is petitioner's expert, Dr. Frye, who offers the singular opinion that Makena's health problems resulted from a vaccine-induced cascade of events--including the development of a seizure disorder--that was facilitated by Makena's mitochondrial point mutation and in turn, produced detrimental levels of excess reactive oxygen species, a condition known as oxidative stress. While genetic testing does indicate that Makena has a mitochondrial point mutation, the detected mutation is not associated in any manner with seizures but exclusively with a type of vision loss that Makena has not suffered.

Respondent's experts, Drs. Jones and Raymond, testified persuasively that the commonly induced but transient state of oxidative stress, such as Makena experienced in this case, cannot produce the type of permanent damage alleged. As Dr. Jones explained, the metabolic effects of the administered vaccines were too remote from the brain and too short-lived to have achieved the degree of harm that petitioner has alleged. As Dr.

Raymond repeatedly observed, Makena's mitochondrial point mutation is associated with vision problems--not seizures, and Makena has not manifested any of the characteristic symptoms of the eye condition linked to her specific genetic mutation. Dr. Raymond further explained, and Dr. Frye conceded, that petitioner's theory of causation relied not on an association between seizures and the particular mutation detected in Makena, but instead on an association between seizures and different mutations found in the same genetic region in which Makena's point mutation occurred. The undersigned found the testimony of respondent's experts more persuasive than the testimony of Dr. Frye.

For these reasons, which are discussed more fully below, the undersigned concludes that petitioner is not entitled to compensation under the Vaccine Program.

III. Factual Background

The facts in this case are established by the contemporaneous medical records and the later-prepared affidavits of Makena's parents and her maternal grandparents. Although Mrs. Bast and her father (Makena's grandfather) were present during the hearing, neither testified. Accordingly, to the extent that any of the affidavit testimony conflicts with or is unsupported by the medical records, the undersigned has credited the contemporaneous medical records. See Cucuras v. Sec'y of Health & Human Servs., 993 F.2d 1525 (Fed. Cir. 1993) (supporting a presumption that medical records created contemporaneously with the events described are generally more accurate and complete than later created testimony).

Makena's medical history is complex. Because the causation theory in this case rests heavily on a finding that Makena had impairments in a number of her body systems, her medical records are addressed in some detail--with particular attention given to the multiple evaluations of her seizures and her various organs.

A. Pre-Vaccination Medical History

Makena was born on October 11, 1998. Pet'r's Ex. 12 at 35. Mrs. Bast had a complicated pregnancy. She was involved in an automobile accident on March 27, 1998, at the beginning of her second trimester, and thereafter developed migraine headaches. Pet'r's Ex. 4 at 2; Pet'r's Ex. 12 at 25. For pain management, Mrs. Bast was prescribed Vicodin.[12] Id. Later in her second trimester, Mrs. Bast contracted a respiratory infection.

[12] Vicodin is "a semisynthetic narcotic analgesic" that acts on the central nervous system and smooth muscle in a manner that is qualitatively similar to that of codeine. Physicians' Desk Reference 581 (66th ed. 2012). Because there are no well-controlled studies of Vicodin use in pregnant women, it is recommended for use during pregnancy "only if the potential benefit justifies the potential risk to the fetus." Id. at 582.

Pet'r's Ex. 19 at 217. To treat the infection, Mrs. Bast was given a one week prescription of the antibiotic Erythromycin[13] on June 19, 1998, and a one week prescription of the antibiotic Keflex[14] on July 1, 2008. Pet'r's Ex. 4 at 3 (Erythromycin is abbreviated to "ESS").[15] Mrs. Bast was given prescription strength Robitusson AC[16] to treat the "persistent cough and congestion" that accompanied this infection. Id. During her third trimester, Mrs. Bast fell and tore the round ligament of her uterus. Pet'r's Ex. 19 at 217. Placed on bed rest, she again was prescribed Vicodin for pain. See Pet'r's Ex. 12 at 25; Pet'r's Ex. 19 at 217.

Notwithstanding the powerful pre-natal chemical exposures Makena experienced, she was carried to full-term and weighed 8 pounds, 13 ounces at birth. Pet'r's Ex. 12 at 29. Her birth was assisted by the uterine stimulant Pitocin.[17] Pet'r's Ex. 13 at 20. During labor, Makena's umbilical cord became wrapped tightly around her neck; it required removal at birth. Pet'r's Ex. 13 at 10; Pet'r's Ex. 13 at 20 (indicating a nuchal cord).[18]

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[13] "Erythromycin is an antibiotic used to treat certain infections caused by bacteria, such as bronchitis; diphtheria; Legionnaires' disease; pertussis (whooping cough); pneumonia; rheumatic fever; venereal disease (VD); and ear, intestine, lung, urinary tract, and skin infections." U.S. National Library of Medicine, PubMed Health, AHFS Consumer Medication Information–Erythromycin, http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000662// (last reviewed 12/11/2012).

[14] Keflex, or the generic drug Cephalexin, is "used to treat certain infections caused by bacteria such as pneumonia and bone, ear, skin, and urinary tract infections." U.S. National Library of Medicine, PubMed Health, AHFS Consumer Medication Information–Cephalexin, http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000762/ (last visited December 14, 2012).

[15] See Neil M. Davis, Medical Abbreviations 120 (15th ed. 2011).

[16] This preparation contains guaifenesin, an expectorant, and codeine, an opiate used for analgesic purposes. See Robitussin Ac, Rxlist.com, http://www.rxlist.com/robitussin-ac-drug-htm (last visited December 14, 2012).

[17] Pitocin causes uterine contractions "by changing calcium concentrations in the uterine muscle cells." Pitocin, Drugs.com, http://www.drugs.com/cdi/pitocin.html (last visited December 14, 2012).

[18] An umbilical cord that is wrapped around a baby's neck during labor is called a nuchal cord. See Dorland's Illustrated Medical Dictionary 1293 (32nd ed. 2012).

On delivery, Makena's Apgar scores were 8 and 9.[19] Pet'r's Ex. 12 at 15. Her newborn exam was normal. Pet'r's Ex. 13 at 20. She was discharged from the hospital the day after her birth. Pet'r's Ex. 12 at 16.

B. Makena's Vaccinations and Subsequent Evaluations

Twelve days after Makena's birth, she was examined by her pediatrician, Dr. Peri Gunay. Pet'r's Ex. 23 at 9. Dr. Gunay noted a slackness (described as "laxity") in Makena's right hip "but [no] click or clunk," one of the common indicators of a hip joint problem.[20] Id. Makena received her first hepatitis B vaccination during this office visit. Id.

Makena returned to Dr. Gunay's office nearly two weeks later for a sick visit. Id. at 6. Makena presented with complaints of slight nasal congestion, and occasional vomiting, but she did not have a fever. Id. Makena's right eye had been "draining green mucous" for one day. In Dr. Gunay's assessment, Makena had "conjunctivitis."[21] Id. Makena was nearly one month old.

On December 4, 1998, when Makena was nearly two months old, she returned to the pediatrician's office for a well-child visit. Pet'r's Ex. 23 at 9. Makena presented at this visit with a mild cold. Id. The back of her head was noted to be flat (specifically her right occiput),[22] but there was no indication of any concern about her growth or

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[19] An Apgar score is "a numerical expression of the condition of a newborn infant . . . [determined by] the sum of points gained on assessment of the heart rate, respiratory effort, muscle tone, reflex irritability, and color." Dorland's at 1682. The scale ranges from 0, the lowest score, to 10, the highest score. U.S. National Library of Medicine, MedlinePlus, Apgar, http://www.nlm.nih.gov/medlineplus/ency/article/003402.htm (last visited on June 26, 2012).

[20] When developmental hip dysplasia (a problem in the hip joint) is present at birth, the abnormality may be detected during a routine physical examination of the newborn. During examination, the physician gently flexes the child's hips in different directions. If the hip is dislocated, dislocatable, or subluxatable, he or she may feel a "clunk" as the hip moves out of alignment. See Hospital for Special Surgery, Developmental Pediatric Hip Dysplasia – An Overview, http://www.hss.edu/conditions_developmental-pediatric-hip-dysplasia-overview.asp (last visited December 14, 2012).

[21] Conjunctivitis is an "inflammation of the conjunctiva [(the delicate membrane that lines the eyelids)], generally . . . associated with a discharge." Dorland's at 405 (emphasis added).

[22] The occiput is "the posterior part of the head." Dorland's at 1310.

development. See id. At this visit, Makena received her first inactivated polio (IPV), diphtheria and tetanus toxoid with acellular pertussis (DTaP), and Hib vaccines, as well as her second hepatitis B vaccine. Id. It is these vaccines that petitioner holds responsible for Makena's subsequent injuries.

Almost four weeks thereafter, on December 30, 1998, Makena returned to the pediatrician's office with cold symptoms that had been present for one week. Pet'r's Ex. 23 at 6. In their later prepared joint affidavit, Makena's parents asserted that "within ten days of the vaccine[,]" Makena developed a "pretty bad" upper respiratory infection which required a pediatric visit. Pet'r's Ex. 25 at 2. Review of a 1998 calendar places this alleged pediatric office visit on or about December 14, 1998. But, Makena's contemporaneous medical records indicate that she saw the pediatrician on December 30, 1998 for symptoms of an upper respiratory infection and, thus, do not corroborate the Basts' later recalled assertions. See Pet'r's Ex. 23 at 6; Pet'r's Ex. 1 at 176. Accordingly, the undersigned finds that Makena's documented sick visit on December 30, 1998, supports a finding that her upper respiratory infection symptoms began on or about December 23, 1998, and not within the 10 days after Makena received her second hepatitis B vaccine, on December 4, 1998,[23] as Makena's parents asserted in their affidavit and as Dr. Frye repeated in his expert opinion.

On January 4, 1999, less than a week after Makena's sick visit to Dr. Gunay's office, Makena started day care. Pet'r's Ex. 19 at 217.

C. The Emergence of Seizure Activity

On Monday, January 11, 1999, nearly five weeks after Makena received her second hepatitis B vaccine, Mrs. Bast called Dr. Gunay's office to report that she had observed Makena having "three brief spells involving stiffening, eye deviation [and] rhythmic movements of extrem[ities]," each for a few seconds in duration. Pet'r's Ex. 23 at 6. Dr. Gunay indicated that Makena--who was then three months of age--was "to be seen ASAP." Id. That same day, Dr. Gunay examined Makena and noted a five-day history of "seizures"[24] with "altered mental status" that included "eye deviation," and

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[23] Dr. Frye identifies the beginning of Makena's abnormal development as the onset of Makena's upper respiratory infection, which he places at 10 days after Makena received her two-month vaccinations. Pet'r's Ex. 59 at 1.

[24] Makena's parents recalled in their jointly sworn affidavit that Makena began to have tics on or about December 21, 1998, "less than three weeks after her immunizations." Pet'r's Ex. 25 at 2. The Basts' later-provided sworn testimony is consistent with the account of symptom onset provided in the affidavit of Sharon

"twitching movements." Id. Dr. Gunay also noted that Makena recently had an upper respiratory infection marked by "nasal cong[estion] [and] cough but no fever." Id. (emphasis added). During the office visit, Dr. Gunay consulted by telephone with Stuart Stein, M.D., a pediatric neurologist, about Makena's symptom presentation, and determined that if the number of Makena's seizures increased, Makena should begin taking the anticonvulsant medication Phenobarbital.[25] Pet'r's Ex. 19 at 216.

The next day, Makena's seizures increased in frequency. The seizures seemed to occur after her feedings. Id.

Dr. Gunay examined Makena again two days after her last emergent office visit and started her on Phenobarbital. Id. Dr. Gunay also ordered an electroencephalogram ("EEG"), which was performed the next day.[26] Id. at 210. Makena's EEG was

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Hamilton, Makena's maternal grandmother. Pet'r's Ex. 31. Ms. Hamilton averred that she became concerned about small tremors that Makena was experiencing around Christmas of 1998. Id. There is no mention of tics or tremors, however, in the medical records from Makena's December 30, 1998 sick visit. See Pet'r's Ex. 23 at 6. Nor is there any mention of tics in the medical records from her subsequent office visit on January 11, 1999, but Mrs. Bast did report at that office visit a five-day history of observing Makena stiffen and move her extremities rhythmically. Id.

Makena's parents also recalled in their later prepared affidavit that "[b]y January 4, 1999, Makena's tics had turned into grand mal seizures that "occurred up to sixty plus times [per] day." Pet'r's Ex. 25 at 2. The record evidence, however, does not show that Makena exhibited any symptoms of seizures prior to January 6, 1999. The medical records do reflect that Makena's parents were diligent about seeking treatment for her ailments during that period of time. Informed by the record evidence and based on Makena's parents' well-documented attentiveness to her medical needs, the undersigned accords more weight to the contemporaneous medical records than to Makena's parents later recollection of events in their joint affidavit. Accordingly, the undersigned finds that, as recorded by Dr. Gunay, Makena's seizures began on or about January 6, 1999.

[25] Phenobarbital is used to control seizures. U.S. National Library of Medicine, PubMed Health, AHFS Consumer Medication Information - Phenobarbital, http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000542/ (last updated May 16, 2011).

[26] An EEG is an electrodiagnostic test "performed to identify and evaluate patients with seizures. Pathologic conditions involving the brain cortex (such as tumors and infarction) can also be detected." Mosby's Manual of Diagnostic and Laboratory Tests, 573 (4th ed. 2010).

"markedly abnormal" with "very active epileptiform potentials…in the right frontal central area."[27] Pet'r's Ex. 1 at 165.

On January 15, 1999, approximately nine days after the onset of Makena's seizure symptoms, Dr. Stein saw Makena in his office for a neurological evaluation. Pet'r's Ex. 19 at 214. She exhibited symptoms of a "seizure disorder." See id. She also exhibited signs of weakness and diminished muscle tone in her body ("hypotonia") and in her face ("myopathic facies"). Pet'r's Ex. 15 at 93. Dr. Stein postulated that Makena might have a metabolic disorder or have suffered a post-infectious encephalopathy. See Pet'r's Ex. 19 at 214; Pet'r's Ex. 15 at 93 (questioning whether Makena's recent upper respiratory infection might have "activated an existing metabolic disorder" that manifested as seizures).

While in Dr. Stein's office, Makena had at least three seizures that lasted longer than the ones she usually experienced. Pet'r's Ex. 19 at 216. The increasing frequency and length of Makena's seizure activity prompted Dr. Stein to admit Makena to the hospital for treatment with intravenous Dilantin,[28] a computed tomography (CT)[29] scan to rule out a brain "lesion," and monitoring. Id. at 218. Dr. Stein also sought to rule out certain factors as potentially causal of Makena's seizures. Dr. Stein identified those factors as a brain abnormality, an infectious process, and a disorder of energy metabolism. Id.

Testing of Makena's cerebrospinal fluid and a CT scan performed during her hospitalization ruled out a post-infectious encephalopathy. Pet'r's Ex. 23 at 166. However, the CT scan suggested that the formation of Makena's brain was abnormal. See Pet'r's Ex. 1 at 162 (noting the possibility of a "subtle anomaly . . . with agenesis of

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[27] Epileptiform activity is indicative of the brain disturbances that result in seizures (known as epilepsy) "or its manifestations." Dorland's at 633.

[28] Dilantin is the brand name for the generic anticonvulsant phenytoin, "used to control certain type[s] of seizures, and to treat and prevent seizures that may begin during or after surgery to the brain or nervous system. It works by decreasing abnormal electrical activity in the brain." U.S. National Library of Medicine, PubMed Health, AHFS Consumer Medication Information - Phenytoin, http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000549/ (last updated May 1, 2009).

[29] Computed tomography (CT) of the brain "consists of a computerized analysis of multiple tomographic x-ray images taken of the brain tissue at successive layers, providing a three-dimensional (3-D) view of the cranial contents." Mosby's at 1080. The test is indicated when central nervous system disease is suspected, and can aid in the diagnosis of brain tumors, infarction, bleeding, and hematosis. Id.

the corpus callosum").[30] From Makena's lab results, Dr. Stein detected a carnitine insufficiency causing him to question whether Makena might have an energy metabolism disorder.[31] Pet'r's Ex. 23 at 167.

During Makena's hospitalization, she intermittently exhibited signs of temporary paralysis after her seizures, a condition known as Todd's paralysis."[32] Id. at 162, 166.

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[30] Agenesis of the corpus callosum ("ACC") is "a birth defect in which the structure that connects the two hemispheres of the brain (the corpus callosum) is partially or completely absent." National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Health (NIH), Agenesis of the Corpus Callosum Information Page, http://www.ninds.nih.gov/disorders/agenesis/agenesis.htm (last visited December 14, 2012).

Subsequent treaters shared Dr. Stein's concern that Makena's brain formation was abnormal. Another of Makena's evaluating neurologists, Dr. Gospe, ordered a review of Makena's January 1999 MRI scan by James Brunberg, M.D., a pediatric neuroradiologist. In Dr. Brunberg's view, the scan "was abnormal" and was marked by "an area of subtle abnormal cortical thickening in the right frontal lobe" that he believed could "represent a neuronal migration abnormality" (aberrant brain cell movement). Pet'r's Ex. 1 at 54 (emphasis added).

[31] Organic acid levels and carnitine levels may be diagnostic indicators of mitochondrial disease. Lab Evaluation, United Mitochondrial Disease Foundation, http://www.umdf.org/site/pp.aspx?c=8qKOJ0MvF7LUG&b=8032187 (last visited on December 14, 2012). The National Institute of Neurological Disorders and Stroke (NINDS) and the Centers for Disease Control and Prevention (CDC) both identify the United Mitochondrial Disease Foundation as a resource for information on mitochondrial disease. See NINDS, Non-NINDS Funding Resources, Neuromuscular http://www.ninds.nih.gov/funding/funding_announcements/additional_funding_resources.htm# (last visited December 14, 2012); CDC, Autism Spectrum Disorders, Mitochondrial Disease, http://www.cdc.gov/ncbddd/autism/mitochondrial.html (last visited June 26, 2012).

Carnitine is found in skeletal muscle and the liver and is important for the metabolism of fatty acids. Dorland's at 297.

[32] Todd's paralysis is "hemiparesis or monoparesis lasting for a few minutes or a few hours, or occasionally for several days, after an epileptic seizure." Dorland's at 1378. It may also be referred to as post-epileptic paralysis. Id; see also NINDS, (NIH), NINDS Todd's Paralysis Information Page, http://www.ninds.nih.gov/disorders/toddsparalysis/toddsparalysis.htm (last visited December 14, 2012) (describing Todd's paralysis as a neurological condition experienced

On discharge from her two-day hospitalization, Makena was diagnosed with a seizure disorder and an absent corpus callosum.[33] Pet'r's Ex. 19 at 212. To control her seizures, she was sent home taking two anti-seizure medications, Dilantin and Phenobarbitol. Id., Pet'r's Ex. 23 at 162.

On January 20, 1999, three days after her hospital discharge, Makena saw Dr. Stein for a follow-up evaluation. Pet'r's Ex. 19 at 208. Dr. Stein identified Makena's condition as an "idiopathic seizure disorder." Pet'r's Ex. 23 at 168. He proposed treating Makena with carnitine to address the possible energy metabolism disorder he believed might be contributing to her persistent seizure activity.[34] Id. The records indicate that subsequent therapeutic treatment with carnitine and Gabitril[35] did not diminish the number of Makena's seizures; instead her seizures increased to about 20 to 30 a day. Pet'r's Ex. 23 at 162-63.

One week later, Makena was hospitalized for the second time. Pet'r's Ex.11 at 98. She required monitoring by machine because her seizures were accompanied by apneic episodes. See id. A scan of her brain by magnetic resonance imaging (MRI) the day after her hospital admission was "abnormal."[36] Pet'r's Ex. 1 at 141. The scan showed

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by individuals with epilepsy, who after having a seizure, experience a brief period of temporary paralysis).

[33] The corpus callosum is "an arched mass of white matter [in the brain]," composed of three layers of transverse fibers that connect the brain's two cerebral hemispheres. Dorland's at 417.

[34] Dr. Stein had treated other patients with mitochondrial disorders using anticonvulsants and carnitine successfully. After a year of no seizure activity, the patients were weaned from the anticonvulsants but continued to take the carnitine. Pet'r's Ex. 23 at 169. Dr. Stein acknowledged not knowing whether the patients' success was due to the suppressive effects of one year of anticonvulsants, the continued administration of carnitine, or the natural progression of the seizure disorder. Id.

[35] Gabitril is the brand name for the generic anticonvulsant tiagabine, a drug used in combination with other medications to treat partial seizures (a type of epilepsy). U.S. National Library of Medicine, PubMed Health, AHFS Consumer Medication Information-Tiagabine, http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001027/ (last revision: September 1, 2009). Tiagabine is understood to stimulate the naturally occurring chemicals in the brain that prevent seizure activity. Id.

[36] Magnetic resonance imaging (MRI) is a "noninvasive diagnostic technique that provides valuable information about the body's anatomy . . . based on how hydrogen

"[f]ocal thickening and irregularity of the right frontal lobe grey matter" that was "suggestive of [a] focal migrational anomaly," a birth defect caused by the abnormal migration of neurons in the developing brain and nervous system. [37] Id. at 141-42. A report accompanying the scan results indicated that Makena also had a "[t]iny left frontal lobe subdural hematoma", id. at 142, that may have resulted from her vacuum extraction at birth.[38] Pet'r's Ex. 11 at 97. Makena was discharged after a two-day hospital stay. Pet'r's Ex. 11 at 90.

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atoms behave in a magnetic field when disturbed by radiofrequency signals." Mosby's at 1166.

[37] Neuronal migration disorders (NMDs) are:

> a group of birth defects caused by the abnormal migration of neurons in the developing brain and nervous system. In the developing brain, neurons must migrate from the areas where they are born to the areas where they will settle into their proper neural circuits. Neuronal migration, which occurs as early as the second month of gestation, is controlled by a complex assortment of chemical guides and signals. When these signals are absent or incorrect, neurons do not end up where they belong. This can result in structurally abnormal or missing areas of the brain in the cerebral hemispheres, cerebellum, brainstem, or hippocampus. . . .
>
> Symptoms vary according to the abnormality, but often feature poor muscle tone and motor function, seizures, developmental delays, mental retardation, failure to grow and thrive, difficulties with feeding, swelling in the extremities, and a smaller than normal head. . . . Several genetic abnormalities in children with NMDs have been identified. Defects in genes that are involved in neuronal migration have been associated with NMDs, but the role they play in the development of these disorders is not yet well-understood.

NINDS, NIH, What is Neuronal Migration Disorders? http://www.ninds.nih.gov/disorders/neuronal_migration/neuronal_migration.htm (last visited December 14, 2012) (emphasis added). Makena is documented as having a number of the symptoms associated with this disorder.

[38] A hematoma is "a localized collection of blood, usually clotted, in an organ, space, or tissue, usually due to a break in the wall of a blood vessel." Dorland's at 832. The notes accompanying this observation indicate the importance of correlating this observation with clinical data "for accidental or non-accidental trauma, such as head injury during a seizure." Pet'r's Ex. 1 at 142. The doctor's note from the date of her

On February 1, 1999, when Makena was almost four months old, she was referred to the Regional Center of Orange County Department of Developmental Services, a provider of services to individuals with developmental disabilities and their families, for an eligibility determination. Pet'r's Ex. 19 at 115. Makena qualified for services through the Early Start Program,[39] because her global developmental delay and infantile spasms[40] put her at risk for various developmental disabilities. Id. at 108.

