

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 05-0136V

Filed: June 24, 2015

For Publication

LAURA HOLT, parent of
A.H.T., a minor,

Petitioner,

v.

SECRETARY OF THE DEPARTMENT
OF HEALTH AND HUMAN SERVICES,

Respondent.

*
* Autism; Entitlement;
* Mitochondrial
* Disorder;
* Hepatitis B Vaccine;
* Encephalopathy;
* Colic; Gastrointestinal
* Problems; Diagnosis;
* Timing; Lack of Logical
* Connection
*
*

Andrew D. Downing, *Van Cott & Talamante, PLLC, Phoenix, AZ for petitioner.*

Alexis B. Babcock, *U.S. Dept. of Justice, Washington, DC, for respondent.*

DECISION¹

Vowell, Chief Special Master:

On January 21, 2005, Laura Holt [“Ms. Holt” or “petitioner”] filed a “short-form” petition seeking compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §300aa-10, *et seq.*² [“Vaccine Act” or “Program”] on behalf of her

¹ The E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002), requires that this decision be publicly available. In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

² The National Vaccine Injury Compensation Program [“Vaccine Program”] is set forth in 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.* (2006). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

daughter, A.H.T. Such petitions, authorized by Autism General Order #1,³ alleged in a summarized fashion that the vaccinee has a disorder on the autism spectrum.⁴

However, petitioner now appears to be repudiating ASD as the claimed injury, while nevertheless asserting that the neurological symptoms relied on for the ASD

³ By electing to file a Short-Form Autism Petition for Vaccine Compensation, petitioner alleged that:

As a direct result of one or more vaccinations covered under the National Vaccine Injury Compensation Program, the vaccinee in question has developed a neurodevelopmental disorder, consisting of an Autism Spectrum Disorder or a similar disorder. This disorder was caused by a measles-mumps-rubella (MMR) vaccination; by the “thimerosal” ingredient in certain Diphtheria-Tetanus-Pertussis (DTP), Diphtheria-Tetanus-acellular Pertussis (DTaP), hepatitis B, and Hemophilus Influenza Type B (Hib) vaccinations; or by some combination of the two.

Autism General Order #1, 2002 WL 31696785 (Fed. Cl. Spec. Mstr. July 3, 2002), Exhibit A, Master Autism Petition for Vaccine Compensation at 2. In filing a short-form petition, petitioner joined the Omnibus Autism Program [“OAP”]. A more detailed discussion of the OAP and the effects of joining it can be found in the OAP test case decisions. See, e.g., *Dwyer v. Sec’y, HHS*, No. 03-1202V, 2010 WL 892250, at *3 (Fed. Cl. Spec. Mstr. Mar. 12, 2010).

⁴ I use the abbreviation “ASD” to refer to the broad category of autism spectrum disorders. These disorders were defined for petitioner by Dr. (Ph.D.) Laurie Grimes, a clinical psychologist who evaluated A.H.T. in 2004. Her report, which was provided to Ms. Holt (see Petitioner’s Exhibit [“Pet. Ex.”] 17, pp. 154-55), stated:

Autism, also referred to as pervasive developmental disorder (PDD) or autism spectrum disorder (ASD), is a term for a *spectrum* of handicaps in which there are impairments in social communication. The *level* and *nature* of impairment varies from child to child so that no two people with autism have the same blend of communication challenges. Social communication includes behaviors such as facial expression, emotional gesture, melody (prosody) of speech, and knowledge of social rules (pragmatics) of communication that are used in human interaction to convey cognitive and emotional information. Social communication skills develop early in life and are a primary mode for learning about the environment through non-verbal means. Autism is sometimes associated with a lack of language skills, odd and stereotyped behaviors, profound inability at social interaction, and/or mental retardation. While such children may have varying degrees of some of these problems, others have normal intelligence and language and only mild deficits in social interaction skills. What is shared by all people with autism are handicaps in dealing with other people due to their inability to use and understand common verbal, gestural, and expressive communication. Current research uses four domains to evaluate social communication: **affective reciprocity** (one’s ability to send and receive social signals to others using facial expression, tone of voice, and social and emotional gestures), **emotional joint attention** (one’s efforts to share interests with others – show things, talk reciprocally, smile socially, direct others’ attention to objects of interest, show affection), **verbal joint attention** (one’s ability to be verbal social[ly], to use give-and-take conversation, to show interest in others), and **theory of mind** (in young children seen as social imagination; one’s ability to converse appropriately; one’s ability to infer another’s intentions).