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discharge suggests, however, that the discovered hematoma was secondary to Makena's vacuum-extraction at birth. Pet'r's Ex. 11 at 97.

[39] The Early Start Program is a state-run program in California providing:

> teams of service coordinators, healthcare providers, early intervention specialists, therapists, and parent resource specialists [to] evaluate and assess infants or toddlers and provide appropriate early intervention and family support services for young children from birth to three years of age.

California Department of Developmental Services, Early Start Homepage, http://www.dds.ca.gov/earlystart (last visited December 14, 2012).

[40] Infantile spasms that produce chaotic brain waves (described as hypsarrhythmia) during EEG testing are described as West Syndrome, a condition that leads to developmental regression. The spasms usually begin in the first year of life, typically between 4 to 8 months. Infants may have several hundred spasms or dozens of clusters of spasms daily. Birth injury, metabolic disorders, and genetic disorders can lead to such spasms. Office of Rare Diseases Research, NIH, Genetic and Rare Disease Information Center (GARD)–West syndrome, http://rarediseases.info.nih.gov/GARD/Condition/7887/West_syndrome.aspx (last visited December 14, 2012).

> The prognosis for children with infantile spasms is dependent on the underlying causes of the seizures. The intellectual prognosis for children with infantile spasms is generally poor because many babies with infantile spasm have neurological impairment prior to the onset of spasms. Spasms usually resolve by mid-childhood, but more than half of the children with infantile spasms will develop other types of seizures. There appears to be a close relationship between infantile spasms and Lennox-Gastaut Syndrome, an epileptic disorder of later childhood.

NINDS, NIH, NINDS Infantile Spasms Information Page, http://www.ninds.nih.gov/disorders/infantilespasms/infantilespasms.htm (last visited on December 14, 2012).

After her referral for disability services, Makena saw Raman Sanker, M.D., another pediatric neurologist, for further evaluation. Pet'r's Ex. 23 at 162-63. Dr. Sanker noted that prior to the onset of Makena's seizures, she developed "a viral prodrome" at "around the time that she started in Day Care." Id. at 162. A measure of Makena's head circumference put Makena in the 50 percentile for her age.[41] Id. at 163. On examination, Makena exhibited a preference for gazing to the right and lying on her right side. Id. Her face was intermittently weak on the left side. Id. She exhibited a mild head lag and was unable to sit alone. Id.

Dr. Sanker ordered additional EEG testing. Id. The performed EEG was read as markedly abnormal. Pet'r's Ex. 23 at 164. Makena suffered several clinical seizures during the EEG. Id. Petitioner was referred to the Advanced Epilepsy Management Clinic at the University of California at Irvine. See Pet'r's Ex. 23 at 161.

Makena was seen several days later at the Advanced Epilepsy Management Clinic by Tallie Z. Baram, M.D., a pediatric neurologist. Pet'r's Ex. 1 at 168; see also Pet'r's Ex. 23 at 161. Dr. Baram requested another EEG. Pet'r's Ex. 23 at 160. The obtained EEG "[did] not show classical hypsarrhythmia,[42] but [did] show[] a very irritative encephalopathy." Id. Dr. Baram noted that Makena seemed "to have developed an infantile spasm type variant over the past month" and concluded that Makena had an "abnormal brain, likely a [neuronal] migration abnormality, associated with a multifocal, irritative cortex."[43] Id. Dr. Baram identified Makena's condition as severe multifocal epilepsy. Id. She recommended first treating Makena's infantile spasms (also known as West syndrome) before addressing the source of the spasms. Dr. Baram proposed

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[41] The medical records from Makena's pediatrician, Dr. Gunay, indicate that Makena's head circumference went from the 75th percentile at birth to the 10th percentile at nine months. Pet'r's Ex. 1 at 89. According to the leading textbook in pediatrics, there is a correlation between a small head circumference and developmental delay. See Nelson Pediatrics at 2007.

[42] Hypsarrhythmia is "an electroencephalographic abnormality sometimes observed in infants, with random high-voltage slow waves and spikes that arise from multiple foci and spread to all cortical areas." The abnormality is seen most commonly in cases of "jackknife seizures" which are also known as infantile spasms. See Dorland's at 908, 1688.

[43] As mentioned earlier in this decision, see n.29, another pediatric neurologist, Dr. Brunberg, reviewed this MRI scan independently in August 1999. It was his opinion as well that the area of subtle abnormal cortical thickening in Makena's right frontal lobe may have been indicative of "a neuronal migration abnormality." Pet'r's Ex. 1 at 54.

administering adrenocorticotropic hormone (ACTH),[44] restricting Makena's medication to Phenobarbital, and "allow[ing] [Makena's] parents to treat [her] with pyridoxine."[45] Id.

One week after her consultation with Dr. Baram, Makena was examined by Keith DeOrio, D.O., a family physician who offered alternate healing therapies.[46] Pet'r's Ex. 36 at 2; see http://drdeorio.com. Dr. DeOrio noted that Makena was "on Phenobarbital," that her "liver [enzymes were] elevated," and that she was having up to 55 seizures per day. Id. Since his first examination of Makena in 1999, Dr. DeOrio has continued to monitor Makena on an ongoing basis. Pet'r's Ex. 36 at 24.

Two weeks after Dr. DeOrio examined Makena, Dr. Baram examined Makena a second time. Pet'r's Ex. 23 at 157. She noted that Makena's maternal grandfather, one of her primary caretakers, expressed concern that Makena was unable to hear sounds. Id. Dr. Baram indicated that based on the "truly terrible" results of Makena's most recent EEG, it was likely that Makena could not "process outside information" during the episodes of "very abnormal hypsarrhythmic activity,"[47] as measured on her EEGs. Id. In Dr. Baram's view, Makena had "hypsarrhythmia, with a form of infantile spasm" of unknown etiology. Id. Dr. Baram again recommended ACTH, particularly since it did not appear from Makena's "significant evaluation" prior to Dr. Baram's examination that Makena had "a mitochondrial disorder or any other disorders which would preclude her from starting on ACTH." See id. Dr. Baram remarked that Makena's parents were "uncomfortable with the current [treatment] regimen, specifically because of their concern about her liver function elevation." Id.

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[44] Adrenocorticotropic hormone (ACTH) is a steroid used "for the treatment of infantile spasms in infants and children younger than 2 y[ears]." Drug Information Online, Corticotropin, http://www.drugs.com/ppa/corticotropin-adrenocorticotropic-hormone-acth.html (last visited December 14, 2012).

[45] Pyridoxine is "one of the forms of vitamin B_6." Dorland's at 1563.

[46] Petitioner states in her later-filed affidavit dated January 28, 2010, that Makena has been receiving holistic and/or homeopathic treatment since she was three years old. Pet'r's Ex. 56. The records support a finding, however, that Makena began receiving such treatment from Dr. DeOrio when she was four months old.

[47] Makena's EEG, performed on February 26, 1999, at the University of California Irvine, showed suppression of hypsarrhythmia and periodic epileptiform discharges from the left brain. Pet'r's Ex. 1 at 132. Additional testing revealed that her liver enzymes were elevated. Id. at 129. The elevation in her liver enzymes was attributed to her treatment with Phenobarbital. Pet'r's Ex. 41 at 47.

On March 22, 1999, three weeks after Dr. Baram last examined Makena, Makena presented to the Advanced Epilepsy Management Clinic for re-evaluation following her completion of "a two-week dose of ACTH, at a high dose." Pet'r's Ex. 23 at 155. Dr. Baram felt that Makena had "responded beautifully to ACTH in terms of the infantile spasms." Id. Makena's clinical seizures had almost resolved, and her EEG testing was modestly improved.[48] See id. She had become alert, and demonstrated that she could visually track and hear. Id. Based on Makena's improvement, Dr. Baram recommended tapering the ACTH treatment and treating Makena's emerging focal seizure disorder with topiramate.[49] Id.

In March of 1999, additional blood work was performed on Makena to rule out any infectious process. Pet'r's Ex. 1 at 121- 25. The results were negative. Id.

D. The Filing of a VAERS Report

On March 5, 1999, two months after the onset of Makena's symptoms, Dr. Gunay, Makena's pediatrician, filed a Vaccine Adverse Events Reporting System (VAERS) report.[50] Pet'r's Ex. 23 at 175. Dr. Gunay reported that Makena developed seizures after

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[48] On March 18, 1999, an EEG was conducted that showed multifocal sharps with suppression, compatible with a pattern of hypsarrhythmia. Pet'r's Ex. 15 at 73.

[49] Topiramate is an anticonvulsant that is "used alone or with other medications to treat certain types of seizures in people who have epilepsy." U.S. National Library of Medicine, PubMed Health, AHFS Consumer Medical Information – Topiramate, http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000998/ (last revision May 16, 2011).

[50] The National Childhood Vaccine Injury Act (NCVIA) of 1986 requires health professionals and vaccine manufacturers to report to the U.S. Department of Health and Human Services (HHS) specific adverse events that occur after the administration of routinely recommended vaccines. Vaccine Adverse Event Reporting System (VAERS), About the VAERS Program, http://vaers.hhs.gov/about/index (last visited on December 14, 2012) (emphasis added).

The Vaccine Adverse Event Reporting System (VAERS) is a "national vaccine safety surveillance program" co-sponsored by the Food and Drug Administration (FDA) and CDC. Id. A passive surveillance system, VAERS collects information about adverse events and possible side effects that occur after the administration of vaccines licensed for use in the United States. Id. Some adverse events occur coincidentally following vaccination, while others may be caused by vaccination." VAERS, Are All Adverse Events Reported by VAERS Caused by Vaccines, http://vaers.hhs.gov/about/faqs#causality (last visited December 14, 2012).

a December 4, 1998 administration of IPV, hepatitis B, DTaP and Hib vaccines. Id. at 175, 189. Dr. Gunay identified the onset date for Makena's seizures as January 6, 1999. Id. at 175. The report indicates that at the time of her vaccine administration, Makena had a mild upper respiratory infection. Id.

E. Metabolic Testing

On July 2, 1999, Dr. Stein saw Makena for the first time since January of 1999. Pet'r's Ex. 23 at 147. She was nearly nine months old at the time. Dr. Stein again ordered metabolic testing, Id. at 148, which was normal with the exception of a high lactic acid level in Makena's urine.[51] Pet'r's Ex. 1 at 95. By letters to Dr. Gunay dated July 2, 1999 and July 16, 1999, Dr. Stein reviewed Makena's status since his last evaluation of her, stating "[s]he had been treated appropriately for infantile spasms with hypsarrhythmia and subsequently was started on vitamin B6. Id. at 98. The family [is] interested in some detailed testing for pyridoxine-responsive seizure disorder." Id. Dr. Stein continued to question whether Makena had a metabolic disorder or whether she was acidotic as a result of her multiple seizures. Id. at 105. Dr. Stein ordered a serum ammonia level because there was evidence of "liver function abnormalities." Id. He also referred Makena to another pediatric neurologist, Dr. Sidney Gospe, for additional testing. Id. at 104; see also Id. at 54.

Dr. Gospe admitted Makena to the hospital on August 9, 1999, to evaluate her for pyridoxine-dependent seizures. Pet'r's Ex. 1 at 54. Dr. Gospe used a 48-hour video EEG to capture several clinical and electrographic seizures. Id. After the first day of EEG monitoring, Makena received an intravenous bolus of pyridoxine, immediately after one of her recorded seizures. Id. After the administration of pyridoxine, there was no change in the background EEG, and Makena continued to have seizures throughout the rest of

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For many reasons, VAERS reports "are not regarded as strongly probative on the causation issue." Raybuck v. Sec'y of Health & Human Servs., 98 Fed. Cl. 713, 718 (2011) (internal citations omitted); see also Analla v. Sec'y of Health & Human Services, 70 Fed. Cl. 552, 558 (Fed. Cl. 2006).

[51] Respondent's expert, Dr. Raymond, posited that "[t]he most likely explanation" for Makena's elevated lactate level was "her frequent seizures which temporarily compromised her oxygenation and perfusion." Resp't's Ex. A at 6. Elevated blood concentration levels of lactate may reflect poor lactate synthesis in the body's tissues as well as poor lactate metabolism by the liver, see Mosby's at 341-42, and petitioner's expert, Dr. Frye, acknowledged that Makena's month-long anticonvulsant therapy also would have yielded elevated liver function tests, Tr. at 80.

the second day. Id. Dr. Gospe concluded that Makena did not have pyridoxine-dependent seizures. Rather, he attributed her intractable seizures to "a developmental brain anomaly." Id. at 55 (emphasis added). Dr. Gospe recommended another MRI to better characterize Makena's brain anomaly so that a determination could be made regarding whether she was a suitable candidate for surgery. Id. at 55.

Dr. Gospe considered Makena's prior extensive neurological evaluations that failed to reveal any specific metabolic abnormalities. Pet'r's Ex. 1 at 54. He did not believe Makena's epileptic encephalopathy was secondary to a previous hepatitis immunization.[52] Id. at 55. He recommended that Makena continue to receive vaccines. Id.

During his examination of Makena, Dr. Gospe observed bilateral breast development. Pet'r's Ex. 1 at 55. He noted that Makena--who was nearly ten months old--showed evidence of precocious puberty that might "be secondary to her [epileptic] encephalopathy."[53] Id. Alternatively, her precocious breast development might have been attributable to "exogenous estrogen ingestion or possibly secondary to a previous or current medication." Id. Dr. Gospe recommended additional hormone testing for Makena. Id.

Dr. Gospe also recommended a further work-up for Makena's hip dislocation. Pet'r's Ex. 21 at 8. On August 30, 1999, an x-ray showed what appeared to be a fractured joint in Makena's right hip. Pet'r's Ex. 1 at 28. Makena was referred to David Skaggs, M.D., an orthopedic surgeon, at Children's Hospital Los Angeles, for investigation of possible hip dysplasia.[54] Id. at 27.

On September 8, 1999, Makena received a brain scan that showed a "decrease" in the maturation of her brain's white matter. Pet'r's Ex. 1 at 43-44. The scan results were

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[52] In the accompanying medical records, it appears that Makena's medical history was initially taken by Dr. Anatoly Brodsky, a resident for the attending physician (Dr. Gospe). Pet'r's Ex. 21 at 6-9. The medical history reflects that "[Makena] had conjunctivitis develop after hepatitis B vaccine. Primary pediatrician recommended holding off on further immunizations until this is worked up." Id. at 7.

[53] In response to questioning from Makena's parents, Dr. Gospe indicated that while he attributed Makena's pubertal development to her epilepsy, he did not attribute her epilepsy to the vaccines she received. Pet'r's Ex. 23 at 121.

[54] Developmental dysplasia of the hip refers to "a spectrum of pathology in the development of the hip joint." Nelson Pediatrics at 2356.

indicative of an abnormality in Makena's brain development. Nelson Pediatrics Online (Ch. 33: Intellectual Disability- Pathology and Pathogenesis).

Dr. Stein subsequently evaluated Makena for lysosomal storage diseases[55] in September 1999. Pet'r's Ex. 1 at 35. The medical records reflect that this testing was unremarkable. Id. Dr. Stein also performed some additional blood work for mitochondrial disorders. Id. at 33. This testing was inconclusive for any known mitochondrial disorders. Id. at 33-34. However, Makena did have elevated blood and urine lactate levels and her glutaric acid was also elevated. Id. at 33. Because of the elevation in Makena's glutaric acid and in her lactate levels, Dr. Stein started Makena on a cocktail of vitamins for mitochondrial disorders. Id. at 34.

On September 13, 1999, Dr. Stein also ordered genetic testing of Makena's mitochondrial DNA. Pet'r's Ex. 1 at 36. The testing showed a G15257A "[p]oint mutation,"[56] that was interpreted as the mildest primary mutation of Leber's hereditary optic neuropathy ("LHON"). Id. LHON is "a rare hereditary disorder . . . preferentially expressed in males." Dorland's at 1269. The condition is characterized by the "degeneration of the optic nerve" and "a progressive loss of central vision and scotoma."[57] Id. (emphasis added).

Nearly two weeks after detection of her point mutation, Makena was seen by Florencio Ching, M.D., a pediatric ophthalmologist. Pet'r's Ex. 1 at 38. The purpose of the examination was to rule out eye changes attributable to Makena discovered genetic mutation. Id. Although the examination showed that Makena had "reduced visual fixation development," Dr. Ching attributed Makena's poor visual fixation to her seizure

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[55] Lysosomal storage disease occurs when lysosomal enzyme defects result in the progressive accumulation of undigested products in the cell. See Dorland's at 1089. There are nearly 50 of these inherited disorders altogether, and they may affect different parts of the body, including the skeleton, brain, skin, heart, and central nervous system. National Organization of Rare Disorders, Lysosomal Storage Disorders, http://www.rarediseases.org/rare-disease-information/rare-diseases/byID/1132/viewAbstract (last visited December 14, 2012). These inherited metabolic diseases are characterized "by an abnormal build-up of various toxic materials in the body's cells as a result of enzyme deficiencies." Id.

[56] A point mutation is "a mutation resulting from a change in a single base pair in the DNA molecule, caused by the substitution of one nucleotide for another." Dorland's at 1214.

[57] Scotoma refers to "an area of lost or depressed vision within the visual field, surrounded by an area of less depressed or of normal vision." Dorland's at 1682.

medication. Id. He found "no evidence of any eye changes that would point to [the expression of a LHON] mitochondrial disorder." Id.

F. Makena's Cardiac Testing

On October 18, 1999, when Makena was one year old, she had a normal cardiac evaluation by Michael Rebolledo, M.D., a pediatric cardiologist. Pet'r's Ex. 23 at 114-15. Dr. Rebolledo noted that Makena had "a history of a complex seizure disorder, developmental delay, [and] a brain abnormality on her MRI." Id. at 115. Dr. Rebolledo deemed it unlikely that Makena had a disorder of energy metabolism. Id.

G. Allergy Testing

On October 25, 1999, Makena was evaluated for allergies by Ellen Reich, M.D., an immunologist. Pet'r's Ex. 1 at 26. Petitioner sought the evaluation because Makena had presented to the emergency room two months earlier with "tongue swelling, throat swelling, and difficulty breathing" after eating strawberry yogurt. Id. Makena's physical exam was remarkable only for her poor muscle tone. During the exam, Mrs. Bast expressed her concern that Makena may have a yeast allergy.[58] Id. Specific testing established that Makena reacts allergically to cow's milk, soybeans, and peanuts. Id. at 20-25. Her allergies were described as moderate.[59] Id.

H. Further Treatment Recommendations

On October 1, 1999, Dr. Gunay, Makena's pediatrician, wrote a letter supporting Makena's receipt of "aggressive physical therapy and infant stimulation" to address her right-sided spasticity, which had resulted in the additional complications of a stiff neck, a flattened head on the right side and right hip impairment. Pet'r's Ex. 58 at 39.

Dr. Stein examined Makena in November of 1999 shortly after her first birthday. Pet'r's Ex. 1 at 17-19. This appears to be Makena's last documented visit to a pediatric

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[58] The Physicians' Desk Reference lists hypersensitivity to yeast as a contraindication to receipt of the hepatitis B vaccine. Physicians' Desk Reference at 2018.

[59] None of Makena's allergies were shown to be severe according to her test results. Pet'r's Ex. 1 at 20-25. Makena's own allergy test results contradict Dr. Frye's characterization that she had "severe food allergies" that were indicative of "systemic dysfunction." Pet'r's Ex. 59 at 3.

neurologist. At the time of this visit, Makena had been taken "off of Topomax and all usual anticonvulsant medications." Id. at 17. Dr. Stein declined to explore other anticonvulsant therapy because the family previously had been unwilling to try using other agents. Id. Dr. Stein noted that Makena's parents discontinued, after one month, the cocktail of riboflavin and CoQ10 he had recommended while Makena was being evaluated for a possible mitochondrial disorder. Id. at 18. It was during this visit that Makena's parents expressed their concern that Makena's health issues stemmed from mercury toxicity. Id. at 19.

Dr. Stein further recommended that Makena's parents consider the insertion of an abdominal vagal nerve stimulator to manage her seizure disorder.[60] Pet'r's Ex. 1 at 17-18. Dr. Stein observed that Makena was receiving only homeopathic medications. Id. at 17.

Over the next year, Makena received alternative, physical, and occupational therapy at least three times weekly, based solely on the recommendations of Dr. DeOrio. Pet'r's Ex. 5 at 2-7, 41; Pet'r's Ex. 36 at 29, 30 (recommendations dated February 1, 2000, and again on June 1, 2001). As Mrs. Bast explained in her later-filed affidavit, she refused to seek further treatment for Makena from neurologists because they relied primarily on drugs to control Makena's seizures. Pet'r's Ex. 56;[61] see also Pet'r's Ex. 58 at 135 (a physical therapy re-evaluation noting that Makena's primary care was provided by her pediatrician, Dr. Gunay, and her homeopathic doctor, Dr. DeOrio).

On May 30, 2000, Dr. DeOrio reported that initially Makena had "upwards of 55 seizures per day, along with neuromuscular weakness and poor attention and [weak] focusing abilities." Pet'r's Ex. 36 at 24. In December 2000, at age 26 months, Makena's seizures continued to be intractable, and her development fell into the three- to nine-month age range in different evaluation categories. Pet'r's Ex. 19 at 256.

By letter dated February 9, 2002, Dr. DeOrio provided a written opinion in support of Makena's vaccine claim indicating that he had treated Makena since she was four months old. Pet'r's Ex. 36 at 31. He stated that after reviewing her medical records, it was his opinion that Makena had suffered conjunctivitis, in "reaction to her first Hepatitis

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[60] Vagus nerve stimulation is designed to prevent seizures by sending regular, mild pulses of electrical energy to the brain from the vagus nerve in the neck. Epilepsy Therapy Project, Vagus Nerve Stimulation, http://www.epilepsy.com/epilepsy/Vns (last visited December 14, 2012). The pulses are supplied through wiring that runs from a mechanical device (placed under the chest wall) to the vagus nerve. Id.

[61] This later jointly-filed affidavit refers to a document to which Mrs. Bast swore independently. Distinguishing Pet'r's Ex. 56 from Pet'r's Ex. 25 (the earlier-filed joint affidavit from both of Makena's parents).

B vaccine." Id. He advised Makena's parents to have a liver panel performed to check the status of her liver enzymes, and the results of that testing showed that Makena "had extremely elevated liver enzymes, which could be indicative of Hepatitis." Id. Dr. DeOrio further opined that Makena's brain damage was caused by the thimerosal in the vaccines she received.[62] Id. The records indicate that Makena was evaluated for heavy metal toxicity, see id. at 33-56, but petitioner did not rely on Dr. DeOrio's offered opinion regarding vaccine-induced heavy metal toxicity at hearing or in her post-hearing briefing.

I. Eligibility for Services

By letter dated January 29, 2002, the Regional Center of Orange County informed the Basts that Makena was eligible for certain services based on an evaluation of her medical records by a developmental pediatrician. Pet'r's Ex. 58 at 2. The reviewing developmental pediatrician found support in Makena's records for the diagnoses of "mental retardation" and "uncontrolled seizure disorder." Id. The reviewing developmental pediatrician noted the omission of a "cerebral palsy" diagnosis from Makena's records even though the documented findings of her "[a]bnormal neurologic exam," "abnormal tone in her extremities," and "delay in motor skills" would have been consistent with and supportive of such a diagnosis.[63] Id.

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[62] According to Dr. DeOrio, "Makena had the mercury toxicity level of a 45-year-old man." Pet'r's Ex. 36 at 31. Dr. DeOrio appears to have reached this conclusion based on laboratory test results for heavy metal toxicity obtained from two sources, Doctor's Data and Great Smokies Laboratory. Id. at 33-56. These two laboratories, however, received heavy criticism during the omnibus autism proceedings (OAP) for the unreliability of their testing methods and the irreproducibility of their test results. Mead v. Sec'y of Health & Human Servs., No. 03-245V, 2010 WL 892248, at *105 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (calling into question the reliability of laboratory results from Doctor's Data and Great Smokies Laboratory). Not only was the premise for Dr. DeOrio's assessment of Makena's mercury toxicity dubious, the theory of vaccine-induced mercury-toxicity was considered and rejected in the second set of OAP test cases. Mead v. Sec'y of Health & Human Servs., No. 03-245V, 2010 WL 892248, at *112-13 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); Dwyer ex rel. Dwyer v. Sec'y of Health & Human Servs., No. 03-1202V, 2010 WL 892250, at *112-13 (Fed. Cl. Spec. Mstr. Mar. 12, 2010).

[63] Cerebral palsy describes "a large group of persisting, nonprogressive motor disorders appearing in young children and resulting from brain damage caused by birth trauma or intrauterine pathology. The disorders are characterized by delayed or abnormal motor development . . . [and are] often accompanied by mental retardation, seizures, or ataxia." Dorland's at 1365 (emphasis added). As explained in a treatise on brain injuries, in approximately 10 percent of patients with cerebral palsy, the disorder has

Among the records filed from the Regional Center is an October 30, 2001, case manager's notation that she had discussed the issue of Makena's putative diagnosis of cerebral palsy with Mrs. Bast. Mrs. Bast indicated that she "did not want [cerebral palsy listed] as an eligibility diagnosis because she [felt] that Makena's condition [was] due to immunizations and she currently has a lawsuit addressing this allegation." Pet'r's Ex. 42 at 39. Mrs. Bast did "not want anything in writing that might jeopardize the legal route that is being taken." Id. Accordingly, in a letter dated December 18, 2001, Mrs. Bast challenged the Regional Center's presumptive diagnosis of cerebral palsy for Makena. See id. at 686-87. She refused to have Makena evaluated by the medical team at the Regional Center insisting instead on a service eligibility determination for Makena based exclusively on a diagnosis of vaccine-induced seizure disorder. Id.

J. Endocrinology Evaluations

On May 5, 2003, when Makena was four and one-half years old, her pediatrician Dr. Gunay, referred her to an endocrinology clinic for an evaluation of her precocious puberty. See Pet'r's Ex. 41 at 44-47. Makena was examined by Dr. Marjan Haghi, an endocrinologist, who found "no other chronic conditions other than the seizure disorder." Id. at 44 (emphasis added). Dr. Haghi was of the view that Makena's history and physical findings were most consistent with "benign premature adrenarche,"[64] id. at 45, and noted that it was "not uncommon for children with seizure disorders or central nervous system lesions to present with early pubertal changes." Id. at 46 (emphasis added).

Dr. Haghi wrote that Makena's cognitive skills remained at the "12-18 month level," and her motor skills were in the 9 month to 12 month range, although she was not yet rolling or sitting. Pet'r's Ex. 41 at 45. Dr. Haghi also wrote that Makena had no known allergies or medication reactions, other than a "phenobarbital[-]caused . . . elevation in liver enzymes." Id. A bone age assessment indicated that Makena was 2 years 9 months, rather than her nearly five years of age. Id. at 41. As read by the radiologist, Makena showed "retarded bone age." Id.

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been associated with asphyxia--such as Makena experienced--during childbirth. See Geoffrey Miller, "Cerebral Palsies," in Static Encephalopathies of Infancy and Childhood 13-27 (Geoffrey Miller & Jeanette C. Ramer eds., 1992).

[64] Adrenarche refers to the augmented adrenal secretion responsible for the physical changes typically observed at eight years of age. Dorland's at 33.

More than one year later, on July 13, 2004, Makena was again evaluated for precocious pubertal changes. Pet'r's Ex. 41 at 24-26. Almost six years old, Makena had a medical history "significant for a seizure disorder and an as yet uncharacterized autoimmune disorder."[65] Id. at 24 (emphasis added). A chemistry panel noted to have been performed five months before the evaluation was "unremarkable," particularly with respect to Makena's liver enzymes.[66] Id. at 25.

K. Sensorimotor Evaluation

In April of 2005, Makena was referred for a sensorimotor evaluation by her speech therapist because her visual responses were difficult to interpret. As Makena was learning to use the communication equipment, she showed "difficulty meeting the gaze of others" and exhibited "tracking problems." Pet'r's Ex. 40 at 15. Her sensorimotor evaluation revealed her profound problems "voluntarily aiming and moving her eyes" and sustaining "convergence in order to keep her eyes aligned." Id. at 18.

L. Most Recent Evaluations in the Record

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[65] No medical records have been filed to support the assertion that Makena has an autoimmune condition. While the record does contain references to Makena's "autoimmune syndrome," there is no evidence in the record that she was ever diagnosed with an autoimmune syndrome. See Pet'r's Ex. 58 at 117 (an occupational therapy progress summary from February 5, 2006, indicating, without further elaboration, that Makena has an autoimmune disorder). Dr. Frye testified on cross-examination that Makena was never tested for autoimmunity. Tr. at 109. Notwithstanding the acknowledged absence of testing, and the lack of medical record evidence supporting a diagnosis of an autoimmune condition in Makena, there are several references to Makena's autoimmune disorder in the Regional Center of Orange County records. Pet'r's Ex. 42 at 78.

[66] To the extent that petitioner alleges that Makena suffered liver damage as a result of her received hepatitis B vaccines, the only evidence of possible liver impairment in the record is several findings of elevated lactate levels and elevated liver enzyme levels during the period of time that Makena was on anticonvulsant therapy. As Dr. Raymond pointed out, Makena's liver enzyme levels were at the high end of the normal range prior to the initiation of her treatment with three anticonvulsants, and they returned to the normal range after her anticonvulsant therapy was discontinued. Dr. Raymond explained, and Dr. Frye conceded, that anticonvulsants can increase liver enzyme production. See Tr. at 139 (Dr. Raymond); Tr. at 80 (Dr. Frye).

On July 24, 2006, when Makena was eight years old, Dr. DeOrio summarized her clinical presentation, indicating that Makena "presents with a severe seizure disorder resulting from a Hepatitis B vaccine given at three months of age," Pet'r's Ex. 45 at 324, and she "experienced severe heavy metal poisoning from the mercury preservative thimerosal." Id. Among Dr. DeOrio's diagnostic impressions of Makena's various medical conditions were the following assessments: "Immune Dysfunction Syndrome,[67] Autoimmune Disease,[68] Severe Allergies and Hypersensitivity Reactions,[69] [and] Grand Mal Seizures." Id.

According to a more recent questionnaire completed by Mrs. Bast as part of a multidisciplinary assessment of Makena when she was nearly 11 years old, Makena continues to have seizures daily. See Pet'r's Ex. 55 at 5, 34. Makena has not taken any medications to control her seizures since she was a year old, nor is there any record evidence that she has been evaluated by a neurologist since the discontinuation of her seizure medication. See Pet'r's Ex. 1 at 17-19 (November 19, 1999 evaluation by Dr. Stein expressing concern that Makena has stopped taking anticonvulsant medications). Makena does take several supplements. Pet'r's Ex. 55 at 34. According to her mother, Makena suffers from "a depressed immune system which makes Makena more susceptible to communicable diseases." Id. Makena is wheelchair-bound and remains

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[67] The undersigned has not found the term "Immune Dysfunction Syndrome" in the consulted medical dictionaries, and it is unclear what Dr. DeOrio intends to describe using this diagnostic reference. Nor are there any medical testing results in the record that would appear to support Dr. DeOrio's assessment of Immune Dysfunction Syndrome.

[68] An autoimmune disease is "a disorder caused by an immune response directed against self-antigens." Dorland's at 528. There are a variety of autoimmune diseases and tests may be done to diagnose an autoimmune disorder. These tests include: antinuclear antibody tests, complete blood count, C-reactive protein, and erythrocyte sedimentation rate. U.S. National Library of Medicine, MedlinePlus, Autoimmune Disorders, http://www.nlm.nih.gov/medlineplus/ency/article/000816.htm (last visited on December 14, 2012). There is no record evidence that Dr. DeOrio ever performed any testing to assess Makena's autoimmune disorder. Nor does Dr. DeOrio identify her disorder with any further specificity.

[69] The record evidence documenting Makena's allergies include the testing performed in 1999 by Dr. Reich after Makena's emergency room visit, see Petr's' Ex. 1 at 20-25, and the subsequent allergy testing performed in 2008 by Dr. Geier as he prepared to offer an expert opinion of vaccine-related causation in this case, see Pet'r's Ex. 50 at 5-6 (finding positive allergic reactions to milk, wheat, corn, peanuts, soybeans, beef, and eggs).

significantly developmentally delayed, although no formal measure of this delay the occurred because Mrs. Bast declined cognitive and adaptive behavior assessments of Makena during that particular evaluation.[70] Id. at 31-32.

It appears from this record that Makena's referenced conditions are ongoing.

Before turning to an evaluation of petitioner's vaccine claim, the undersigned reviews the applicable legal standards.

IV. Applicable Legal Standards

A. Elements of Petitioner's Case

To receive compensation under the Vaccine Act, petitioner must demonstrate either that: (1) Makena suffered a "Table injury" – by receiving a covered vaccine and subsequently developing a listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as amended by 42 C.F.R. § 100.3; or (2) Makena suffered an "off-Table Injury," one not listed on the Table as a result of her receipt of a covered vaccine. See 42 U.S.C. §§ 300aa-11(c)(1)(C)(ii)(I); Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1321 (Fed. Cir. 2010); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1320 (Fed. Cir. 2006).

Entitlement to Program compensation is presumed for Table injuries, which meet the time period specified in the Vaccine Injury Table. 42 U.S.C. § 300aa-11(c)(1)(C)(i). For off-Table injuries, however, petitioner must show that the vaccine caused the claimed injury by proving not only that the received vaccinations were a substantial factor in causing the condition for which compensation is sought, but also that such injury would not have occurred but for the received vaccinations. Pafford v. Sec'y of Health & Human

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[70] On February 7, 2001, Makena was functioning at a five- to nine-month developmental age level. Pet'r's Ex. 36 at 21. Additional testing performed when she was just over five years old revealed that Makena's cognitive skills were still measured at three to nine months, and her social and emotional skills were measured at six months. See Pet'r's Ex. 55 at 16. Her receptive and expressive language skills were measured at nine months of age. Id.

Petitioner's awareness of Makena's profound developmental delay was reported to Dr. Geier, who observed in his written report that according to Makena's mother, she "never made any of her developmental milestones during the first year of life." Pet'r's Ex 48 at 2 (emphasis added).

Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006) (citing Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352 (Fed. Cir. 1999)).

Petitioner here alleges that Makena suffered "off-Table injuries," specifically seizures, an encephalopathy, and liver damage, as a result of a hepatitis B vaccination she received. Petition at 2.[71] To establish causation-in-fact, petitioner must present: (1) a medical theory causally connecting the vaccination to the injury; (2) a logical sequence of cause and effect showing the vaccination was the reason for the injury; and (3) a proximate temporal relationship between the vaccination and the injury. Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

B. Petitioner's Burden of Proof

To prevail on her claim, petitioner must demonstrate, by a preponderance of the evidence, that the vaccine at issue caused the alleged injury. Capizzano, 440 F.3d at 1320. This standard requires proof that the vaccine more likely than not caused the vaccinee's injury. Althen, 418 F.3d at 1279. If petitioner fails to prove any one of the three Althen prongs, her claim must fail. Id. at 1278-79.

Under the Vaccine Act, causation-in-fact is determined on a case-by-case basis. There are "no hard and fast per se scientific or medical rules." Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548 (Fed. Cir. 1994). A petitioner may rely upon circumstantial evidence to prove her case, Capizzano, 440 F.3d at 1325-26, and "close calls" regarding causation are resolved in favor of petitioner, Althen, 418 F.3d at 1280. But, the claims of petitioner alone, unsubstantiated by medical records or by medical opinion, cannot support an award of Program compensation. 42 U.S.C. § 300aa-13(a)(1).

1. Evaluating the Opinions Offered by Experts

An "indicia of reliability" is necessary to support an expert witness's assertions. Moberly, 592 F.3d at 1324. When the opinion of a medical expert is offered in support of a claim, it must be evaluated; the reliability of an expert's opinion is not presumed. See Ultimo v. Sec'y of Health & Human Servs., 28 Fed. Cl. 148, 152 (1993) ("Simply because a witness is found qualified to testify as an expert does not mean that the trier of fact must accept his testimony.").

The reliability of an expert's theory can be evaluated in a number of ways. First, the expert's qualifications to testify on particular subjects – that is, any specialized

[71] The original petition did not allege a causal mechanism for the alleged vaccine-related injury. No amended petition was filed. The proposed causal mechanism, which shifted over time, was first explored in expert reports.

knowledge, experience, training, or education of the witness that would inform the offered opinion – may be considered. See Boehmer v. Sec'y of Health & Human Servs., No. 90-317V, 1991 WL 242995, at *2 (Fed. Cl. Spec. Mstr. Oct. 31, 1991) (While the Federal Rules of Evidence do not govern proceedings under the Vaccine Act, "guidance can be gleaned from them [to include FRE 702][72] as to what standards to apply in weighing expert opinion testimony."). A well-informed opinion of causation that is rooted in soundly explained medicine or science reasonably merits greater evidentiary weight than an ill-advised theory of harm. Shaw v. Sec'y of Health & Human Servs., No. 01-707V, 2009 WL 3007729, at *22 (Fed. Cl. Spec. Mstr. Aug. 31, 2009). Certainly, "[t]he value that a specialist brings to an evaluation of particular medical problems cannot be ignored." Id.; see also Pafford, 451 F.3d at 1359 (affirming the rejection of an expert's testimony because he lacked proper certifications in the specialty areas in which he testified); Waleryszak v. Sec'y of Health & Human Servs., 45 Fed. Cl. 573, 578 (1999) (finding no abuse of discretion in a decision to accord greater weight to the testimony of an expert whose specialty was diagnosing and treating illnesses, than to the testimony of the opposing expert whose specialty was managing the care of afflicted patients, because the skills of diagnosis were more pertinent to the issues presented in the case), aff'd sub nom. Waleryszak v. Sec'y of Health & Human Servs., 45 Fed. Cl. 573 (Fed. Cl. 1999) dismissed sub nom. Waleryszak v. Sec'y of Health & Human Servs., 250 F.3d 753 (Fed. Cir. 2000); Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1347, 1349 (Fed. Cir. 2010) (affirming a decision based, in part, on a finding that an expert's testimony was more persuasive due to his professional experience as a co-director of the only medical center devoted to the health condition at issue); Locane v. Sec'y of Health & Human Servs., 99 Fed. Cl. 715, 726-27 (2011) (finding ample evidence to support the determination that an expert's extensive study and treatment of, as well as publication on, the medical condition at issue rendered his opinion more persuasive than that of the opposing expert, who had "much less experience" specific to the medical condition at issue), aff'd, 685 F.3d 1375 (Fed. Cir. 2012); Doe 11 v. Sec'y of Health & Human Servs., 2008 WL 649065, at *16 (Fed. Cl. Spec. Mstr. Jan. 31, 2008), vacated sub nom., 83 Fed. Cl. 157 (Fed. Cl. 2008), remanded to 2008 WL 4899356 (Fed. Cl. Spec. Mstr. Oct. 29, 2008) (according greater weight to the opinion of an expert with specialization and certification in the medical conditions at issue than to the opinion of the opposing expert who "acknowledged" a lack of expertise in such ailments), 87 Fed. Cl. 1 (Fed. Cl. 2009) aff'd sub nom Doe v. Sec'y of Health & Human Services, 601 F.3d 1349 (Fed. Cir. 2010) cert. denied, 131 S. Ct. 573, 178 L. Ed. 2d 414 (U.S. 2010); Poulos v. Sec'y of Health & Human Servs., No. 90-2315V, 1994 WL 470622, at *5 (Fed. Cl. Spec. Mstr. Aug. 17, 1994) (finding an expert opinion more persuasive because the expert specialized in the medical condition at issue, with more than 60% of his patients suffering from the condition itself).

[72] FRE 702 governs the circumstances in which a witness qualified as an expert may offer opinion testimony.

Second, the four factors established by the Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993) for evaluating the reliability of expert testimony can be considered.[73] These factors serve as "a tool or framework for

[73] The four Daubert factors are:

(1) Whether a theory or technique can be (and has been) tested;

(2) Whether the theory or technique has been subjected to peer review and publication;

(3) Whether there is a known or potential rate of error and whether there are standards for controlling the error; and

(4) Whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran ex. rel. Terran v. Sec'y of Health & Servs., 195 F. 3d 1302, 1316 n.2 (Fed. Cir. 1999) (citing Daubert, 509 U.S. at 592-95).

The first and second Daubert factors may influence a special master's determination of reliability because "the absence of publication within the medical field…makes testing, duplication of results, and falsifiability impossible for others to perform." Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 224 (2011) (quoting Veryzer I, No. 06-522V2010 WL 2507791, at *23); see also id. (affirming the special master's exclusion of an expert's theories because the expert did not submit for peer review his research supporting his theory of causation, but instead "guarded his opinion on these matters [as] proprietary and secret")(alteration in original).

The third Daubert factor concerning any detectible errors associated with the proposed theory and the manner of controlling for those errors also informs the reliability determination. See Mead v. Sec'y of Health & Human Servs., No. 03-215V, 2010 WL 892248, at *103 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (noting that the laboratories that provide the type of testing on which petitioner relies in this case have received "a lot of criticism" for reporting unreliable test results).

The fourth Daubert factor, general acceptance of a theory within the relevant scientific community, may further influence the reliability inquiry. See Daubert, 509 U.S. at 594 ("[A] known technique which has been able to attract only minimal support within the community" may properly be viewed with skepticism.) (internal citations omitted); Jarvis v. Sec'y of Health & Human Servs., No. 90-1366V, 1997 WL 639043, at *17 (Fed. Cl. Spec. Mstr. Sept. 22, 1999) ("The theory need not have the endorsement of

conducting" an inquiry into the reliability of an offered expert's opinion. Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 736 (2009)(quoting Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 2000)). See also Terran, 195 F.3d at 1316 (holding that the Daubert framework can be applied when determining what, if any, weight to accord to expert testimony in Vaccine Act cases); Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (indicating that it is "well-settled law" in vaccine cases that the Daubert factors assist in the weighing of expert opinion evidence that already has been admitted).

The Daubert factors serve to remind that an offered opinion must be supported by more than a subjective belief or an unsupported speculation. See also Veryzer, 98 Fed. Cl. at 224 (recognizing that it "is not an overly strict construction of Daubert to require that [the expert's] methodology correspond to a single Daubert factor") (internal citations omitted).

Third, the size of the gap between the scientific data and the opinion proffered may be considered when evaluating the reliability of an expert's opinion. Doe 78 v. Sec'y of Health & Human Servs., No. XX, 2010 WL 3154546, at *9 (Fed. Cl. Spec. Mstr. July 26, 2010) (citing Snyder, 88 Fed. Cl. at 745). Too great of an analytical gap between the data and the opinion proffered calls into question the soundness of the expert's opinion. Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1339 (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 136, 146 (1997)).

2. Determining When the Burden of Proof Shifts from Petitioner to Respondent

The Federal Circuit has stated that it is petitioner's burden to do the "heavy lifting" to meet the imposed legal standard of preponderant evidence. Althen, 418 F.3d at 1280. Respondent "is permitted to offer evidence to demonstrate the inadequacy of the petitioner's evidence on a requisite element of the petitioner's case-in-chief." Stone v. Sec'y of Health & Human Servs., 676 F.3d 1373, 1380 (Fed. Cir. 2012) (citing de Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008)).

Should petitioner meet her burden under Althen, the burden then shifts to respondent to demonstrate, by preponderant evidence, that the injury was caused by a factor unrelated to the administration of the vaccine. 42 U.S.C. § 300aa-13(a)(1)(B); de Bazan, 539 F.3d at 1352. If respondent fails to meet this burden, then petitioner prevails on her vaccine claim. Id.

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all or even a majority of the experts in the field, but a significant minority must support petitioners' alleged theory.").

Here, petitioner has failed to satisfy her burden, and the claim she presented does not involve a close call. Petitioner has not shown entitlement to an award of Program compensation. But before turning to a detailed Althen analysis, a summary of petitioner's causation theory and its attendant problems follows.

V. Summary of Petitioner's Theory of Causation

Petitioner's expert, Dr. Frye, based his opinion of vaccine-related causation on the premise that vaccines "induce detrimental physiological effects that can lead to neurological disorders" characterized by pronounced cognitive impairments. Pet'r's Ex. 51 at 3 (Frye report). He described two biological mechanisms by which such harm could occur. Id.

Relying on "both animal and human research," Dr. Frye first asserted that vaccines can induce autoimmunity. Id. Postulating that vaccine-induced autoimmunity led to Makena's medical problems, Dr. Frye stated that autoimmunity and over-activation of the immune system "appear[] to be related to several neurological disorders that [a]ffect cognitive development in childhood." Id. at 4.

The difficulty with this proposed mechanism of harm is the lack of evidence that Makena has an autoimmune condition--whether vaccine-induced or otherwise. Dr. Frye acknowledged that Makena was never tested for any of the autoantibodies associated with neurodevelopmental conditions and epilepsy. Tr. at 34 (citing Pet'r's Ex. 64). Moreover, petitioner's expert immunologist, Dr. Bellanti, declined to find that Makena had an autoimmune condition after a review of her medical records. See Pet'r's Ex. 46 at 10. Accordingly, the principal record support for the claim that Makena has an autoimmune condition comes from the record notes of Dr. DeOrio, a family practitioner with no disclosed expertise in immunology, but who has continued to see Makena. The basis for Dr. DeOrio's diagnostic impression that Makena has immune dysfunction and an autoimmune disorder is unexplained.[74] See Pet'r's Ex 36 at 27 and Pet'r's Ex 45 at 324. Apart from Dr. DeOrio's seemingly conclusory notations, evidence that Makena sustained a vaccine-induced autoimmune reaction is wanting.

Alternatively, Dr. Frye relies on several medical articles and two case reports (including one involving Hannah Poling, a vaccinee whose parents filed a successful Vaccine Table Injury claim on her behalf) for his proffered opinion that vaccines are able to "progressively weaken[]" mitochondria and thereby "induce" and "significantly exacerbate[]" mitochondrial dysfunction in subjects like Makena who meet the "criteria for a probable mitochondrial disorder." Pet'r's Ex. 59 at 3-4. Allowing that a range of

[74] Dr. Geier, one of petitioner's retained but non-testifying witnesses, similarly opined, without much explanation, that Makena has an "immunological dysfunction." Pet'r's Ex. 48 at 3.

genetic and environmental factors can lead to mitochondrial dysfunction, id. at 5-6, Dr. Frye posits that the vaccines Makena received in December 1998, aggravated her underlying mitochondrial disorder by increasing her oxidative stress level and causing metabolic decompensation that led to the development of her seizure disorder and neurodevelopmental problems. See id. at 4-5; Tr. at 13.

As the experts in this case explained, mitochondria are organelles within a cell that produce cellular energy essential to human health. Resp't's Ex. A at 4. Importantly, mitochondria serve to maintain the structure and function of different organs in the body, including the brain, heart, gastrointestinal tract and eyes. Resp't's Ex. C at 2 (Dr. Jones); Tr. at 18 (Dr. Frye). If mitochondria are not functioning properly, various organs in the body are adversely affected. Id.