Id., pp. 144-45 (emphasis original).

diagnosis constitute at least part of the compensable injury.⁵ An amended petition, which does not use the terms “ASD” or “autism,” was filed on September 22, 2011.⁶ This petition alleges that, as the result of a hepatitis B vaccination received on April 4, 2002, A.H.T. experienced a variety of symptoms affecting her feeding, sleeping, temperament, and gastrointestinal function. Petition at 1. However, petitioner does not appear to be claiming that these particular symptoms are the injury for which she seeks compensation. Rather, she contends that this vaccination “significantly aggravated an underlying mitochondrial disorder,”⁷ presumably with the manifestations being the symptoms exhibited following the vaccination, and causing “the resulting encephalopathic event.” Petition, ¶¶ 15-16. The reference to an “encephalopathic event” is ambiguous, in that it could refer to symptoms after the vaccination or the behavioral symptoms that resulted in her sensory integration disorder diagnosis many months after the vaccination, and other diagnoses, including ASD, over the ensuing years.⁸

⁵ Ms. Holt claimed not to understand the term “autism spectrum disorder” during her testimony. Transcript [“Tr.”] at 73. However, throughout A.H.T.’s medical records, Ms. Holt and A.H.T.’s physicians used the terms “autism,” “pervasive developmental disorder,” and “PDD-NOS.” See, e.g., Pet. Exs. 47, p. 2052 (intake form for Dr. Andrew Levinson, dated May 23, 2010, with petitioner indicating that A.H.T. had been diagnosed with autism and pervasive developmental delay-not otherwise specified and that she was seeking biomedical treatment for that condition); 17, p. 145 (notation in report provided to A.H.T.’s parents that one test had shown her to be at “moderate risk for autism spectrum disorder”). Moreover, Ms. Holt frequently reported that her maternal uncle had autism, a disorder on the autism spectrum, reflecting her understanding of the condition and term. See, e.g., Pet. Exs. 39, p. 1826; 41, p. 1832. Other health care providers used the term “autism spectrum” in A.H.T.’s medical records. See, e.g., Pet. Exs. 30, p. 1231 (noting that delayed sleep was seen in “individuals on the autism spectrum”); 44, p. 1878 (letter indicating A.H.T. had an original diagnosis “on the autism spectrum”). The pages of each exhibit were not individually numbered, resulting in the large page numbers for later-filed exhibits.

⁶ Hereinafter, unless the context clearly indicates otherwise, any references to “petition” are to this amended petition.

⁷ A mitochondrial disorder is one affecting the function of the mitochondria—organelles contained in varying numbers in virtually every cell of the body. Tr. at 424-25. The mitochondria use oxygen and food to produce adenosine triphosphate [“ATP”], the primary source of energy for all bodily functions, through a process labeled “the respiratory chain” or “electron transport chain” [“ETC”]. Tr. at 300, 424-25. Problems with energy production in the ETC can occur as the result of genetic defects in either the mitochondria’s own DNA [“mtDNA”] or in the DNA found in the nucleus of cells themselves [“nuclear DNA” or “nDNA”]. Tr. at 430. The sole function of the mtDNA is to make proteins that are components of the ETC. Tr. at 433. When a DNA defect results in clinical symptoms, a person is said to have a “primary” mitochondrial disease or defect. Other bodily processes including metabolic disorders, hypoxia, and some drugs may also affect the ETC, causing diminished ETC function, producing “secondary mitochondrial dysfunction.” Tr. at 398, 428-29. In the absence of an identified genetic defect or the presence of clusters of symptoms fitting a known mitochondrial syndrome, diagnosing a mitochondrial disorder is difficult. See generally, Pet. Ex. 79 (expert report of Dr. Frances Kendall); Respondent’s Exhibit [“Res. Ex.”] G (expert report of Dr. Shawn McCandless). Doctor Kendall’s report indicated that the “vast majority of pediatric mitochondrial disease” involves nDNA, with about 10% related to defects in mtDNA. Pet. Ex. 79 at 2494.