Petitioner's theory of significantly exacerbated mitochondrial dysfunction rests on the premise that Makena has an underlying mitochondrial disorder (a genetic point mutation for LHON) and evidence of multi-systemic issues that satisfy the diagnostic criteria for mitochondrial dysfunction referenced in the 2002 Bernier article, filed as Petitioner's Exhibit 63. Dr. Frye asserts that the problems noted in Makena's records involving her neurologic system (as evidenced by her seizures), her hepatic system (as evidenced by her elevated liver enzyme levels), her endocrine system (as evidenced by her growth issues and her precocious puberty), and her gastrointestinal system (as evidenced by the documented reports of chronic constipation[75]) are sufficient to establish that she has mitochondrial dysfunction and, thus, a particular vulnerability to the increased oxidative stress levels she experienced as a result of the vaccines administered to her in December 1998. See Tr. at 33, 79-84.

The difficulties with petitioner's alternatively proposed mechanism of harm (involving an exacerbated mitochondrial dysfunction theory) are three-fold. The difficulties extend to both the general and specific propositions that petitioner's expert, Dr. Frye, has put forward.

First, Dr. Frye's testimony about oxidative stress reveals a striking gap between his understanding and the scientific community's understanding of the concept. He relies on an outdated understanding of oxidative stress and a flawed postulate concerning the relationship between oxidative stress and oxidative damage. In addition, the two- to four-

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[75] When asked to point to supportive record evidence of Makena's constipation, Dr. Frye was unsure about whether any such support existed in the medical records. Tr. at 82. The undersigned has found mention that Makena experienced "some episodes of constipation" in Makena's records. See Pet'r's Ex. 38 at 44-45; Pet'r's Ex. 61. The reviewed records also reflect that Makena's constipation appeared to resolve with a change in medication. Pet'r's Ex. 42 at 152.

week time frame that he identified as medically appropriate for the onset of neurodegenerative symptoms following vaccination is too soon (by decades)--as understood by experts on the subject of oxidative stress--for Makena to have suffered the degree of injury alleged. Compare Tr. at 71 (Dr. Frye) with Tr. at 221-22. (Dr. Jones).

Second, Dr. Frye bases his opinion of causation not on the particular mitochondrial point mutation detected in Makena, but on the general protein location of her point mutation to speculate about the cause of her injuries. In focusing on the general protein location of Makena's point mutation and its potential health risks, Dr. Frye ignored: (1) the expected manifestation of Makena's particular mitochondrial point mutation; (2) the concern expressed by various treating and consulting neurologists who carefully evaluated Makena finding that her health problems stemmed from a congenital brain malformation;[76] and (3) the multiple prenatal and perinatal risk factors to which Makena was exposed.[77]

Third, 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 by first excluding other conditions that might have a multi-systemic effect. See Tr. at 85. The physicians who examined Makena repeatedly suggested that Makena's intractable seizure disorder was related to the structural abnormalities in her brain. Makena's last neurological examination was in 1999. Her family has not consulted further with any seizure specialists since that time even though improvements in genetic testing and other diagnostic tools in the intervening period might offer a better understanding of the genesis of Makena's seizure disorder. Moreover, the specialists who have examined Makena attribute her elevated liver enzyme levels and her signs of precocious puberty to her seizure disorder and her anti-convulsant medication, and not to an independent mitochondrial disorder.[78]

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[76] Makena was examined by a number of specialists for the purpose of ruling out a mitochondrial disorder. None of the specialists detected evidence of a mitochondrial disorder, nor did her laboratory testing over time support such a finding.

[77] To the extent that environmental factors influence changes in genetic expression, these factors are often prenatal and perinatal factors. Hazlehurst v. Sec'y of Health & Human Servs., No. 03-654V, 2009 WL 332306, at *34 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), aff'd, 88 Fed. Cl. 473 (2009), aff'd, 604 F.3d 1343 (Fed. Cir. 2010) (citing Dr. Cook's testimony from the Cedillo hearing).

[78] Further puzzling about Dr. Frye's opinion of causation was his choice to focus exclusively on the impact of the received vaccines without addressing why he failed to acknowledge the possible impact of various congenital, prenatal, and perinatal factors noted in Makena's records. By failing to address these factors, as many of Makena's

As discussed more fully in the following Althen analysis, the preponderant evidence does not support petitioner's theory of vaccine causation.

VI. Evaluating Petitioner's Vaccine Claim under the Althen Standard

A. Althen Prong One: Petitioner's Medical Theory

Under Althen Prong 1, petitioner must put forth a biologically plausible theory explaining how the received vaccines could have caused the sustained injury. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009). Under this prong, petitioner must make a showing that the received vaccines "can" cause the alleged injury. Pafford, 451 F.3d at 1355-56.

The offered medical theory must be supported by either the vaccinee's medical records or the opinion of a competent physician. Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992). Support for the offered medical theory must also include an explanation that "pertains specifically to the [claim made in] petitioner's case." Moberly, 592 F.3d at 1322. See Veryzer v. Sec'y of Health & Human Servs., No. 06-0522V, 2010 WL 2507791, at * 24 (Fed. Cl. Spec. Mstr. 2010) (noting that the relevant inquiry is whether, based on facts known to medical science and logical inferences drawn by a qualified expert, the vaccine at issue is more than likely to have caused the alleged injury), aff'd, 100 Fed. Cl. 349 (2011), aff'd, 475 F. App'x 765 (Fed. Cir. 2012).

Petitioner's theory of causation need not be medically or scientifically certain, Knudsen, 35 F.3d at 548-49, but it must be informed by "sound and reliable medical or scientific explanation," id. at 548; see also Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both 42 U.S.C. § 300aa-13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioner relies upon a medical opinion to support her theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Human Servs., 618 F. 3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980)) ("An expert opinion is no better than the soundness of the reasons supporting it.").

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various treaters did, Dr. Frye advanced a theory of causation that was materially different than that offered by Makena's treating specialists.

Dr. Frye has opined that Makena's injuries were caused by vaccine-induced autoimmunity. Alternatively, he has opined that the hepatitis B vaccine administered to Makena significantly exacerbated her mitochondrial dysfunction.

1. Petitioner's Theory of Autoimmunity

As noted earlier, the difficulty with Dr. Frye's first causation theory concerning vaccine-induced autoimmunity is that there is no reliable evidence that Makena suffered from an autoimmune condition. Although Makena's treating physician, Dr. DeOrio, a family practitioner, documented his impression that she had an autoimmune disease, that diagnosis is not supported by the details of her medical records. Nor has Dr. DeOrio identified the basis for his diagnostic impression that Makena suffered from such a condition.

Moreover, petitioner's own expert, Dr. Bellanti, an immunologist, acknowledged that he could not offer an opinion that Makena's condition was "an autoimmune reaction to either Makena's vaccines or [to] an infectious process." Pet'r's Ex. 46 at 10. Dr. Bellanti recommended additional investigation and case review by both a pediatric neurologist and a geneticist to determine whether the brain abnormalities detected in Makena were due to a "structural brain dysgenesis." Id. at 9-10

Dr. Frye's opinion regarding vaccine-induced autoimmunity appears to rest heavily on Dr. DeOrio's conclusory and unsupported opinion that Makena has developed an autoimmune condition as a result of her vaccinations. This theory of vaccine-related causation, however, cannot stand in this case because it is based on a condition that has not been shown to exist in Makena.[79] Broekelschen, 618 F.3d at 1345-46 (When there is some dispute about a petitioner's diagnosis, special masters may find whether a preponderance of evidence supports any proposed diagnosis before evaluating whether a vaccine caused that illness).; see also Hibbard v. Sec'y of Health & Human Services, No. 07-446V, 2011 WL 1766033 (Fed. Cl. Apr. 12, 2011) review denied, decision aff'd, 100 Fed. Cl. 742 (Fed. Cl. 2011) aff'd, 698 F.3d 1355 (Fed. Cir. 2012) (same).

2. Petitioner's Alternate Theory of Mitochondrial Dysfunction

On cross-examination, Dr. Frye indicated that his theory of causation in this case does not depend on an autoimmunity premise, but more importantly, on another

[79] The record does include evidence that Makena reacts allergically to milk, soybeans, and peanuts. See Pet'r's Ex. 1 at 20-25. But, there is no credible evidence of any autoimmune condition, and Dr. Frye acknowledged that other than allergy testing, Mackena has never been tested for autoimmunity. Tr. at 109.

mechanism of harm.[80] Accordingly, the undersigned turns to consider the alternative mechanism of harm proposed by Dr. Frye, specifically, a vaccine-induced exacerbation of Makena's mitochondrial dysfunction. Dr. Frye posits that Makena's seizure disorder resulted from vaccine-induced cell death or dysfunction that was caused by oxidative stress.[81]

This theory of vaccine-related causation relies heavily on a finding that the vaccines Makena received created sufficient oxidative stress to trigger mitochondrial dysfunction beyond her already genetically-compromised mitochondrial function. See Tr. at 18-22. This vaccine-induced oxidative stress is purported to have overtaxed and, thereby, irreparably damaged Makena's mitochondrial machinery by disrupting the electron transport chain supporting the proper function of Makena's brain. Id.

Dr. Frye explained at hearing that oxidative stress creates reactive oxygen and reactive nitrogen species. Tr. at 19. The species are described as reactive because they have a number of free electrons available to bind with other cell parts. Id. Dr. Frye focused his testimony principally on the impact of too much reactive oxygen species.

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[80] Accordingly, the undersigned does not credit as relevant the filed articles addressing autoimmunity because there is no evidence in the record that Makena has an autoimmune condition that could be implicated as the causal factor that led to her neurological decompensation. See Tr. at 109; see also Pet'r's Ex. 62 (Yonatan Ganor et al., Autoimmune Epilepsy: Some Epilepsy Patients Harbor Autoantibodies to Glutamate Receptors and dsDNA on both Sides of the Blood–Brain Barrier, which may Kill Neurons and Decrease in Brain Fluids after Hemispherotomy, 11 Clinical & Developmental Immunology 241 (2004)); Pet'r's Ex. 64 (Anne M. Connoly et al., Brain-Derived Neurotrophic Factor and Autoantibodies to Neural Antigens in Sera of Children with Autistic Spectrum Disorders, Landau-Kleffner Syndrome, and Epilepsy, 59 Biol. Psychiatry 354 (2006)); Pet'r's Ex. 66 (Harm Hogenesch et al., Vaccine-Induced Autoimmunity in the Dog, 41 Advances in Veterinary Medicine 733 (1999)); Pet'r's Ex. 75 (Rahul Khurana et al., Mitochondrial Oxidative Damage in Experimental Autoimmune Uveitis, 49 Investigative Ophthalmology & Visual Science (2008)); Pet'r's Ex. 80 (Angela Vincent et al., Potassium Channel Antibody-Associated Encephalopathy: A Potentially Immunotherapy-Responsive Form of Limbic Encephalitis, 127 Brain 701 (2004)); Pet'r's Ex. 84 (Harvey S. Singer et al., Antibrain Antibodies in Children with Autism and Their Unaffected Siblings, 178 Journal of Neuroimmunology 149 (2006)); and Pet'r's Ex. 88 (Anne M. Connolly et al., Serum Autoantibodies to Brain in Landau-Kleffner Variant, Autism, and Other Neurologic Disorders, 134 Journal of Pediatrics 607 (1999)).

[81] Dr. Frye used the terms vaccine-induced cell death and cell dysfunction interchangeably, without addressing the degree of dysfunction necessary to trigger death.

Reactive oxygen species may react with the fats of either the cells that comprise cell membranes, the proteins of the cells that make up the machinery of a cell, or the DNA of the cells that convey the information code instructing the work of other cells. Id. The free electrons that reactive oxygen species provide to mitochondria are important to the production of cellular energy through an electron transport chain composed of a series of five complexes. Id. at 20. As electrons are passed through the complexes that constitute the electron transfer chain, protons are moved from one compartment of the mitochondria to another. Id. When too many free electrons are present, more reactive oxygen species are generated, and damage can occur to the electron transport chain complexes or the cell membrane that preserves the proton gradient. Id. at 20-21. While acknowledging that the body has a variety of systems in place to neutralize free electrons and thereby compensate for the production of excess reactive oxygen species, Dr. Frye asserted that such compensation systems can be overwhelmed when the mitochondria are not functioning properly in the first instance. Id. at 21-22.

In his testimony, Dr. Frye described his theory of vaccine-induced cell death or dysfunction as a sequence of events. First, the administered vaccines "activate" the immune system and cause the immune system to mount a response by producing antibodies against the injected antigen. Tr. at 49-50. "[O]ne of the mechanisms that the immune system uses to defend itself . . . is [the production of] reactive oxygen species." Id. at 50. Dr. Frye explained that the reactive oxygen species "produced… in the immune cells . . . can be released into the body." Id. When asked how reactive oxygen species reach a vaccinated child's brain from the vaccine injection site, Dr. Frye testified that depending on the child, "[i]t could be a local reaction or it could be a systemic reaction [experienced] throughout the body." Tr. at 51.

Dr. Frye described at least three pathways by which reactive oxygen species already present in the body could generate "more reactive oxygen species and [lead to] mitochondrial dysfunction in the brain." Tr. at 52. He noted that the pathways he identified did not necessarily involve "direct" harm to the brain. Id.

The first proposed pathway involves reactive oxygen species activating the immune system to produce proinflammatory cytokines that affect the brain and cause changes in mitochondrial function. Id. at 59. The second pathway involves excess reactive oxygen species in the body that leads to mitochondrial dysfunction. Id. The third pathway involves reactive oxygen species placing an undue demand on--and thereby depleting--certain vitamins and other co-factors that otherwise would be available to support brain function. Id. at 59-60.

Dr. Frye explained that regardless of the particular pathway involved, the biological effect would be the same. "[A]s the body becomes overloaded by the reactive oxygen species[,] there is a cascade of processes" that can cause metabolic decompensation and which can affect the brain, the metabolism of the brain and the

amount of reactive oxygen species in the brain. Tr. at 52-53. Dr. Frye posited that excessive reactive oxygen species create oxidative stress, and when oxidative stress persists, oxidative damage occurs. Oxidative damage causes impairment in various bodily systems. Id.

As discussed more fully in the subsections that follow, Dr. Frye's proposed theory of causation is not supported by sound and reliable science. He offers an older view of oxidative stress then has been held by the scientific community for the past decade. He relies on literature that predates the understanding of oxidative stress that has been gained in the last 10 years. He also relies on literature that is of questionable relevance to the facts of this case.

Dr. Frye fails to rebut testimony and evidence that oxidative stress is a necessary component for proper cellular signaling and the body possesses sufficiently robust antioxidant levels to address to address the levels of reactive oxygen species generated by administered vaccines. He also fails to rebut testimony and evidence that the reactive oxygen species generated by vaccination is locally metabolized and too short-lived to create a cascade of events that would impact a vaccinee's brain.

Moreover, Dr. Frye relies on a flawed comparison between the manner in which infections cause harm and the manner in which he posits Makena's received vaccines caused harm. Finally, although Dr. Frye cites case reports and literature pointing to an association between fever and metabolic decompensation, he does not explain how that association is relevant in Makena's circumstance where no fever has been documented.

a) Dr. Frye's theory of oxidative stress is based on an outdated understanding of oxidant imbalance

As the conducted proceedings revealed, petitioner's theory of vaccine-induced cell death or dysfunction is based on a model of unregulated oxidative stress. Pet'r's Br. at 6. Under this paradigm, oxidative stress is created by an imbalance between oxidants and antioxidants in the body, with the former outweighing the later.[82] Tr. at 211.

Dr. Frye explained that by design, vaccines trigger an immunologic reaction. Tr. at 49. He posited that a vaccine-induced immune reaction could create an imbalance in or improper regulation of oxidative stress levels that could lead to oxidative damage. He asserted that the human body's detoxification system is more susceptible to becoming overloaded by excessive reactive species in an individual with mitochondrial dysfunction.

[82] During his direct testimony, respondent's expert, Dr. Jones, sketched and marked as Respondent's Trial Exhibit 1, the imbalance model that Dr. Frye described. See also Tr. at 212 (describing his drawing of Dr. Frye's theory).

See Tr. at 21-22. Dr. Frye urged that if such an individual were overwhelmed by an imbalance between oxidants and antioxidants, that person could begin to suffer from metabolic decompensation. Id. Evidence of metabolic decompensation would be expected to manifest as impaired functioning in different body systems, such as the hepatic, endocrine, and gastrointestinal systems. See Pet'r's Ex. 63 at 1 (2002 Bernier article); Tr. at 79-84 (Dr. Frye); Tr. at 144-51 (Dr. Raymond).

Dr. Jones challenged the plausibility of Dr. Frye's proposed theory of harm because it rested on an outmoded view of how oxidative stress causes damage. See Tr. at 209. Dr. Jones testified that although the "concept of oxidative stress [urged by Dr. Frye] has been around for half a century, that . . . concept is wrong," as it is now understood. Tr. at 214.

Dr. Jones explained that, in the past decade, research focused on the enzymes that generate oxidants has changed the scientific community's understanding of the purpose of oxidant generation. Tr. at 209. This research has effected a "major shift" in the way scientists view "the concept[] of oxidative stress." Tr. at 210. Oxidants are now understood to operate as positive signaling molecules, and their presence is essential to the proper functioning of the human body. The ongoing production of oxidants is currently understood to be a necessary part of normal metabolism. Tr. at 209-10; see also Resp't's Ex. I. Dr. Jones testified that based on this shift in understanding, oxidative stress is more properly characterized as merely "a disruption" of the body's important signaling pathways, than as the intrinsically deleterious occurrence that Dr. Frye describes. Tr. at 215.

Dr. Jones testified that the present understanding of oxidative stress has come from studies that have tested and detected a critical flaw in the imbalance theory of oxidative stress. As predicted by the researchers, heavy doses of administered antioxidants would be expected to protect against human disease, were the imbalance model of oxidative stress an accurate one. Tr. at 213-14. But, double-blind interventional trials with free radical scavenging antioxidants demonstrated otherwise;[83]

[83] Double-blind studies, in which neither the subjects of the experiment nor the persons administering the experiment know the critical aspects of the experiment, merit significant weight among researchers because such studies guard against both experimenter bias and placebo effects. See FAQs About Clinical Studies, http://www.cc.nih.gov/participate/faqaboutcs.shtml; see also Reference Manual on Scientific Evidence, 3d Ed. Federal Judicial Center and National Research Council, 2011 ["Reference Manual on Scientific Evidence"] at 658 (noting that the "gold standard in clinical epidemiology and in the testing of pharmaceutical agents is the randomized double-blind cohort study in which the control and intervention groups are perfectly matched").

that is, significantly increasing the dose of antioxidants given to the study subjects had no protective effect against disease. Id.; see also Resp't's Exs. L-S. As related by Dr. Jones, the failure of these "trials to show protection in humans . . . tells us that [the imbalance] concept of oxidative stress . . . is wrong." Tr. at 214.

As a leading expert on the subject of oxidative stress, Dr. Jones stated that "the old way of looking at [oxidative stress--as embraced by Dr. Frye--] . . . is not an adequate description" of how disease processes occur. Tr. at 215. He added that "there are so many pathways in the cell that depend upon these types of [beneficial] signaling processes that . . . at present we can't separate these [pathways] out individually" and associate them with the onset or evolution of harmful disease. Id. Because contemporary understanding of the role of oxidative stress in cellular signaling has "reinterpret[ed] . . . the literature with regard to oxidant generation and oxidants in all the pathological or biological mechanisms," Tr. at 210, Dr. Jones discounted, as obsolete, Dr. Frye's theory that reactive oxygen species can cause oxidative injury and in turn, neurologic dysfunction by mere vaccine stimulation of the immune system. Tr. at 209, 214, 237.

Dr. Jones did acknowledge, however, and discuss the particular circumstances--which he carefully explained were not present in this case--in which an oxidant imbalance could create sufficient oxidative stress to lead to disease or marked deterioration. See Tr. at 219. Such circumstances involve either a significant antigenic exposure to chemicals or a state of imbalance over a prolonged period of time such as occurs with age-related damage.[84] See Tr. at 219-22. Dr. Jones stated that damage or injury by the mechanism proposed by Dr. Frye would require a degree of exposure or a period of time orders of magnitude greater than the administered vaccines or the few weeks contemplated by the vaccine-related theory presented here.[85]

b) The relevance of the literature on which Dr. Frye relied to support his theory that vaccine-induced oxidative stress caused Makena's neurodegeneration is questionable

Respondent's expert, Dr. Jones addressed a number of the articles on which Dr. Frye relied as support for the theory that vaccines can increase oxidative stress to harmful

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[84] Dr. Jones pointed out that a very good understanding of oxidative stress in the context of the aging process has developed over the past several decades. Tr. at 220.

[85] The difficulty with the timing proposed by Dr. Frye is explored in greater detail in the evaluation of the third Althen prong. Petitioner offered no testimony or evidence to rebut Dr. Jones' testimony concerning the degree of antigenic exposure or length of time required to produce the level of injury by the biological mechanism described by Dr. Frye.

levels in an individual with compromised mitochondrial functioning. Dr. Jones challenged, on the facts of this case, the relevance of the articles Dr. Frye referenced. Tr. at 237-44.

(1) The 2008 Kim article.

Dr. Frye testified that the 2008 Kim article, filed as Petitioner's Exhibit 65,[86] described a mechanism by which reactive oxygen species could cause injury. Tr. at 34. Dr. Jones discussed that mechanism in more detail, Tr. at 236-37, explaining that endoplasmic reticulum is "part of the secretory mechanism of cells," and involves oxidation. Tr. at 237. Dr. Jones added that, if the "normal processing" in a cell is disrupted, the affected cell may experience endoplasmic reticular stress that "signals back through the cell and activates cell death programs." Id. Dr. Jones conceded that this type of stress is a component of certain disease processes, but clarified that it is not part of the process posited to be at work in Makena. Id.

(2) The 2006 Valko article.

Dr. Frye also offered the 2006 Valko article, filed as Petitioner's Exhibit 69,[87] for a discussion about the effect of oxidative stress on cellular function. Tr. at 35. Dr. Jones allowed that the article was "a good review of the chemistry of . . . oxidative reactions . . . [based on] the old way of thinking about oxidative stress." Tr. at 237-38. But Dr. Jones diminished the current value of the review article based on the outcomes of the antioxidant trials, which have shown that the imbalance theory on which Dr. Frye relies "is not really relevant to human disease." Tr. at 238.

(3) The 2008 Riazi article

Citing the 2008 Riazi article, filed as Petitioner's Exhibit 72,[88] Dr. Frye suggested that peripheral inflammation, such as might be found in inflammatory bowel disease, can be triggered by a vaccine and lead to excitability in the central nervous system—even if the central nervous system is not affected directly by inflammation. Tr. at 36. This

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[86] Inki Kim et al., Cell Death and Endoplasmic Reticulum Stress: Disease Relevance and Therapeutic Opportunities, 7 Nature Reviews: Drug Discovery1013 (2008).

[87] M. Valko et al., Free Radicals, Metals and Antioxidants in Oxidative Stress-Induced Cancer, 160 Chemico-Biological Interactions 1 (2006).

[88] Kiarash Riazi et al., Microglial Activation and TNFα Production Mediate Altered CNS Excitability Following Peripheral Inflammation, 105 PNAS 17151 (2008).

article seemed intended to support the inflammatory mechanism Dr. Frye posited as a means of causing harm. But, Dr. Jones criticized Dr. Frye's reliance on this paper, Tr. at 238-39, noting that the "massive, massive inflammation" detectible in inflammatory bowel disease would exceed, by far, any inflammation that might be produced as a result of vaccination. Id. Dr. Jones added that because vaccine-induced inflammation would be markedly less than the inflammation associated with inflammatory bowel disease, there was very little likelihood that administered vaccines could trigger either the type of response documented in the article or the kind of neurologic problems Makena exhibited. Tr. at 239-40.

(4) The 2001 Han article

As support for the proposition that reactive oxygen species are produced in mitochondria, Dr. Frye offered the 2001 Han article, filed as Petitioner's Exhibit 73.[89] Tr. at 36. Dr. Jones testified that the paper was consistent with a large body of work indicating that mitochondria produce superoxide. Tr. at 240. But, because scientific understanding has shifted to recognize that the oxidants produced by mitochondria are necessary signaling molecules and not the harmful agents as they were formerly perceived to be, Dr. Jones questioned the article's usefulness for petitioner's purpose. Tr. at 240-41.

(5) The 2008 Khurana article

Dr. Frye testified that the animal model study in the 2008 Khurana article, filed as Petitioner's Exhibit 75,[90] "shows a sequence of events" leading to an increase in reactive oxygen species in the mitochondria that offers a view of "how a vaccine might actually damage" a cell shortly after the vaccine has been administered. Tr. at 23-24. At hearing, both of respondent's experts challenged Dr. Frye's characterization of the article. See Tr. at 242-43 (Dr. Jones); Tr. at 171-72 (Dr. Raymond).

In the 2008 Khurana article, the researchers sought to determine whether oxidative mitochondrial DNA damage can occur early in cases of experimental autoimmune uveitis, specifically before leukocyte infiltration occurs (which is a measurable indication of an underlying process at work). See Pet'r's Ex. 75 at 1. The goal of the researchers

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89 Derick Han et al., Mitochondrial Respiratory Chain-Dependent Generation of Superoxide Anion and its Release into the Intermembrane Space, 353 Biochem. J. 411 (2001).

90 Rahul N. Khurana et al., Mitochondrial Oxidative DNA Damage in Experimental Autoimmune Uveitis, 49 Investigative Ophthalmology & Visual Science 3299 (2008).

appeared to be to gain an understanding of the source of retinal damage throughout the progression of a case of experimental autoimmune uveitis.

Dr. Jones commented that the article reflected a "sl[e]ight of hand in terms of the science" because the researchers did not show that the damage detected in the mitochondrial DNA was "actually oxidative in nature." Tr. 242-43. Dr. Jones challenged the study's conclusions because in his opinion, the researchers failed to demonstrate that the measure of mitochondrial DNA damage was attributable to oxidative stress alone, and not to some other mechanism, such as errors during mitochondrial DNA replication. See Tr. at 242-44

Respondent's other expert, Dr. Raymond, observed further that the study results could not be extrapolated to provide information about the effects of childhood vaccines because the researchers purposefully injected pulverized bovine retinas to evoke a dramatic cascade of immunologic responses. Id. at 171. Dr. Raymond criticized Dr. Frye's effort to compare the effect of injected ground cow retinas to that of administered vaccines as completely "nonsensical." See id. at 171-72.

(6) The 2010 Phillips article

Dr. Frye testified that the 2010 Phillips study, filed as Trial Exhibit 2,[91] showed that biomarkers of oxidative stress continue to be observable for a period of 14 days following a vaccination. Tr. at 72-73. Dr. Frye posited that the presence of biomarkers after vaccination supports his theory that vaccines can cause injury by oxidative stress fairly quickly after vaccine administration. Tr. at 45, 73. But Dr. Frye failed to distinguish the detected oxidative stress biomarkers from those oxidants understood by experts in the field to be necessary components of normal bodily function and immunologic responsiveness. According to respondent's expert, Dr. Jones, a widely recognized specialist in quantifying oxidation and its impact on cellular signaling, the mere presence of oxidants is not dispositive of an unfolding disease process. Id. at 226; Resp't's Ex. T (1988 Tribble article), and Resp't's Ex. U.[92] Moreover, because "reactive species are very short-lived," they are difficult to measure and quantify directly. Tr. at 225. For this reason, Dr. Jones explained, breath tests ultimately were abandoned as a technique for measuring reactive species because the test measurements were rather easily skewed by "what [someone] ate." Tr. at 230. Reiterating that "oxidants are

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91 Michael Phillips et al., Effect of Influenza Vaccination on Oxidative Stress Products in Breath, 4 J. Breath Res. 026001 (2010).

92 Diane Tribble and Dean Jones, Oxygen Dependence of Oxidative Stress: Rate of NADPH Supply for Maintaining the GSH Pool During Hypoxia, 39 Biochemical Pharmacology 729 (1990).

necessary for normal [cellular] signaling" and are an important component of immune function, Tr. at 216, Dr. Jones challenged Dr. Frye's theoretical premise "that a physiological level of [oxidant] generation" is necessarily deleterious. Tr. at 216-17.

The articles on which Dr. Frye relied were problematic for petitioner because they failed to lend the supportive weight to petitioner's theory that Dr. Frye proposed. But more troubling for petitioner were the flawed underpinnings of Dr. Frye's oxidative stress theory.

c) Reactive oxygen species is necessarily present in the human body

Dr. Frye's theory of vaccine-related causation is based on the postulate that vaccines can produce sufficient, additional reactive species to overwhelm the body's antioxidant system. Tr. at 49-53. Dr. Jones explained that for reactive oxygen species to have the effect that Dr. Frye proposes, the species must be present in a sufficient quantity at the proper cellular location. See Tr. at 226-29. Dr. Jones refuted the notion that the antioxidant system could be overcome by the level of oxidants produced by an immunologic response to an administered vaccine. Tr. at 229 (stating "there's really no chance that . . . could happen") (emphasis added).

Oxidant-producing reactive oxygen species are now understood not only to provide critical signaling for cells, but also to have a role in the body's normal immunologic responses. As Dr. Jones explained at hearing, the generation of oxidants during an immunologic response serves to "enhance[]" normal cell signaling; "[i]t's part of how the system works." Tr. at 216.

Drawing on his expertise in the quantification of redox biology, Dr. Jones further explained that reactive oxygen species are very short-lived and thus, are difficult to measure precisely in the body. Tr. at 225. Particularly difficult to quantify is the amount of intermediate oxidants that are generated as part of the body's oxidative metabolism. See Tr. at 225. Although there has been some success in developing techniques to measure oxidation, "the methods are not [singularly] quantitative." Id. What has been determined from close expert study is that "a tenfold increase" in oxidant production is "insignificant relative to the [body's] overall metabolism." Tr. at 226. Thus, a very positive oxidation signal is "not necessarily relevant to a disease process at all." Id. Without more rigorously reliable quantification techniques, however, a more precise relationship between vaccine-induced oxidation and the body's oxidative metabolism is difficult to demonstrate or measure. See Tr. at 225-26. Nonetheless, Dr. Jones emphasized that the oxidant production attributable to vaccine administration was incapable of overwhelming the body's metabolism.

d) The body's capacious antioxidant levels make it very unlikely that the reactive oxygen species generated by Makena's received vaccines could have caused the harm alleged

Respondent's expert, Dr. Jones, has published the study results of his own original research quantifying oxidants in the 1998 Tribble article. As part of his effort to quantify oxidants, he measured the relationship between oxidants and the depletion of thiols (or antioxidants) in liver cells. Tr. at 232-33; Resp't's Ex. T (1988 Tribble article).[93] This research revealed that 10 times more oxidants than thiols in the liver cells were required to overwhelm the naturally-occurring antioxidant levels. Id. The amount of oxygen used in the study exceeded the amount of oxygen ordinarily present in the body's cells by more than a thousand-fold. Because the body's naturally-occurring antioxidant system is much too robust to be affected by the level of oxidation triggered by received vaccines, Dr. Jones dismissed Dr. Frye's model of vaccine-induced oxidative damage as an implausible one for overwhelming the body's thiol system. Tr. at 233.

Moreover, Dr. Jones noted that reactive oxygen species linger in the body for short durations only and, thus, great variations in oxidation levels can occur over brief periods of time. See Tr. at 225-26, 277. Because reactive oxygen species are short-lived, Dr. Jones averred that vaccine-induced reactive oxygen species could not have persisted in Makena's body for a sufficient length of time to have caused the degree of harm alleged.

e) The distance between Makena's vaccine injection site and her brain make it very unlikely that the reactive oxygen species generated at the injection site adversely impacted her brain

During his hearing testimony, Dr. Jones addressed the significance of where initial oxidant generation occurs. He explained that because locally-generated oxidants are "locally metabolized," Tr. at 227, Dr. Frye's theory "that oxidants generated within the site of a vaccination" could be transported to the brain to cause injury is not scientifically tenable. Tr. at 227.

Petitioner offered no countervailing expert testimony concerning either the body's ample antioxidant capacity available to manage reactive oxygen species levels, the brief duration of reactive oxygen species once produced, or the localized metabolism of generated oxidants.

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[93] Diane Tribble et al., Effect of Hypoxia on tert-Butylhydroperoxide-Induced Oxidative Injury in Hepatocytes, 34 Molecular Pharmacology 413 (1988).

f) Dr. Frye's extrapolation from the effect of infections to that of immunizations is flawed

In an effort to describe the mechanism by which vaccines could cause the degree of injury Makena suffered, Dr. Frye compared infectious processes to the immunologic impacts of immunization. Dr. Frye argued that it is well-recognized in the medical community that children with mitochondrial disorders are predisposed to neurodegenerative events when they develop infections. See Tr. at 62-63. He defined neurodegenerative events to include "loss of speech[,] . . . loss of motor function[,] and changes in behavior." Tr. at 64. Attributing Makena's seizure onset to vaccine stimulation in the general vicinity of her LHON point mutation, Dr. Frye urged that the causal sequence of events in Makena's case unfolded in the same manner in which infections have triggered neurodegenerative events in children with mitochondrial disorders.

As support for the proposition that vaccines given to children with underlying metabolic diseases (such as mitochondrial disorders) can result in neurologic decompensation,[94] Dr. Frye pointed to the 2002 Edmonds article, filed as Petitioner's Exhibit 79.[95] The researchers in the 2002 Edmonds article found that neurological degeneration could occur in children with diagnosed metabolic disorders during the seven-day period following an infection.

Dr. Frye also relied on the 2008 Barshop article, filed as Petitioner's Exhibit 61,[96] for the proposition that "[an] intercurrent infection is a stimulus for . . . decompensation in [the context of] metabolic disease [in general] and mitochondrial disease in particular." Tr. at 65. The Barshop study involved a survey of specialists in the field of medical biochemical genetics and their attitudes toward and their adopted vaccination practices for patients with metabolic or mitochondrial disease. The prevailing view among the specialists consulted was that the benefits of vaccination are outweighed by the risks associated with wild-type infection in these patients. See Pet'r's Ex. 61 at 2.

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[94] Decompensation occurs when "the counterbalancing of any defect of structure or function" fails. Dorland's at 399.

[95] Joseph L. Edmonds et al., Otolaryngological Manifestations of Mitochondrial Disease and the Risk of Neurodegeneration with Infection, 128 Arch. Otolaryngol. Head Neck Surg. 355 (2002).

[96] Bruce A. Barshop & Marshall L. Summar, Attitudes Regarding Vaccination Among Practitioners of Clinical Biochemical Genetics, 95 Molecular Genetics & Metabolism 1 (2008).

Dr. Jones assailed, as inaccurate, the postulate that the physiologic reaction after vaccination is similar to the response induced by infection, Resp't's Ex. C at 4, and pointed out that "[m]uch of the speculation by Dr. Frye about how vaccination[s] could exacerbate mitochondrial disease . . . [was] extrapolated from studies of responses to [actual] infection, not to vaccination." Id.; see also Tr. at 224-25. As Dr. Jones explained, an infectious process allows a live virus or bacterium to damage cells and tissues; it is the damage that triggers the onset of and determines the severity of the infected sufferer's symptoms. Id.; Resp't's Ex. C at 4. An adenovirus, for example, is characterized by a sore throat, sneezing, runny nose, headache, chills, and occasionally diarrhea; it also can trigger seizures. Contrastingly, vaccines produce a different physiologic reaction. Although immune cell activation after vaccination generates oxidative stress, it does not cause cell or tissue damage. Id. Dr. Jones further distinguished the immune activation following vaccination as involving "lymphocytes and B cells" and "not the phagocytic cells that are really very actively destroying invading organisms" during infectious states. Tr. at 224-25. Dr. Frye offered no rebuttal to this aspect of Dr. Jones's testimony.

g) Dr. Frye appears to ignore the important role of fever in metabolic decompensation

During his testimony, Dr. Frye repeatedly referenced a study that had not been filed with the court prior to the hearing. Tr. at 67-68. Nor was the referenced study filed into the record after the hearing. The undersigned, however, is familiar with the study, specifically the 2009 Shoffner article, because Dr. Frye previously has relied on it in at least one other case in the Vaccine Program. See Paluck ex rel. Paluck v. Sec'y of Health & Human Servs., No. 07-889V, 2011 WL 6949326, at *9 (Fed. Cl. Spec. Mstr. Dec. 14, 2011) vacated on other grounds, No. 07-889V, 104 Fed. Cl. 457 (2012).[97] The referenced

[97] In the Paluck case, Dr. Frye proffered a very similar causation theory to the one he presented in this case even though the two cases are factually distinguishable. The vaccinee in Paluck had a documented mitochondrial disorder while Makena has only a documented mitochondrial point mutation.

When the vaccinee in the Paluck case turned a year old, he received a set of vaccines that included two live but attenuated vaccines, specifically the mumps-measles-rubella vaccine and the varicella vaccine. Two days after receipt of the vaccines, the vaccinee in Paluck developed a fever and then developed another fever seven days later. Makena, who was much younger at the time of her vaccines, did not develop a fever during the nearly five weeks between her immunizations and the onset of seizures.

As in the Paluck case, Dr. Frye emphasizes here that Makena's course resembles that of Hannah Poling. But Dr. Frye's effort to liken the course of other vaccinees to that of Hannah Poling must be closely scrutinized because Hannah Poling's factual

study is attached as an exhibit to this decision. See Court Ex. 1 (See John Shoffner et al., Fever Plus Mitochondrial Disease Could be Risk Factors for Autistic Regression, 25 Journal of Child Neurology 429 (2009)).

The 2009 Shoffner article is a retrospective study of 28 children who were diagnosed with both an autism spectrum disorder and a mitochondrial disease. The purpose of the study was to assess the relationship between autistic regression and fever in patients with mitochondrial disease. See Court Ex. 1 at 1. The researchers who conducted the study acknowledged that "[p]atients with mitochondrial diseases, like many patients with metabolic diseases, are at an increased risk of neurologic regression in conjunction with stressors such as fever, infection, and dehydration." Id. (emphasis added). Speaking directly to the relationship between vaccination and regression, the researchers stated that in "no case" had they observed regression following vaccination "unless fever was present." Id. at 4 (emphasis added).

Why Dr. Frye chose to rely on this article is puzzling. The study focused on autistic subjects with a mitochondrial disease who experienced a regression in skills when they developed a fever after either an infection or a vaccination. Makena does not have autism. Nor does the record in this case show that Makena developed a fever during the nearly five weeks between her receipt of the vaccines at issue and the onset of her seizure episodes.

Moreover, the symptoms with which Makena did present after vaccination do not meet the definition of regression adopted by the researchers in the 2009 Shoffner article. The researchers in that study defined autistic regression as a "loss of developmental skills that included speech, receptive skills, eye contact, and social interests" in individuals under 3 years of age. Court Ex. 1 at 2. Concluding that "vaccines did not appear [to be] related to the neurologic regression" in patients "with [identified] mitochondrial disease[s] and autistic spectrum disorders," id. (emphasis added), the researchers recommended vaccinating children with mitochondrial diseases in those circumstances in which aggressive fever control and proper hydration were monitored closely by the children's physicians. See id.

Although Dr. Frye acknowledged that the researchers in the 2009 Shoffner article identified "fever" as the "trigger for neurodegeneration" that manifested as autism in children with mitochondrial disorders, Tr. at 66-67 (emphasis added), he emphasized that vaccination had triggered the onset of fever in four of the studied cases. Dr. Frye relies

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circumstances were unique. Her post-vaccinal symptoms were notable in their severity and persistence but those striking symptoms did improve over time.

on the 2009 Shoffner article in a manner that is at variance with the study's own focus on the combination of fever and mitochondrial disorders as the risk factors for autistic regression. Id.

Dr. Frye also appears to have ignored the significance of fever in the two cases of "children with mitochondrial disorders who developed severe decompensation and neurological devastation following exposure to vaccines." Pet'r's Ex. 59 at 4. These two referenced cases are: (1) a case study on Hannah Poling that Dr. Frye co-authored[98] (Pet'r's Ex. 67 (Jon S. Poling et al., Developmental Regression and Mitochondrial Dysfunction in a Child with Autism, 21 J. Child Neurology 170 (2006)); and (2) a descriptive article--but by Dr. Frye's own admission--not a scientific one that appeared in the New York Times.[99] See Pet'r's Ex. 68 (Gardiner Harris, Experts to Discuss One Puzzling Autism Case, as a Second Case Has Arisen, N.Y. Times, June 28, 2008, at A15). As discussed more fully below, both cases involved subjects who experienced significant fever after vaccination. But conspicuously absent in Makena's case is any mention of fever in the weeks after vaccination.

(1) Hannah Poling

The first case to which Dr. Frye referred was that of Hannah Poling, briefly described earlier as a vaccinee whose Program claim was compensated as a Vaccine Table Injury. See 42 U.S.C. § 300aa-14(a). Hannah's alleged injury of a vaccine-related encephalopathy was listed on the Table in association with the DTaP vaccine she received, and the onset of her symptoms occurred within the statutorily prescribed time frame. See 42 U.S.C. § 300aa-14(a). As a Table claim, a presumption of causation attached, and petitioners did not have to prove causation. See 42 U.S.C. §§ 300aa–13(a)(1), –11(c)(1)(C)(ii)(I); see also Althen v. Sec'y of Health & Human Servs., 418 F.3d at 1278 (Fed. Cir. 2005); but see 42 U.S.C. § 300aa-14(a).

Hannah's cited case report offers a "description of an autistic child with mitochondrial dysfunction, growth failure, and abnormal muscle histopathology without seizures or a defined chromosomal abnormality." Pet'r's Ex. 67 at 3 (emphasis added). The relevance of that case report to the facts of this case is not immediately apparent to

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[98] Notably, among the listed four authors of the case study were: (1) Dr. Jon Poling, whose daughter was the subject of the study; (2) Dr. Shoffner, who authored the unfiled 2009 article upon which Dr. Frye relied at hearing in this case; and (3) Dr. Frye.

[99] The article was a report that arose from a gathering of "some of the world's leading experts on . . . [mitochondrial disorders] to discuss the controversial case of a 9-year-old girl from Athens, Ga., who became autistic after receiving numerous vaccinations." Pet'r's Ex. 68.

the undersigned because, as discussed in more detail below, unlike Hannah, Makena did not experience a fever after vaccination. Makena had seizures but did not have any of the types of symptoms that Hannah exhibited following vaccination. Moreover, Makena does not have autism.

Dr. Frye characterized the Poling case as one involving a 19-month-old girl with an undiagnosed mitochondrial disorder, who was immunized with five vaccines.[100] See Pet'r's Ex. 59 at 4. Following her receipt of the vaccines, Hannah developed a high fever and an encephalopathy recognized as a compensable Table Injury under the Vaccine Program.[101] "Within the next week[,] the child . . . underwent a significant developmental regression and eventually develop[ed] . . . intractable seizures." Id. at 4.

As explained in the Poling article, Dr. Frye and the other authors put forth Hannah's case to investigate the possibility that administered vaccines can cause autistic regression in children who have mitochondrial disorders:

> This patient exemplifies important questions about mitochondrial function in autism and developmental regression . . . . If such [mitochondrial] dysfunction is present at the time of infections and immunizations in young children, the added oxidative stresses from immune activation on cellular energy metabolism are likely to be especially critical for the central nervous system, which is highly dependent on mitochondrial function. Young children who have dysfunctional cellular energy metabolism therefore might be more prone to undergo autistic regression between 18 and 30 months of age if they also have infections or immunizations at the same time. Although patterns of regression can be genetically and prenatally determined, it is possible that underlying mitochondrial dysfunction can either exacerbate or affect the severity of regression.

Pet'r's Ex. 67 at 3 (emphasis added).

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[100] Dr. Frye was one of the co-authors of the 2006 Poling article along with Jon Poling, Hannah's father, whom Dr. Frye knew from medical school. See Paluck v. Sec'y of Health & Human Servs., No. 07-889V, 2011 WL 6949326, at *14.

[101] This information comes from the two documents from the Poling case that were made available to the public. See Poling ex rel. Poling v. Sec'y of Health & Human Servs., No. 02–1466V, 2008 WL 1883059, at *1 (Fed.Cl. Apr. 10, 2008) (A ruling on a motion to release information); See also Poling ex rel. Poling v. Sec'y of Health & Human Servs., No. 02–1466V, 2011 WL 678559, at *1 (Fed.Cl. Jan. 28, 2011) (Decision awarding attorneys' fees and costs.)

The Poling article also provided the following additional relevant details:

> Within 48 hours after immunizations to diphtheria, tetanus, and pertussis; Haemophilus influenzae B; measles, mumps, and rubella; polio; and varicella (Varivax), the patient developed a fever to 38.9°C [or 102.2°F], inconsolable crying, irritability, and lethargy and refused to walk. Four days later, the patient was waking up multiple times in the night, having episodes of [backward spasmastic hyperextension of her body known as] opisthotonus, and could no longer normally climb stairs. Instead, she crawled up and down the stairs. Low-grade intermittent fever was noted for the next 12 days. Ten days following immunization, the patient developed a generalized erythematous macular rash beginning in the abdomen. The patient's pediatrician diagnosed this as due to varicella vaccination.

Pet'r's Ex. 67 at 4 (emphasis added).

Likening Makena's clinical course to Hannah Poling's, Dr. Frye asserted that Makena's "immunizations triggered [the] developmental regression, brain injury, and the subsequent development of a seizure disorder." Pet'r's 59 at 6. Dr. Frye testified that both girls had mitochondrial disorders, Tr. at 114, and "within a similar time[]frame" after vaccination, both Makena and Hannah exhibited "signs of neurological dysfunction that . . . progress[ed]" during the ensuing months. Tr. 114.

But contrary to Dr. Frye's characterization, the facts of the two cases are clearly distinguishable. First, the age of the girls at symptom onset was materially different. Hannah was 19 months of age, whereas Makena was only two months old. Second, Hannah and Makena received different vaccines; notably, Hannah received two attenuated viral vaccines, but all of the vaccines that Makena received were inactivated.[102] Third, Hannah's symptoms, including a high fever, presented within 48 hours after her vaccinations. Makena's symptoms, which did not include fever, did not present until more than four weeks after she received the vaccines at issue. Fourth, Hannah's onset symptoms of inconsolable crying, irritability, lethargy and refusal to walk, Tr. at 115-16, were not the same as Makena's onset of seizures. Id. (Dr. Frye acknowledging that Makena's initial symptoms did not compare to Hannah's). Fifth, Hannah's developmental regression after vaccination was readily ascertainable because she had developed a defined set of skills before vaccination, including "normal receptive and expressive language and [the] use of pre-linguistic gestures, such as pointing for joint

[102] Hannah received IPV, DTaP, HIB, and the two attenuated vaccines--MMR and varicella. In contrast, Makena received the IPV, DTaP, HiB and hepatitis B vaccinations. See Pet'r's Ex. 1 at 166.

attention." Pet'r's Ex. 67 at 2. In contradistinction, Makena, who began seizing after her two-month vaccines, exhibited signs of failed progression rather than developmental regression (or the loss of previously acquired skills). Sixth, Hannah Poling carries an autism diagnosis; Makena does not, and Makena's treaters strongly suspected that she had structural brain abnormalities. Lastly, while Hannah's clinical presentation eventually improved, Makena's did not. Id.[103]

(2) The case reported in the newspaper

Petitioner also filed a New York Times article describing a six-year-old girl with an underlying mitochondrial disorder, who received FluMist, a live viral vaccine, in January of 2008 and, within a week, '"became weak with multiple episodes of falling to the ground"' and '"difficulty walking."' Pet'r's Ex. 68 at 1. The girl grew increasingly weak and feverish and '"became more limp, appear[ed] sleepy, [and] act[ed] as if drunk."' Id. She required hospitalization and in April of 2008, she died. Id.

From the details of the news article, Dr. Frye contended, that the young girl, similar to Hannah Poling, had developed an encephalopathy accompanied by a viral-like illness after vaccination. Pet'r's Ex. 59 at 4. The girl subsequently experienced significant neurodegeneration and died.[104] Id. Although Dr. Frye insisted that the two

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[103] Dr. Frye's assertion that Makena's "development resumed after she stopped receiving vaccines" is not supported by the medical records, which suggest that Makena's development was simply significantly delayed. Compare Pet'r's Ex. 59 at 6 with Tr. at 165 (Dr. Raymond) (testifying that Makena "continue[d] to make developmental progress, albeit at a slower level . . . especially with an uncontrolled seizure disorder"). Makena never regressed. Her development never stopped but her development was, and continues to be, profoundly delayed.

[104] Case reports generally carry limited weight on the issue of causation. Case reports have been discussed frequently in this Program. Although providing some circumstantial evidence regarding causation, the limitations of case reports have also been noted. See Campbell v. Sec'y of Health & Human Servs., 90 Fed. Cl. 369 (2009) (noting validity in the special master's observations regarding the limited evidentiary value of case reports); see also Shepperson v. Sec'y of Health & Human Servs., No. 05–1064V, 2008 WL 2156748, at *11 (Fed. Cl. Spec. Mstr. Apr. 30, 2008) (noting a single case report is not "sufficiently probative to begin the evidentiary climb to a preponderance."); Caves v. Sec'y of Health & Human Servs., No. 07–443V, 2010 WL 5557542, at *14 (Fed. Cl. Spec. Mstr. Nov. 29, 2010) (discussing the limited role of case reports), aff'd, 100 Fed. Cl. 119 (2011); aff'd, No. 2011–5108, slip op. (Fed. Cir. Feb. 14, 2012) (per curiam); see also Reference Manual on Scientific Evidence: Reference Guide on Medical Testimony, 2d Ed. Federal Judicial Center, 2000 "["Reference Manual on Scientific Evidence"] at 475 (noting that, in determining medical causation, "[c]ausal attribution based on case

cases similarly involved vaccine injuries, the author of the New York Times article acknowledged that "[n]o one knows whether vaccinations had anything to do with the girls' health problems, and the scientific significance of individual cases is always difficult to assess." Id. But perhaps most pertinent in this case was Dr. Frye's failure to explain how this article furnished affirmative support for Makena's case.

h) Summary evaluation of Althen Prong One

As discussed more fully above, Dr. Frye has postulated that Makena's seizure disorder resulted from vaccine-induced cell death or dysfunction triggered by oxidative stress. This theory is predicated on an outdated hypothesis that oxidative stress is necessarily deleterious, and does not contemplate the beneficial and essential signaling function of oxidative stress. Effecting the degree of damage to or injury in Makena by the mechanism petitioner has proposed here would have required orders of magnitude greater than the degree of exposure afforded by administered vaccines. Or, it would have required a period of time substantially longer than the few weeks contemplated by the presented vaccine-related theory.

After carefully considering the evidence--particularly the filed medical literature and the testimony of Dr. Jones, the undersigned is unpersuaded by Dr. Frye's efforts to compare the effect of infection to the effect of vaccines on the facts of this case. As Dr. Jones explained, an infectious process allows a live virus or bacterium to damage cells and tissues; vaccines produce a different physiologic reaction. Although "immune cell activation after vaccination generates oxidative stress," it does not cause cell or tissue damage. Moreover, the literature on which Dr. Frye relied points to the impact of fever in subjects with mitochondrial disorders -- whether induced by infection or vaccination. But, Makena did not have a documented fever between her vaccinations and her seizure onset.

The medical theory offered by Dr. Frye is inconsistent with the scientific principles of oxidation that are currently recognized as sound and reliable. For these reasons, the undersigned finds that petitioner has failed to satisfy her burden of proof under Althen Prong One.

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studies must be regarded with caution," largely because they lack controls and thus do not provide the level of information or detail found in epidemiologic studies).

B. Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, petitioner must prove "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." Althen, 418 F.3d at 1278. Under this prong, petitioner must show that the received vaccine "did" cause the alleged injury. Pafford, 451 F.3d at 1354.

Petitioner need not make a specific type of evidentiary showing. That is, petitioner is not required to offer "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect . . . ." Capizzano, 440 F.3d at 1325. Instead, petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. See id. at 1325-26.

1. Makena's defined point mutation does not, without more, establish that she had a mitochondrial dysfunction

Dr. Frye proposed a causal sequence that rested first on a finding that Makena had "dysfunctional mitochondria" at the time she received her vaccines. The received vaccines then increased Makena's oxidative stress levels. Tr. at 13. Dr. Frye posited that because Makena's genetic point mutation affected "part of the electron transport chain in [her] mitochondria," it created a dysfunction that permitted more reactive oxygen species to be generated and, in turn, neurological damage to occur. See Tr. at 13. The principal difficulty with this aspect of Dr. Frye's theory, however, is the lack of evidence that Makena's mitochondria were dysfunctional when she received the vaccines of concern to petitioner.

Testing revealed that Makena has a mitochondrial point mutation associated with an eye condition known as Leber's hereditary optic neuropathy (LHON). A rare, hereditary condition, LHON presents with painless vision loss in one eye for a period of weeks or months before the second eye is affected.[105] Resp't's Ex. A at 5. Inherited through the maternal line, LHON is one of the first disorders identified to result from an altered mitochondrial genome. Nelson Pediatrics at 2065, 2067; Dorland's at 1269; Resp't's Ex. A at 5. The defining feature of LHON is optic atrophy, and "[i]n the majority of individuals with LHON, visual dysfunction is the only significant manifestation of the disease." Resp't's Ex. A at 5. Makena has shown no symptoms of this disorder.

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[105] More prevalent in males, LHON typically occurs in persons between the ages of 15 to 35 years; onset of the disorder in childhood is "extremely rare." Resp't's Ex. A at 5.

Undisturbed by the absence of symptoms characteristic of LHON in Makena, Dr. Frye focuses on the protein location of her point mutation. See Tr. at 93. He asserts that other amino acid mutations found in that mitochondrial location (in particular, the cytochrome b protein of complex III of the mitochondria)--but not detected in Makena--have been associated with epilepsy in childhood.[106] Tr. at 14. He further asserts that mutations in the broader genomic region of DNA that encodes proteins in the area of complex III--but not detected in Makena--have been associated with neurodevelopmental disorders. Id. Although Makena has not manifested the characteristic visual field loss most closely associated with the LHON point mutation that she does have,[107] and testing has not shown Makena to have the type of mutations in the protein region on which Dr.

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[106] Cytochrome b, a subunit of complex III, is an electron transfer hemoprotein located in the inner mitochondrial membrane. Dorland's at 465 (defining cytochrome b); Resp't's Ex. A at 5 (Dr. Raymond describing the location of Makena's point mutation).

[107] The record does indicate that Makena developed conjunctivitis prior to her receipt of the vaccines at issue here. Conjunctivitis, however, is an inflammatory condition distinguishable from the degenerative process associated with LHON, the condition for which Makena carries a genetic point mutation. Compare Dorland's at 405 (conjunctivitis) with id. at 1269 (LHON disorder).

Dr. Frye posited that Makena's conjunctivitis was an adverse reaction to her earlier administered vaccines. In support of this proposition, Dr. Frye relied on the listing of conjunctivitis in the Physicians' Desk Reference (PDR) as one of the adverse events reported after vaccination. Tr. at 18. On closer examination, however, the PDR does not say what Dr. Frye suggests. Rather, the PDR states that conjunctivitis is "an adverse reaction [] reported with use of the marketed hepatitis B vaccine. [But, i]n many instances, the relationship to the vaccine was unclear." Physicians' Desk Reference at 2019 (emphasis added).

In the view of the undersigned, the PDR listing alone does not make it more likely than not that Makena's conjunctivitis was an adverse vaccine reaction to her received vaccines. Moreover, with no evidence linking Makena's conjunctivitis to her LHON point mutation, the undersigned is not persuaded on this record that Makena's earlier conjunctivitis was consistent with the kind of eye involvement that would support a finding of mitochondrial dysfunction. The undersigned does not rely solely on this factor, however, in concluding that petitioner has failed to satisfy prong two of Althen.

Frye focuses to support his theory, he nonetheless maintains that Makena's received vaccinations triggered the expression of her mitochondrial abnormality.

Dr. Raymond, respondent's expert, observed during his testimony, that Makena's point mutation is present in "0.3 percent of the population," and there is no evidence of the type of cascade of deleterious events described in this case occurring in others with the same point mutation. Tr. at 158. Based on the dearth of evidence corroborating Dr. Frye's theory that the LHON mutation is "an at-risk gene" for the claimed neurologic injury, Dr. Raymond dismissed it as speculative and strained. Tr. at 158; see also Tr. at 247-48 (Dr. Jones stating that he is "not sure that you can really interpret anything with regard to that variation having any disease or dysfunction at all"); cf. Tr. at 133, 155-56 (Dr. Raymond stating that the G15257A gene mutation may not be pathogenic).

Dr. Raymond, who has extensive and well-regarded expertise in the area of neurogenetics, questioned the relevance of Dr. Frye's testimony regarding other amino acid point mutations in the cytochrome b protein to Makena's case. Tr. at 182–83. Dr. Raymond explained that Makena has a "very specific genetic alteration that has only been associated with Leber's." Tr. 183 (emphasis added). He noted that the association between "other alterations" in the cytochrome b genetic region and epilepsy "does not at all speak to Makena's situation" because genetic testing has not shown Makena to have any of the "other alterations" in the cytochrome b gene. Id.

As Dr. Frye has pointed out, Makena's mitochondrial point mutation does occur in the same genomic region as other mutations associated with seizure disorders and neurodevelopmental problems, but Makena has not been shown to have any of those other mutations. Although Dr. Frye does not clearly indicate how those other mutations might be implicated in this case, to the extent that he is urging the undersigned to infer that such mutations exist because Makena has manifested a seizure disorder and has demonstrated neurodevelopmental problems, the undersigned declines to do so.

Because Makena's point mutation alone does not rise to the level of a mitochondrial dysfunction, Dr. Frye also has applied the diagnostic criteria outlined in the 2002 Bernier article in an effort to show that Makena's mitochondrial functioning is impaired. As discussed more fully in the following subsection, an application of the Bernier criteria does not support a preponderant finding of mitochondrial dysfunction.

2. Makena's clinical symptoms do not meet the diagnostic criteria of mitochondrial dysfunction as set forth in the 2002 Bernier article upon which Dr. Frye heavily relies

Citing the broad criteria for mitochondrial respiratory chain dysfunction outlined in the 2002 Bernier article, see Petr's' Ex. 63 at 1 (2002 Bernier article),[108] Dr. Frye asserts that Makena's mitochondrial point mutation made her vulnerable to mitochondrial dysfunction.

In the 2002 Bernier article, the researchers identified diagnostic criteria in a pediatric patient population referred for mitochondrial investigations, and proposed modified diagnostic criteria for mitochondrial disorders that could be applied to adults as well as children. The researchers classified patients according to three diagnostic categories, "definite," "probable," and "possible," based on the presence of two classes of criteria: major or minor.[109] These two classes of criteria reflect certain clinical, histological, biochemical, functional or molecular symptoms.[110]

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[108] F.P. Bernier et. al, Diagnostic Criteria for Respiratory Chain Disorders in Adults and Children, 59 Neurology 1406 (2002). References to the diagnostic criteria set out in this article incorrectly appear in the transcript as the "Venair criteria," rather than the "Bernier criteria." See, e.g., Tr. at 86.

[109] A copy of the table setting forth these diagnostic criteria is attached to this decision and is designated as Court Exhibit 2.

[110] The major criteria are: (1) Clinically complete respiratory chain encephalomyopathy, OR a mitochondrial cytopathy (fulfilling the three conditions outlined in the 2002 Bernier article and discussed in Dr. Frye's testimony); (2) histological presentment of more than 2% ragged red fibers in skeletal muscles; (3) decreases in certain enzyme or respiratory chain complex activity levels; (4) functional symptoms characterized by fibroblast ATP synthesis rates greater than three standard deviations below mean; and (5) identification of a nuclear or mitochondrial DNA mutation of undisputed pathogenicity. Pet'r's Ex. 63 at 2.

The minor criteria are described as: (1) Clinical symptoms compatible with a respiratory chain defect; (2) histological showing of greater than 2% subsarcolemmal mitochondrial accumulations in a patient under16 years of age; (3) antibody-based demonstration of a defect in respiratory chain complex expression or decrease in percentage activity of respiratory chain complexes in tissues and cell lines; (4) functional symptoms characterized by fibroblast ATP synthesis rates less than 2-3 standard deviations below mean or fibroblasts unable to grow on media with glucose replaced by galactose; (5) identification of a nuclear or mitochondrial DNA mutation of probable pathogenicity; and (6) one or more metabolic indicators of impaired respiratory chain function. Pet'r's Ex. 63 at 2.

Patients must exhibit two major criteria, or one major criterion and two minor criteria for a 'definite' diagnosis of a mitochondrial disorder. A 'probable' diagnosis requires the presence of one major criterion and one minor criterion, or alternatively, three minor criteria. A 'possible' diagnosis requires the presence of a single major criterion or two minor criteria. Pet'r's Ex. 63 at 2.

Dr. Frye's testimony focused on just one of the major criteria defined in the 2002 Bernier article, namely a clinical mitochondrial cytopathy which must meet three particular conditions. Tr. at 31-34; Pet'r's Ex. 59 at 3. These three conditions include: (1) an unexplained combination of multi-systemic symptoms that is essentially pathognomonic for a respiratory chain disorder, and symptoms must include at least three of the following organ system presentations -- namely neurologic, muscular, cardiac, renal, nutritional, hepatic, endocrine, hematologic, otologic, ophthalmologic, dermatologic, or dysmorphic; (2) a progressive clinical course with episodes of exacerbation (such as might occur following intercurrent illnesses) or a family history that is strongly indicative of a mitochondrial DNA mutation (to include at least one maternal relative other than the proband whose presentation predicts a probable or definite respiratory chain disorder); and (3) other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing, which may include metabolite, enzyme, or mutation analyses, imaging, electrophysiological studies, and histology. Pet'r's Ex. 63 at 2.

As inferred from his reports and his testimony, Dr. Frye asserts that Makena has satisfied the major criterion of a clinical mitochondrial cytopathy (and its three component conditions) for a finding of 'possible' mitochondrial dysfunction according to the Bernier criteria. As evidence of the first of the three conditions, that is, Makena's "unexplained combination of multi[-]systemic symptoms," Dr. Frye pointed to the various notations in Makena's records relating to her seizures (which implicate her neurologic system), her elevated liver enzyme levels (which implicate her hepatic system), her growth and precocious puberty issues (which implicate her endocrine system), and the documented reports of her chronic constipation (which implicate her gastrointestinal system). Tr. at 78-84.

Respondent's expert, Dr. Raymond--who possesses expertise in both neurology and genetics--expressed doubt that Makena has a frank mitochondrial disorder. Dr. Raymond observed, however, that "the broadness of the diagnostic criteria" set forth in the 2002 Bernier article--upon which Dr. Frye relies--does not allow ready exclusion of the possibility that Makena has such a disorder.[111] Resp't's Ex. A at 6.

[111] For purposes of this discussion, the terms "mitochondrial dysfunction" (preferred by Dr. Frye) and "mitochondrial disorder" (preferred by Dr. Raymond) are used interchangeably.

A closer examination of Dr. Frye's application of the Bernier diagnostic criteria to Makena's symptoms, however, reveals that the constellation of Makena's symptoms do not preponderate in favor of a finding that Makena has a mitochondrial disorder, as defined by the Bernier criteria.

The undersigned turns to address each of the three conditions, specifically the multi-systemic involvement, the episodes of an exacerbated clinical course, and the exclusion of other disorders.

3. Makena's symptoms affecting her multiple body systems are entirely consistent with her well-documented seizure disorder

Each of Makena's systems alleged to have been affected is examined in turn.

a) Her neurologic system

The record indicates that Makena has an intractable seizure disorder, and the early, aggressive efforts to treat her seizure condition returned very limited success. That she has significant neurologic dysfunction is not in dispute; but, there is little record evidence to establish that she has suffered the necessary multi-systemic symptoms--specifically the type of hepatic, endocrine, or gastrointestinal dysfunction contemplated by the Bernier criteria--that could be deemed consistent with a disordered oxidative metabolism. The Bernier criteria require that such multi-systemic symptoms characteristic of a mitochondrial cytopathy occur in combination without another explanation. Pet'r's Ex. 63 at 2. But here, another explanation has been offered. Many of Makena's treaters and respondent's experts attribute Makena's various symptoms to her seizure condition and corresponding treatment.

Choosing to characterize Makena's frank seizure disorder as a neurologic condition, Dr. Frye contends that as required by the Bernier criteria, Makena's neurologic condition had episodic features. The episodic features to which he refers are Makena's seizure events. Dr. Frye's circularly-reasoned position would appear to ignore the fact that by definition, a seizure disorder is marked by episodic seizure events.

Respondent's expert, Dr. Raymond, challenges the vaccine-relatedness of Makena's seizure disorder. He contends that the constellation of her various symptoms is completely consistent with an epileptic syndrome and does not require a finding of metabolic dysfunction. Nonetheless, identifying those factors that militate against a finding that Makena has a metabolic disorder, Dr. Raymond pointed out that Makena showed "no" evidence of regression, "limited" evidence of multi-system disorder, and

"very limited" evidence of any defect in the oxidative phosphorylation aspect of her metabolism. See Tr. at 131.

Dr. Frye's selective and circular discussion of the facts pertaining to Makena's seizure disorder substantially diminished the persuasiveness of his testimony, and a finding of neurologic impairment, without more, does not establish that Makena's mitochondrial functioning was disordered.

b) Her hepatic system

Dr. Frye claims that Makena suffered liver dysfunction, citing to "an increase in [her] liver enzymes" measured "shortly after she had her onset of seizures." Tr. at 79. Liver enzymes found in blood, instead of liver cells, may be an indication of a liver abnormality, and may be detected by lab testing of blood. Elevated measurements of the liver enzyme SGOT on lab test results may indicate not only injury to liver tissues but alternatively to either the heart, muscle, brain or kidney tissues, all of which contain the same enzyme SGOT. See http://arthritis.about.com/od/diagnostics/a/liverbloodtests.htm. An increase in Makena's liver enzymes was documented in two record notes in February of 1999. The first note, on February 26, 1999, referenced an increased SGOT/PT. Tr. at 80; see also Pet'r's Ex. 1 at 168. The second note, dated February 27, 1999, stated "increased liver enzymes on labs." Id. Dr. Frye acknowledged that other than these two record notations, he had no evidence to support his opinion that Makena suffered from liver dysfunction. Tr. at 81.

Contrary to Dr. Frye's assertions and as explained by respondent's expert Dr. Raymond at hearing, Makena's liver enzyme test results provide scant evidence of a mitochondrial disorder. The results are completely consistent, however, with the initiation of Makena's anticonvulsant therapy. Makena began taking anticonvulsants on January 13, 1999. See Pet'r's Ex. 11 at 135 (noting that Phenobarbital was started on Wednesday, two days before the January 15, 1999 hospital admission). As Dr. Raymond, pointed out at hearing, Makena's first abnormal liver function test results were obtained in February of 1999, shortly after Makena began taking three anticonvulsant medications which are "known to rev up the liver function system." Tr. at 139; see, e.g., Pet'r's Ex. 58 at 74 (discussing the anticonvulsant therapy Makena began in February 1999). Dr. Raymond noted that after Makena discontinued taking the anticonvulsants, her liver function tests returned to normal. See Tr. at 139-41; Pet'r's. Ex. 45 at 624 (July 1999); Pet'r's. Ex. 45 at 600 (Sept. 1999). Dr. Raymond's expert testimony is buttressed by notes from one of Makena's treaters at the Medical Center of University of California, Irvine, dated May 6, 2003, indicating that the administered "phenobarbital caused an elevation in [Makena's] liver enzymes." Pet'r's Ex. 41 at 45. While Dr. Frye did not concede that Makena's February 1999 elevated liver enzyme measures were triggered by her anticonvulsant medication, he did acknowledge that anticonvulsants can cause an increase in liver function tests. Tr. at 80.

c) Her endocrine system

Asserting that Makena showed signs of additional system involvement, Dr. Frye referenced a letter dated August 12, 1999, from Makena's pediatric neurologist, recommending an endocrinologic consultation. Tr. at 81; Pet'r's Ex. 23 at 121. Makena's neurologist noted her "bilateral breast tissue development" during an examination of Makena. At that time, Makena was 10 months old. Attributing her precocious puberty to either a secondary effect of an epileptic encephalopathy, a response to estrogen exposure, or a secondary reaction to medication, Makena's neurologist suggested endocrinologic testing to evaluate Makena's condition.[112] Pet'r's Ex. 23 at 121.

Four years later in May of 2003, the Basts took Makena to UCI Medical Center for an endocrinologic evaluation with "[c]oncern[s]" about her "early pubertal changes." Pet'r's Ex. 41 at 44-46. The Basts reported that Makena had shown slight breast development between five and eight months of age, but did not appear to progress further thereafter. The exam notes make mention of Makena's abnormal hair growth (hypertrichosis),[113] Pet'r's Ex. 41 at 44, but include no mention of a mitochondrial disorder. Id. About a month before she took Makena for the endocrinologic evaluation at UCI, Makena's mother had detected pubic hair growth that raised some concern. Pet'r's Ex. 41 at 44. On examination, the pediatric endocrinologist measured Makena's hormone levels[114] and ordered a comprehensive metabolic profile. Id. at 45. The endocrinologist's diagnostic impression was "benign premature adrenarche." Id. Follow-up visits to the endocrinology clinic on December 5, 2003, and July 13, 2004 confirmed that Makena was experiencing a benign appearance of sexual hair. Id. at 24-28.

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[112] In this same letter, Makena's neurologist, Dr. Gospe, states that he discussed immunizations in response to questions from Makena's mother. In his opinion, "Makena's epileptic encephalopathy was not secondary to a previous hepatitis immunization." Pet'r's Ex. 23 at 121. With the exception of pertussis, he recommended that Makena receive all regular immunizations. Id.

[113] Hypertrichosis, a condition of excessive body hair, can result from endocrinological disorders or growth disorders. Nelson Pediatrics at 2289.

[114] The hormone testing included a check of Makena's levels of: LH, FSH, estradiol, progesterone, testosterone, TCH and ACTH. Such testing is performed to detect hormone imbalances.

Dr. Frye's opinion that Makena's early pubertal changes are evidence of a mitochondrial disorder is not supported by the medical records. Nor is premature breast development the type of endocrinologic manifestation characteristically associated with mitochondrial disorders. Tr. at 145-46 (Dr. Raymond). As respondent's neurogenetics expert Dr. Raymond explained without rebuttal from petitioner, the endocrinologic conditions typically associated with mitochondrial disorders are: diabetes, thyroid diseases, pancreatic issues, and bone marrow suppression. Id. Makena exhibited none of these conditions.

d) Her gastrointestinal system

Dr. Frye claimed that Makena's gastrointestinal system was affected. But the sole gastrointestinal symptom to which Dr. Frye could point was Makena's chronic constipation. Tr. at 84.

Dr. Raymond testified that constipation is a common symptom in children with intellectual disabilities and, thus, without more, should not be viewed as an indication of multi-system abnormality or evidence of a specific mitochondrial problem. Tr. at 147, 177. Dr. Frye did not challenge this aspect of Dr. Raymond's testimony.

4. Makena did not regress or suffer periods of exacerbation after she received the vaccines at issue.

The 2002 Bernier article identifies, as the second major diagnostic indicator of a mitochondrial disorder, "[a] progressive clinical course with episodes of exacerbation." Pet'r's Ex. 63 at 2. But, demonstrating periods of exacerbation in Makena's case is factually difficult. Once Makena's neurodevelopmental problems became apparent--specifically her impaired gross motor skills--they did not improve. Nor did her seizure condition. Consistent with the intractable nature of her seizure condition, she continued to experience repeated seizures--not merely episodic ones--even during the period she was receiving treatment. Makena's clinical picture does not show periods of aggravation and increased symptom severity; rather, it shows the seriousness of her seizure condition.

Dr. Frye posited that Makena's developmental regression occurred after her seizure onset at two months of age, Tr. at 106, and he defined regression as "a loss of skills." [115] Tr. at 33, 64. As he described Makena's clinical course, however, he was unable to point to any evidence that Makena lost skills. On further questioning, Dr. Frye

[115] Dr. Frye pointed to Makena's tics as the earliest symptoms of her abnormal development. Tr. at 103. But, no mention of Makena's tics appears in the medical records. Rather, this symptom was first mentioned in the affidavits prepared by Makena's parents for this vaccine litigation.

tried unconvincingly to conflate regression (the loss of skills) with stagnation (the lack of further skill development). Tr. at 103-09, 120-23. Although he ultimately allowed that Makena's regression was effectively a stagnation of development, Tr. at 107-8, he acknowledged that "there's not much development to lose" at two months of age. Id. at 108.

Dr. Raymond challenged Dr. Frye's loose use of the phrase "developmental regression," a medical term of art meaning a "loss of previously acquired skills." Tr. at 165. Dr. Raymond noted that Makena's records offered no evidence of developmental regression, Tr. at 165, but showed instead that she continued to make limited developmental progress, "albeit at a slower [pace]" once she began seizing. Tr. at 165.

Consistent with Dr. Raymond's testimony and contrary to Dr. Frye's characterization of Makena's clinical course, the record does not show that she regressed after vaccination. Tr. at 131 (Dr. Raymond), Pet'r's Ex. 11 at 135-38 (January 15, 1999, Children's Hospital visit); Pet'r's Ex. 23 at 6-17 (doctor notes from October 1998 through June 1999).

5. As required by the Bernier criteria, petitioner has failed to exclude other possible metabolic or non-metabolic disorders by appropriate testing

The 2002 Bernier article identifies, as the third major diagnostic indicator of a mitochondrial disorder, the exclusion of "[o]ther possible metabolic or nonmetabolic disorders . . . by appropriate testing, which may include metabolite, enzyme, or mutation analyses, imaging, electrophysiological studies, and histology." Pet'r's Ex. 63 at 2.

Dr. Frye argued that Makena's laboratory test results were consistent with a mitochondrial disorder. Tr. at 78. Of particular relevance, in his view, were Makena's "elevated urine and blood lactate" levels, an "elevation [in her] alanine to lysine ratio," Tr. at 89, and her low carbon dioxide level. Tr. at 90. In addition, Dr. Frye noted Makena had elevated liver enzymes when measured at the end of February 1999 (nearly seven weeks after her seizure onset).[116] Tr. at 79-80.

Dr. Raymond countered Dr. Frye's testimony asserting that most of Makena's laboratory results argue against a finding of mitochondrial dysfunction. Tr. at 132-33,

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[116] Dr. Frye provided no dates for the lab work to which he referred during his testimony on cross examination. In an effort to anchor Dr. Frye's testimony to the record, respondent's counsel inquired about particular lab results and the timing of the testing in the context of Makena's broader health picture.

see generally 135-44, 151-52. Dr. Raymond pointed specifically to the results of Makena's testing shortly after the onset of Makena's seizures in January of 1999--when her alleged mitochondrial disorder would have been expected to be in "full" effect--her lab tests showed normal carbon dioxide levels, normal lactates in her blood and urine, [117] a normal amino acid profile, no elevation in pyruvates, a normal alanine to lysine ratio,[118] a normal carnitine level, and a normal ketone level. Tr. at 136-38 (citing Pet'r's Ex. 45 at 682-83, 697, 717, 758-59, 762, 774). Seven months later, in July 1999, Makena's amino acid profile was also essentially normal, her acylcarnitine profile was normal, and the alanine to lysine ratio was in the normal range. Tr. at 140-41 (citing Pet'r's Ex. 45 at 620, 622). Makena's lactate, pyruvate, and carbon dioxide levels were normal on testing performed again in September 1999. Tr. at 141 (citing Pet'r's Ex. 45 at 600, 592).

As a clinician who routinely diagnoses mitochondrial disorders in his practice, Dr. Raymond testified that the clinical markers for which treaters look to diagnose mitochondrial disease were not present in Makena. See Tr. at 132. As her lab testing showed, her blood levels of lactates and pyruvates were normal, even if the levels episodically exhibited a "trivial elevation." Tr. at 132. Makena also had normal amino acids, normal organic acids, and a normal acylcarnitine profile. Because her laboratory measures consistently fell within a normal range, Dr. Raymond asserted that Makena is unlikely to have a mitochondrial disorder. Tr. at 131-32.

Dr. Raymond testified that were Makena to have a mitochondrial disorder affecting her oxidative phosphorylation (the necessary process for the making of energy), evidence of that metabolic dysfunction would be expected to be stronger and more consistent than is present in this case. See Tr. at 134. Dr. Raymond explained that the type of expected evidence would include "elevated lactates, elevated pyruvates, possibly

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[117] At the evaluating lab, the high end of the normal range for lactate levels was 2.1. Pet'r's Ex. 45 at 683. Makena's lactate level was measured at 2.2. Id. Recognizing that her lactate level exceeded the high end of the normal range by a measure of 0.1, Dr. Raymond explained that from a clinical perspective--among "people who do this for a living"--such a marginal increase would not be considered a sign of mitochondrial dysfunction. Tr. at 179 (emphasis added); see also Tr. at 136-37. He added that the artificially high lactic acid levels measured on October 8, 2008, nine years after the onset of Makena's seizures, were not "consistent with [Makena's] condition," Tr. at 191-92, but seemed more likely to have resulted from improper handling. Tr. at 191-92.

[118] Dr. Raymond explained that based on his own extensive clinical experience, he would not have given much weight to the alanine to lysine ratio. Tr. at 137, 140. He addressed the ratio simply to respond to Dr. Frye's contention that elevations in this ratio supported a finding that Makena has a mitochondrial disorder. Dr. Raymond reiterated that in most instances, Makena's metabolic ratios fell within normal limits.

hypoglycemia, as well as a larger anion gap," Tr. at 134, and such elevation levels would be detected readily by testing. See Tr. at 134.

Dr. Raymond observed that other of Makena's test results were not consistent with a mitochondrial disorder. In particular, her cerebral spinal fluid was normal, and her MRIs did not contain the type of characteristic images found in patients with mitochondrial disorders, Tr. at 132, "especially [when the disorder] . . . present[s] [in a] two[-]month[]" old. Tr. at 166-67 (referring to Pet'r's Ex. 45 at 665-66). Dr. Raymond stated that in a two-month old presenting with a mitochondrial disorder, "symmetric abnormalities of the basal ganglia, midbrain, and brain stem" are typically seen on brain imaging, and those abnormalities were not present on Makena's earliest MRIs. Id.

Nor did the MRI performed when Makena was 11 months old consistent with a mitochondrial disorder in a patient of that age. Tr. at 166-67 (referring to Pet'r's Ex. 45 at 606-07). Instead Makena's MRI at 11 months of age was "relatively unremarkable except for some mild delays in myelination, [a pattern] . . . seen [in] individuals with mental retardation developmental issues" but "not consistent" with a patient suffering from a neurodegenerative condition, such as Dr. Frye asserts Makena had. Tr. at 167.

Not only did Makena's brain images fail to show evidence of the neurodegenerative process characteristic of a mitochondrial dysfunction, the results of her cardiologic evaluation were similarly unavailing. Tr. at 168; see Pet'r's Ex. 23 at 115. As Dr. Raymond noted, the pediatric cardiologist who examined Makena for evidence of a cardiac myopathy (heart muscle weakness) assessed her as normal and unlikely to have a "disorder of energy metabolism." Tr. at 168-69 (Dr. Raymond clarifying Dr. Rebolledo's assessment).

Moreover, Makena's ophthalmologist found "no evidence of any eye changes that would point to a mitochondrial disorder." Pet'r's Ex. 23 at 37.

Dr. Raymond acknowledged that Makena's clinical course included some elements that fit the diagnostic criteria for a mitochondrial disorder, Resp't's Ex. A at 6, but asserted--based on his extensive experience diagnosing mitochondrial disorders in children--that the totality of her clinical picture does not support such a diagnosis. Tr. at 131, 152; see also Tr. at 129 (discussing Dr. Raymond's current clinical practice).

The record indicates that all of Makena's treating physicians but Dr. Stein, reached the same conclusion as did Dr. Raymond. See, e.g., Pet'r's Ex. 41 at 18 ("It looks like she had a very significant evaluation and does not appear to have a mitochondrial disorder. . . ."). Dr. Stein, the neurologist who first treated Makena for her seizure disorder, conservatively initiated treatment for a possible mitochondrial disorder with riboflavin and CoQ10, based on his uncertainty about Makena's diagnosis, and the lack of "danger" associated with the treatment therapy he selected against the potential harm if she had an

untreated mitochondrial disorder. Pet'r's Ex. 23 at 108. Having carefully considered the entire record, the undersigned is persuaded that the weight of the evidentiary record militates against a finding that Makena had any disordered mitochondrial function, notwithstanding her detected point mutation.

6. Petitioner diminished the role of Makena's intercurrent upper respiratory infection

Makena had an upper respiratory infection in late December 1998. Pet'r's Ex. 1 at 170. The infection preceded the onset of Makena's symptoms by almost two weeks.

Dr. Frye characterized Makena's upper respiratory infection at hearing as a mild viral illness. Tr. at 117-18. But in his earlier submitted expert report, he had characterized that infection as a severe one. Cf. Pet'r's Ex. 51 at 1, with Pet'r's Ex. 59 at 1. Dr. Frye attributed Makena's upper respiratory symptoms to the vaccines she received rather than to a viral illness, Tr. at 93-94, and on further questioning, Dr. Frye asserted that Makena's upper respiratory infection alone was not sufficient to trigger her metabolic decompensation because "the multiple vaccines that she received [would have] caused more activation to [her] immune system than a . . . mild viral infection would have." Tr. at 118.

Dr. Raymond disagreed and countered that even if Makena had a mitochondrial disorder, "the clear infectious event" was much more likely to have triggered the alleged sequence of events "than a vaccine which [produced] no adverse events at the time" of administration. Tr. at 170. As discussed earlier in this decision, the impact of an infection and a vaccination are immunologically distinguishable.

7. Petitioner's re-challenge argument, asserted for the first time in post-hearing briefing, is unavailing

Petitioner asserted for the first time in her post-hearing briefing that she satisfied her burden of showing a logical sequence of cause and effect with evidence that Makena had experienced a "rechallenge event." Pet'r's Br. at 11-13 (citing Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317 (Fed. Cir. 2006)). Petitioner argued that, '"if [a vaccinee] experiences a rechallenge event, or [petitioner] can demonstrate the presence of pathological markers indicating that the vaccine caused the injury,"' then petitioner must prevail under the Vaccine Program. Pet'r's Br. at 11.

As previously recognized,

> The IOM [Institute of Medicine] has on more than one occasion determined that rechallenge is strongly probative of a causal relationship. See Christopher P. Howson, et al., Institute of Medicine Adverse Effects of

> Pertussis and Rubella Vaccines, 48 (1991) (hereinafter IOM 1991 Report) ("increasing severity of the event with increasing dose number would tend to support a causal interpretation"); IOM Report on Causality, at 21 ("causality is strengthened by evidence that the risk of occurrence of an outcome increases with higher doses or frequencies of exposure"). In fact, in the instance of tetanus and Guillain–Barré Syndrome (GBS), the IOM found a causal relationship based upon evidence of rechallenge. IOM Report on Causality, at 88–89 (relying on Pollard and Selby).

Capizzano v. Sec'y of Health & Human Servs., No. 00-759V, 2004 WL 1399178, at *15 (Fed. Cl. Spec. Mstr. June 8, 2004) determination sustained sub nom, No. 00-759 V, 2004 WL 3049342 (Fed. Cl. Dec. 7, 2004) vacated and remanded sub nom, 440 F.3d 1317 (Fed. Cir. 2006)

Since the issuance of Capizzano, and the release of the IOM 1991 Report, the Institute of Medicine has issued a new report, namely Adverse Effects of Vaccines: Evidence and Causality (2012) (IOM 2012 Report). According to the IOM 2012 Report, a case involving rechallenge--that is a case in which an adverse event occurs after each administration of the same vaccine in the same individual--lends strong support to a finding of causality. Each instance of rechallenge, however, must include documented receipt of a particular vaccine, a clinician's diagnosis of the health outcome, and similar periods of reasonable latency. Institute of Medicine, Adverse Effects of Vaccines: Evidence and Causality 46-47 (Kathleen Stratton et al., eds. 2012). The evidence of causality is greatly diminished for relapsing-remitting health outcomes as opposed to monophasic conditions, which are otherwise recognized as singularly occurring events. Id.

Here, petitioner contends that Makena suffered the "relatively mild" reaction of conjunctivitis to the hepatitis B vaccine she received on October 23, 1998. Pet'r's Br. at 12. Petitioner argues that conjunctivitis is an adverse event associated with the hepatitis B vaccine without filing supportive evidence for that proposition. Petitioner appears to have relied solely on the temporal association between Makena's receipt of a hepatitis B vaccine and her subsequent development of conjunctivitis.

Petitioner adds that the administration of Makena's second hepatitis B vaccine on December 4, 1998, caused Makena to develop symptoms of an upper respiratory infection which were "much more severe than [the symptoms] following her first [reaction]." Pet'r's Br. at 12. Petitioner argues that Makena's development of an upper respiratory infection, much like her conjunctivitis, was "evidence of a robust immune response," Pet'r's Br. at 12, and both ailments were side effects of the administered vaccines. Petitioner further argues that Makena's upper respiratory infection was "the first clinical manifestation of [the] excessive oxidative stress [imposed] on Makena's mitochondria" by her vaccines. Id.;(citing Tr. at 1, 93-94, 97). Petitioner urges the

undersigned to accept that "all of Makena's subsequent symptoms are the sequelae of her vaccinations and part of the rechallenge event" that adversely affected Makena's neurologic condition. Pet'r's. Br. at 13. Petitioner has offered little more than her own assertions regarding the vaccine-relatedness of Makena's conjunctivitis and upper respiratory infection. Absent more, the undersigned cannot, and does not, accord much weight to these assertions.

The medical theory offered by Dr. Frye requires a finding that Makena had "dysfunctional mitochondria" at the time she received her vaccines. Dr. Frye applied the Bernier criteria to establish that Makena has a mitochondrial disorder. But he failed to apply them properly, and he failed to exclude other conditions--such as Makena's seizure disorder--that could have caused Makena's symptoms. His application of the Bernier criteria to Makena's case failed to show by preponderant evidence that Makena has a mitochondrial disorder.[119] Nor do Makena's voluminous medical records offer support for such a finding. Although one of her early treating neurologists considered the possibility that Makena might have had a metabolic disorder, extensive testing did not show that Makena had such as disorder. Moreover, Makena failed to respond to a standard treatment protocol for a mitochondrial disorder.

Makena's mitochondrial dysfunction is critical to Dr. Frye's theory of vaccine-related injury because it speaks to how a vaccine administered in Makena's thigh was responsible for the neurodegeneration in her brain. Absent preponderant evidence that Makena's mitochondria were dysfunctional at the time that she received the vaccines of concern to petitioner, there is no factual predicate to support Dr. Frye's theory of vaccine-related causation in this case. See Hibbard v. Sec'y of Health & Human Servs., 698 Fed. 3d. 1355, 1368-69 (Fed. Cir 2012); Rice (Fed. Cl.)

C. Althen Prong Three – Timing

Under Althen prong three, petitioner must establish that Makena's injury occurred within a time frame that is medically appropriate for the alleged mechanism of harm. See Pafford, 451 F.3d at 1358 ("Evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the 'but-for' prong of the causation analysis."). Petitioner may satisfy this prong by producing "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." De Bazan, 538 F.3d at 1352.

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[119] Dr. Frye also failed to establish that Makena had a "possible" mitochondrial disorder as defined by the Bernier diagnostic tool.

Petitioner may discharge her burden by showing: (1) when the condition for which she seeks compensation first appeared after vaccination and (2) whether the period of symptom onset is "medically acceptable to infer causation." Shapiro v. Sec'y of Health & Human Servs., No. 99-552V, 2011 WL 1897650, at *13 (Fed. Cl. Spec. Mstr. Apr. 27, 2011), aff'd in relevant part, vacated in non-relevant part, No. 99-552V, 101 Fed. Cl. 532, 536 (2011). The appropriate temporal association will vary according to the particular medical theory advanced in the case. See Pafford, 451 F.3d at 1358.

Although Dr. Frye indicated in his expert report that Makena's abnormal development began "approximately 10 days after [her] 2 month vaccinations,"[120] Pet'r's Ex. 59 at 1, he did not address whether this time period for symptom onset was a medically appropriate one for the biological mechanism of injury he had proposed. Not until the hearing, did Dr. Frye offer that two to four weeks is the medically appropriate time frame for a received vaccination to trigger the onset of neurodegenerative symptoms in a subject with mitochondrial disease. Tr. at 71. Makena's first neurologic symptoms were her seizures, and these symptoms first presented narrowly beyond the time frame proposed by petitioner's expert.

But most importantly, Makena's injury, as proposed by Dr. Frye, cannot be supported by current scientific thinking about oxidative stress. Dr. Frye posited at hearing, that in the context of a mitochondrial disease, the medically appropriate time frame between vaccination and the onset of neurodegenerative symptoms is within two to four weeks. Tr. at 71. As support for this proposition, Dr. Frye relied on an animal model study, filed as Petitioner's Exhibit 75 (2008 Khurana article),[121] and a human study, filed as Trial Exhibit 2 (2010 Phillips article).[122] Dr. Frye also relied on the 2009 Shoffner article, not filed in this case but familiar to the undersigned, for the proposition

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120 In determining when the symptoms of Makena's injury first appeared, Dr. Frye relied most heavily on the reports of Makena's parents. The Basts asserted that Makena first developed a severe upper respiratory infection in mid-December, approximately 10 days after receiving her two month vaccinations. See Pet'r's Ex. 25 at 2. Makena's medical records, however, place the infection nearly two weeks later, toward the end of December 1998.

121 Rahul N. Khurana et al., Mitochondrial Oxidative DNA Damage in Experimental Autoimmune Uveitis, 49 Investigative Ophthalmology & Visual Science 3299 (August 2008).

122 Michael Phillips et al., Effect of Influenza Vaccination on Oxidative Stress Products in Breath, 4 J. Breath Res. 026001 (2010).

that regressive symptoms can occur within two weeks of vaccination.[123] See Tr. at 67, 71.

Conceding that "[no] good models [exist for] . . . the sequence of events or the type[s] of events that we're talking about," Tr. at 75, Dr. Frye offered the 2008 Khurana study to show that mitochondrial DNA damage could occur within a 12-day period following vaccinations. Tr. at 74. But respondent's expert Dr. Jones criticized Dr. Frye's reliance on this animal model study designed to determine when DNA damage occurs in experimental autoimmune uveitis. See Pet'r's Ex. 75. The study, detailed in the 2008 Khurana article, involved the injection of bovine retinal extract into rats to determine timing of onset of mitochondrial damage in cases of experimental autoimmune uveitis. Id. Dr. Jones criticized the article as a scientific "sl[e]ight of hand," Tr. at 242, because the study merely suggested a problem with mitochondrial replication but did not demonstrate that oxidative damage had occurred. See Tr. at 243-44. Dr. Raymond also criticized Dr. Frye's reliance on the 2008 Khurana article, asserting that it had "absolutely nothing to do with [the] vaccination of children." Tr. at 171.

Dr. Frye also offered the 2010 Phillips article to show that markers of oxidative stress could be found in breath up to 14 days after vaccination. See Tr. at 73. The researchers in this study measured volatile organic compounds in breath samples of 33 normal healthy human subjects at intervals of two, seven, and 14 days after the administration of a live attenuated influenza vaccine in the nasal mist form. Trial Ex. 2 at 1-2. The researchers hypothesized that the composition of breath volatile organic compounds following vaccination is affected by an increase in oxidative stress and by inhibition of the enzyme, cytochrome p450. See Trial Ex. 2 at 3.

Respondent's experts criticized Dr. Frye's reliance on this study noting that none of the subjects suffered any damage from the hypothetical presence of oxidative stress. Moreover, the undersigned questions the relevance of this study because Makena did not receive any live, attenuated vaccines. Nonetheless, Dr. Frye proposes a two- to four-week time frame for his biological mechanism of the vaccine-induced damage of oxidative stress based on this study of breath samples at 14 days after vaccination.

Disputing the timing proposed by Dr. Frye, Dr. Jones--a leading expert in the area of oxidative stress--testified that even if petitioner's theory of oxidative damage were sound on the facts of this case, the two- to four-week interval that Dr. Frye proposes between vaccination and the onset of Makena's seizures was much too short a period of time for oxidative stress to have caused the degree of injury alleged. Dr. Jones asserted, that because damage caused by oxidation requires a significantly longer period of time as

[123] See J. Shoffner et al., Fever Plus Mitochondrial Disease Could be a Risk Factor for Autistic Regression, 25 Journal of Child Neurology 429 (2009).

demonstrated by the aging process, petitioner's posited vaccine injury "simply could not [have] occur[ed] within a four[-]week period." Tr. at 221-22.

Dr. Jones pointed to the 2006 Stadtman article, filed as Petitioner's Exhibit 91,[124] to show that the changes associated with aging and attributable to oxidation--such as the pigment accumulation in the eyes and changes to skin texture--require a time frame more protracted than four weeks. Tr. at 220-22. Dr. Jones allowed that even if the oxidative changes implicated in the aging process were found to be responsible for the triggering of seizures (a correlation that has not been shown in any of the aging studies), the time frame required to produce damage of the magnitude alleged here is substantially greater than Dr. Frye has proposed. See Tr. at 222.

Dr. Frye has proposed a time frame for Makena's injury that does not comport with the well-established understanding that neurodegenerative injury caused by oxidative stress requires decades, rather than weeks. Because the timing of events in Makena's case was too short for the biological mechanism proposed, petitioner's claim fails to satisfy Althen Prong Three.

1. Petitioner did not assert nor does the record support a claim of significant aggravation

Petitioner did not claim significant aggravation in her petition or assert such an argument at hearing.

"To prove a claim for significant aggravation, "petitioner[] must establish the combined causation factors identified in Whitecotton . . . and the Althen causation factors." Raybuck v. Sec'y of Health & Human Servs. No. 06-846V, 2010 WL 4860778, at *12 (Fed. Cl. Spec. Mstr. Nov. 9, 2010). Therefore, to establish a prima facie case of significant aggravation, petitioner must show by preponderant evidence that: (1) the vaccinee had the injury prior to the administration of the vaccines; (2) the vaccinee's post-vaccinal condition constitutes a "significant aggravation" (as defined under the Act) of her prior injury; (3) the vaccinee's current medical condition is a "significant aggravation" of the condition as it existed prior to the vaccination; (4) a reliable medical theory causally connecting such a significantly worsened condition to the December vaccines Makena received; (5) a logical sequence of cause and effect showing that the received vaccines were the reason for the significant aggravation; and (6) a proximate temporal relationship between these vaccinations and the alleged significant aggravation. See Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144-45 (2009); see also Whitecotton v. Sec'y of Health & Human Servs., 81 F.3d 1099, 1107 (Fed. Cir. 1996)

[124] Earl R. Stadtman, Protein Oxidation and Aging, 40 Free Radical Research 1250 (2006).

(setting forth a four-prong test for significant aggravation). Petitioner must also show that but for the vaccination, the vaccinee would not have suffered the injury. See Hennessey v. Sec'y of Health & Human Servs., No. 01-190V, 2009 WL 1709053 at *41 (Fed. Cl. Spec. Mstr. May 29, 2009) review denied, decision aff'd, 91 Fed. Cl. 126 (Fed. Cl. 2010).

In this context, Makena has not provided any medical opinion explaining how her vaccinations could have significantly aggravated her pre-existing condition. In short, the same deficiencies in her current petition for vaccine-related causation plague her significant aggravation claim.

VII. Conclusion

Petitioner has asserted a theory of vaccine-induced mitochondrial decompensation. Pivotal to petitioner's claim is a finding that Makena had a mitochondrial disorder. Although Makena had a documented mitochondrial point mutation, she did not have a probable mitochondrial disorder according to the diagnostic criteria set forth in the 2002 Bernier article. Further undercutting petitioner's theory of causation was petitioner's expert Dr. Frye's reliance on an outmoded model of oxidative stress. The unrebutted testimony of respondent's expert, Dr. Jones, made clear that the mere presence of oxidative stress--particularly in the amounts induced by vaccination--is not harmful. Nor is the immunological response to vaccination comparable to that of infectious damage. Such oxidative stress is short-lived and is unable to overwhelm the body's robust metabolism. Moreover, damage of the degree suffered by Makena would have required decades of oxidative stress. Petitioner's theory of vaccine-induced metabolic decompensation in a subject with mitochondrial dysfunction is neither scientifically tenable nor factually supported on this record. For the reasons set forth in more detail in this decision, petitioner has failed to satisfy the prongs of Althen, and her claim must be dismissed. The Clerk of the Court shall enter judgment accordingly.

IT IS SO ORDERED.

s/Patricia E. Campbell-Smith
Patricia E. Campbell-Smith
Chief Special Master

COURT EXHIBIT 1

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Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression

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Abstract

Autistic spectrum disorders encompass etiologically heterogeneous persons, with many genetic causes. A subgroup of these individuals has mitochondrial disease. Because a variety of metabolic disorders, including mitochondrial disease show regression with fever, a retrospective chart review was performed and identified 28 patients who met diagnostic criteria for autistic spectrum disorders and mitochondrial disease. Autistic regression occurred in 60.7% (17 of 28), a statistically significant increase over the general autistic spectrum disorder population ($P < .0001$). Of the 17 individuals with autistic regression, 70.6% (12 of 17) regressed with fever and 29.4% (5 of 17) regressed without identifiable linkage to fever or vaccinations. None showed regression with vaccination unless a febrile response was present. Although the study is small, a subgroup of patients with mitochondrial disease may be at risk of autistic regression with fever. Although recommended vaccinations schedules are appropriate in mitochondrial disease, fever management appears important for decreasing regression risk.

Keywords

mitochondria, oxidative phosphorylation, autistic spectrum disorders, vaccinations, fever, autistic regression

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Autistic spectrum disorders encompass an etiologically heterogeneous spectrum of persons with disturbances in language, perception, and socialization. Linkage and association studies identified a number of susceptibility loci with specific gene mutations identified in a small percentage of cases.[1-12] A subset of patients with autistic spectrum disorders harbor oxidative phosphorylation defects in their tissues, which in some cases are caused by mutations in nuclear DNA or mitochondrial DNA genes.[13,14] Two large series of 210 and 69 autistic spectrum disorder patients had abnormalities in metabolic markers of mitochondrial disease, which included increase in the blood lactate or the lactate-to-pyruvate ratio in 17% to 20%.[15,16]

Mitochondria are cytoplasmic structures with an inner and outer membrane separated by an intermembrane space. Oxidative phosphorylation uses about 95% of the oxygen delivered to tissues, producing most of the adenosine triphosphate (ATP) that is required by cells. Expression of genes involved in oxidative phosphorylation and the assembly of its 5-enzyme complexes (complex I, complex II, complex III, complex IV, and complex V) within the inner mitochondrial membrane is a highly ordered and coordinated process requiring both mitochondrial DNA genes and nuclear DNA genes. Optimal oxidative phosphorylation function requires aggregation of complexes I, III, and IV into supercomplexes.[17-21] Complex V uses the electrochemical gradient created by complexes I, III, and IV as a source of energy for synthesizing ATP. Organs such as brain with high ATP requirements, yet low ATP reserves, are susceptible to the detrimental effects of oxidative phosphorylation defects.

Patients with mitochondrial diseases, like many patients with metabolic diseases, are at increased risk of neurologic regression in conjunction with stressors such as fever, infection, and dehydration. Autistic regression occurs prior to 3 years of age in approximately 25% of children with autism, in whom developmental abnormalities were previously

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Table 1. Clinical and Laboratory Features of Autistic Spectrum Disorder Plus Mitochondrial Disease Group

	Study group frequency
Clinical	
Motor developmental delay and hypotonia	46.4% (13/28)
Fatigue with activity	42.9% (12/28)
Epilepsy	39.3% (11/28)
Abnormal growth or weight gain	10.7% (3/28)
Affected siblings	35.7% (10/28)
Muscle histology	
Nondiagnostic muscle histology	100% (28/28)
a. Ragged red fibers	0% (0/28)
b. Cytochrome c oxidase–deficient fibers	0% (0/28)
Metabolic abnormalities	
Increased lactate, pyruvate, alanine (blood, urine, cerebrospinal fluid)	46.4% (13/28)
Cerebral folate deficiency	4.5% (1/22)
Oxidative phosphorylation defects	
Complex I defect (enzymology)	50% (14/28)
Complex I and complex III defects (enzymology)	17.9% (5/28)
Complex I, complex III, and complex IV defects (enzymology)	17.9% (5/28)
Complex V defects (high-resolution respirometry; clear native complex V enzymology)	14.3% (4/28)
Abnormal oxidative phosphorylation subunit protein chemistry (Western blot)	71.4% (20/28)
Muscle mitochondrial DNA depletion	5.0% (1/20)
Muscle coenzyme Q10 deficiency	7.1% (1/14)

unrecognized.[22,23] The etiology of this regression is unknown. To investigate whether a relationship between autistic regression and fever may exist, we retrospectively reviewed charts of 28 patients with autistic spectrum disorder in whom mitochondrial defects were identified using a multifaceted diagnostic approach.

Methods

To assess the relationship of autistic regression with fever and vaccination in autistic spectrum disorder patients harboring oxidative phosphorylation enzyme defects, we performed a retrospective chart review and identified 28 patients who met diagnostic criteria for autistic spectrum disorders and diagnostic criteria for mitochondrial diseases. The study was approved by the Georgia State University Institutional Review Board. Mitochondrial disease was diagnosed according to standard criteria.[24-27] All patients included in the study met *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) criteria for autistic spectrum disorder. Autistic regression was defined as loss of developmental skills that included speech, receptive skills, eye contact, and social interests in individuals <3 years of age. A relationship between fever and autistic regression is defined as regression beginning within 2 weeks of a febrile episode without the suggestion of infectious meningitis or encephalitis.

The age range of the patients at the time of evaluation of mitochondrial disease was 1.5 to 19.3 years (mean ± standard deviation = 5.6 ± 4.1 years; median age = 4.0 years). Asperger syndrome was diagnosed in 7.1% (2/28). One sibling pair was included in the group. Because criteria for mitochondrial disease diagnosis require a multifaceted evaluation approach, only patients with detailed diagnostic data were included in the study. Oxidative phosphorylation enzymology in mitochondria isolated from fresh muscle biopsy,[28,29] clear native gel assessment of the adenosine triphosphatase activity of complex V,[30] Western blot of selected oxidative phosphorylation subunits,[31] muscle coenzyme 10 quantitation,[32] high-resolution respirometry (polarography) of fresh/living muscle,[33] and muscle mitochondrial DNA copy number quantitation[34] was performed as described. The laboratory biochemical and genetic details of the mitochondrial evaluation of these patients are reported separately (manuscript in preparation).

Chi-square analysis was used to assess whether autistic regression occurs at higher frequency in autistic spectrum disorder patients with mitochondrial disease than in the general population of autistic spectrum disorder patients. The frequency of autistic regression in the general population of patients with autism was estimated to be 25%.[22,23]

Results

A total of 28 individuals were selected for this study because they met mitochondrial disease and autistic spectrum disorder diagnostic criteria. Clinical and laboratory features are summarized in Table 1. Clinical features of the 28 patients with autistic spectrum disorder included motor developmental delay and hypotonia 46.4% (13 of 28), fatigue with activity 42.9% (12 of 28), epilepsy 39.3% (11 of 28). Abnormal growth or impaired weight gain (<5% levels) was observed in 10.7% (3 of 28). Affected siblings were identified in 35.7% (10 of 28). Brain magnetic resonance imaging (MRI) was unremarkable in 27 patients. Brain imaging data were not available in 1 patient.

Routine muscle pathology, including cytochrome c oxidase and succinate dehydrogenase histochemistry was normal or showed only nonspecific changes in all cases (28 of 28).

Metabolic abnormalities characteristic of mitochondrial diseases were identified. Abnormal increases in blood, urine, or cerebrospinal fluid lactate, pyruvate, or alanine were identified in 46.4% (13 of 28). Cerebrospinal fluid 5-methyltetrahydrofolate was tested in 78.5% (22 of 28) of the autistic spectrum disorder group. A defect in cerebral folate metabolism was suspected in a single patient who harbored a complex V defect (patient cerebrospinal fluid 5-methyltetrahydrofolate = 49 mmol/L, reference

Table 2. Autistic Regression and Fever

Clinical group	Study group frequency
Autistic regression	60.7% (17/28)
No autistic regression	39.3% (11/28)
	Subgroup frequency
Autistic regression with fever	70.6% (12/17)
A. Fever with vaccination	33.3% (4/12)
B. Fever without vaccination	66.7% (8/12)
Autistic regression without fever[a]	29.4% (5/17)

[a] Autistic regression was not associated with vaccination.

range 50-187). Cerebrospinal fluid 5-methyltrahydrofolate levels in this range are associated with disease manifestations of cerebral folate deficiency.[35,36]

A detailed biochemical assessment of mitochondrial function was performed. The following distribution of oxidative phosphorylation enzyme defects was observed: isolated complex I defect in 50% (14 of 28), combined complexes I and III defects in 17.9% (5 of 28), combined complexes I, III, and IV defects in 17.9% (5 of 28), and an isolated complex V defect in 14.3% (4 of 28). Additional abnormalities of oxidative phosphorylation were observed in the skeletal muscle that further supported the diagnosis of mitochondrial disease. Protein chemistry assessment by quantitative Western blot of selected subunits from complexes I to V was abnormal in 71.4% (20 of 28). Of the 20 patients tested, a single patient had depletion of skeletal muscle mitochondrial DNA (mitochondrial DNA/nuclear DNA ratio: 0.94; 5%-95% reference interval 0.71-0.84). In this assay, larger ratios indicate lower numbers of mitochondrial DNAs in the muscle sample. Of the 14 patients tested, a single patient who was diagnosed with Asperger syndrome had skeletal muscle coenzyme Q10 deficiency (muscle coenzyme Q10 = 133 pmol/mg protein, 5%-95% reference interval 171.4-540.5).

One sibling pair was included in the group. Two brothers with autistic spectrum disorders had defects in mitochondrial coupling consistent with a defect in complex V function. Both brothers had significant fatigue with activity and experienced multiple episodes of neurologic regression, all with febrile episodes. Fever was typically idiopathic, with no infectious source identified. The length of time required for recovery lengthened with each febrile event. Regression in these siblings could last for weeks or even several months before they would begin regaining skills. Both brothers received a complete vaccination schedule without incident.

In this pilot study, autistic regression was identified in 60.7% (17 of 28) of the study participants representing a statistically significant increase over the estimated 25% reported in the general population of autistic spectrum disorders patients (χ^2, $P < .0001$; Table 2). Autistic regression was not identified in 39.3% (11 of 28). The 17 individuals with autistic regression could be divided into 2 groups, those who regressed with fever (70.6%, 12 of 17) and those who regressed without identifiable linkage to fever or vaccinations (29.4%, 5 of 17). Autistic regression and fever was not associated with vaccination in 8 of 12 (66.7%) and was associated with a febrile response to vaccination in 4 of 12 (33.3%). Information about the precise vaccine schedule associated with a febrile response was not available. No individual showed regression with vaccination unless a febrile response was present.

Fever as reported by parents was >101°F (oral or rectal) with cases as high as 105°F. The precise fever duration was difficult to ascertain because patients were usually managed in the home. The duration of the fever appeared to extend for at least 3 to 7 days in conjunction with decreased oral intake. Although dehydration and other metabolic changes could also be variables important to increasing the risk of neurologic deterioration, these variables could not be assessed in this retrospective study.

Discussion

Autistic spectrum disorders encompass a highly heterogeneous group of patients in whom the clinical manifestations are caused by a diverse array of gene defects. An important autistic spectrum disorder subgroup has mitochondrial disease. The clinical suspicion of mitochondrial disease in autistic spectrum disorders is increased when patients have additional clinical features that include hypotonia and motor delay, fatigue with activity, metabolic abnormalities, poor growth, epilepsy, and affected siblings. Increases in metabolites such as lactate, pyruvate, and alanine in blood, urine, or cerebrospinal fluid can be important findings that support a diagnosis of mitochondrial disease. However, metabolic testing is often normal in mitochondrial disease, even in patients with severe disorders.[37,38] Although hypotonia, motor developmental delay, and fatigue are observed, the muscle histology shows only nonspecific changes. This finding is consistent with routine histopathologic assessments of most patients with mitochondrial disease who rarely have diagnostic features such as cytochrome c oxidase–deficient fibers and ragged-red fibers.

Like most groups of patients with mitochondrial disease, the diverse array of mitochondrial defects observed in autistic spectrum disorders likely represents a variety of mutations in genes that impair the function of oxidative phosphorylation. The biochemical heterogeneity observed in the autistic spectrum disorder group is similar to the biochemical heterogeneity observed in other groups of patients with mitochondrial disease. Diagnosis of mitochondrial disease is complex, requiring a multifaceted and well-coordinated clinical and laboratory approach. In most individuals, no single test is sufficient for the diagnosis of mitochondrial disease. As expected from the complex pathophysiology of mitochondrial diseases, the biochemical and genetic data is complex and requires significant clinical and laboratory experience for correct interpretation. For example, activity measurements obtained from oxidative phosphorylation enzymology depend, in part, on the stability of the individual oxidative phosphorylation enzymes, the functioning of individual enzyme subunits, as well as the presence of adequate supercomplex formation (aggregates of complexes I, III, and IV). Heterogeneous categories of oxidative

phosphorylation enzyme defects are commonly observed in patients with pathogenic mitochondrial DNA or nuclear DNA mutations in oxidative phosphorylation genes. Due to the complexities in mitochondrial disease pathogenesis, oxidative phosphorylation enzyme defects are highly variable even among groups of individuals who harbor identical mutations.[29,39] As reflected in mitochondrial disease diagnostic criteria, oxidative phosphorylation enzymology alone is usually not sufficient for reaching an appropriate diagnosis.[40] Assessment of fresh/living muscle by high-resolution respirometry (polarography) and by protein chemistry are essential aspects of patient diagnosis. Protein chemistry approaches can assess supercomplex formation and oxidative phosphorylation enzyme assembly as well as the integrity of specific enzyme subunits. Proper assessment of oxidative phosphorylation subunits can detect oxidative phosphorylation defects that are not evident in oxidative phosphorylation enzymology.[41]

In all patients with mitochondrial disease, identification of treatable metabolic changes such as deficiencies in coenzyme Q10 and defects in cerebral folate metabolism is important. Patients with mitochondrial disease are at increased risk of developing a defect in cerebral folate metabolism.[42,43] Cerebral folate deficiencies are also reported in autistic spectrum disorders.[44-46] Because individuals with autistic spectrum disorders reported in the literature, with cererbral folate deficiencies, were not assessed for mitochondrial disease, it is unclear whether the incidence of cerebral folate deficiency differs within various autistic spectrum disorder subgroups. Cerebral folate defects are important to identify because patients may respond to treatment with folinic acid.

Although the number of patients in this pilot study is small, the data suggest that a subgroup of patients with mitochondrial defects may be at increased risk of autistic regression. The rate of autistic regression in this highly selected group of individuals was approximately twice the rate of regression reported in the general population of patients with autistic spectrum disorder. This risk of autistic regression may be enhanced by prolonged fever that occurs with or without vaccinations. Fever is associated with regression in patients with many types of mitochondrial diseases as well as in a broad array of other classes of metabolic disease. In no case did we observe regression with vaccination unless fever was present. Although some patients with autistic spectrum disorder report improvement in symptoms with fever,[47,48] this phenomenon was not observed in our autistic spectrum disorder patients with mitochondrial disease.

Conclusions

Fever may be a risk factor for autistic regression in a subgroup of patients with mitochondrial disease. Fever is likely to be a clinical marker that is associated with a cascade of metabolic changes in the cells of these patients. This 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. However, increased body temperature alone may not be without risk. In vitro decreases in oxidative phosphorylation enzyme activity with increased temperature occurs, particularly in cell lines from patients with mitochondrial diseases.[49-52]

These data emphasize the need for larger studies investigating the role of fever, plus coexisting metabolic abnormalities in patients with mitochondrial disease who experience autistic regression. Children 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 Pediatric guidelines without consequences, particularly when physicians are sensitive to fever control and hydration. In our patients with mitochondrial disease and autistic spectrum disorders, the vaccines did not appear related to the neurologic regression. Unfortunately, many children with abnormal development caused by mitochondrial diseases are not diagnosed leaving physicians without management guidelines. Enhanced awareness of the clinical symptoms of mitochondrial diseases among physicians and referral to experts in mitochondrial disease for proper evaluation is important for identification of treatable defects, for genetic counseling, and for incorporation of appropriate management plans into patient care, particularly during periods of fever, infection, and dehydration.

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Declaration of Conflicting Interests

The authors declared a potential conflict of interest (eg, a financial relationship with the commercial organizations or products discussed in this article) as follows: John Shoffner, MD, and Keith Hyland, PhD, are owners of Medical Neurogenetics, LLC. Other coauthors are employees of Medical Neurogenetics, LLC.

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COURT EXHIBIT 2

Table 1 *Major diagnostic criteria**

Clinical

Clinically complete RC encephalomyopathy† ***or*** *a mitochondrial cytopathy defined as fulfilling all three of the following conditions*

Unexplained combination of multisystemic symptoms that is essentially pathognomonic for a RC disorder. Symptoms must include at least three of the organ system presentations described elsewhere,[14] namely neurologic, muscular, cardiac, renal, nutritional, hepatic, endocrine, hematologic, otologic, ophthalmologic, dermatologic, or dysmorphic.

A progressive clinical course with episodes of exacerbation (e.g., following intercurrent illnesses)

or *a family history that is strongly indicative of a mtDNA mutation (at least one maternal relative other than the proband whose presentation predicts a probable or definite RC disorder).*

Other possible metabolic or nonmetabolic disorders have been excluded by appropriate testing, which may include metabolite, enzyme, or mutation analyses, imaging, electrophysiological studies, and histology.

Histology

>2% ragged red fibers in skeletal muscle

Enzymology‡

>2% COX-negative fibers if <50 years of age

>5% COX-negative fibers if >50 years of age

<20% activity of any RC complex in a tissue

<30% activity of any RC complex in a cell line

<30% activity of the same RC complex activity in ≥ two tissues

Functional

Fibroblast ATP synthesis rates >3 SD below mean

Molecular

Identification of a nuclear or mtDNA mutation of undisputed pathogenicity

* Modifications to the original adult diagnostic criteria[5] that were developed in this study are shown in italicized text.

† Presentations include Leigh disease, Alpers disease, lethal infantile mitochondrial disease, Pearson's syndrome, Kearns-Sayre syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), neuropathy, ataxia, and retinitis pigmentosa (NARP), mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE), and Leber's hereditary optic neuropathy (LHON).[5]

‡ Enzyme activities represent percentage of normal control mean relative to an appropriate reference enzyme such as citrate synthase or RC complex II.

RC = respiratory chain; mtDNA = mitochondrial DNA; ATP = adenosine triphosphate.

Table 2 *Minor diagnostic criteria**

Clinical

Symptoms compatible with a RC defect†

Histology

1%–2% ragged red fibers if aged 30–50 years

Any ragged red fibers if <30 years of age

>2% subsarcolemmal mitochondrial accumulations in a patient < 16 years of age

Widespread electron microscopic abnormalities in any tissue

Enzymology

Antibody-based demonstration of a defect in RC complex expression

20%–30% activity of any RC complex in a tissue

30%–40% activity of any RC complex in a cell line

30%–40% activity of the same RC complex activity in ≥ two tissues

Functional

Fibroblast ATP synthesis rates 2–3 SD below mean

Fibroblasts unable to grow on media with glucose replaced by galactose

Molecular

Identification of a nuclear or mtDNA mutation of probable pathogenicity

Metabolic

One or more metabolic indicators of impaired RC function

* Modifications to the original adult diagnostic criteria[5] that were developed in this study are shown in italicized text.

† In addition to the symptoms listed elsewhere,[5] we regarded pediatric features such as stillbirth associated with a paucity of intrauterine movement, neonatal death or collapse, movement disorder, severe failure to thrive, neonatal hypotonia, and neonatal hypertonia as minor clinical criteria.[6,9,14] The adult criteria required muscle or neurologic involvement,[5] but these do not have to be present in the modified general criteria.