⁸ The filed medical records do not establish when and how A.H.T. was first diagnosed with an ASD. At the hearing, petitioner used several pages of an intake form dated August 12, 2005, that she completed for Dr. Phillip DeMio. See Petitioner’s Trial Exhibit [“Pet. Tr. Ex”] 1. This document contains petitioner’s assertion that A.H.T. was diagnosed with pervasive developmental delay in September 2004 by Dr.

The amended petition in this case and petitioner's apparent disavowal of an ASD diagnosis appear to be part of the trend by some former OAP petitioners to re-characterize their children's diagnoses as something other than ASD, in an attempt to render irrelevant the impressive body of evidence produced in the OAP test cases establishing that vaccines are exceedingly unlikely to be responsible for ASD.⁹ The filing (or amendment) of claims for compensation based on the particular theory advanced in this case—that a vaccine significantly aggravated an underlying mitochondrial disorder, causing manifestation of ASD or a similar neurological disorder—stems from another, and widely-publicized, vaccine injury case. In that case, discussed more extensively in n.76 and in Section IV, Part B(1)(a) below, a child with a mitochondrial disorder and autistic symptoms received compensation based on her presentation with severe neurological symptoms within the Table injury¹⁰ period for the vaccines that she received.

Vinjay Puri. Doctor Puri, a pediatric neurologist, evaluated A.H.T. on September 16, 2004. The records from this visit do not reflect a pervasive developmental disorder or delay diagnosis. Rather, he diagnosed a sensory integration disorder, night terrors, and a mild language loss or regression. Pet. Ex. 31, p. 1265. The intake form also reflects that someone in the Jefferson County Public School system diagnosed A.H.T. with autism in February 2005. Pet. Tr. Ex. 1, p. 1. The records reflecting this diagnosis were not filed and thus it is unclear what diagnostic testing, if any, led to the school district's conclusions. I note that in October 2004, Dr. Grimes, a clinical psychologist, administered standard diagnostic tests for ASD. She concluded that A.H.T. "has demonstrated behaviors that were suggestive of ASD, though [the test results] do not support that diagnosis at this time." Pet. Ex. 17, p. 146. This is the only mention of diagnostic testing for ASD in the record. However, ASD, autism, and PDD-NOS (pervasive developmental disorder-not otherwise specified) diagnoses appear throughout A.H.T.'s medical records after 2005. See, e.g., Pet. Exs. 16, pp. 133, 142; 19, p. 214; 27, pp. 629-30; 31, pp. 1245-46; 38, p. 1689; 51, pp. 2188-89. I also note that in Jan. 2005, just days after filing the short-form petition in this case and thereby joining the OAP, petitioner and Mr. Tipton revoked permission for Dr. Grimes to disclose A.H.T.'s negative test results for autism to the school system. Pet. Ex. 17, pp. 161-62. Three months later, they wrote Dr. Grimes, requesting that she "correct" her October 2004 evaluation. *Id.*, pp. 157-58. In doing so, they pointed out the presence of "very abnormal autistic-like behaviors" in A.H.T. *Id.*, p. 158. Both of respondent's experts were unwilling to opine that A.H.T. had ASD, in view of the lack of diagnostic testing, but noted the presence of symptoms commonly seen in children with ASD. Tr. at 537, 545, 560-61.

⁹ Since January 2007, I have been one of the small group of special masters assigned primarily to the "autism docket." I presided over two of the six OAP test case hearings and issued decisions in each. These lengthy decisions were necessitated by one of the purposes for the omnibus proceeding—to create a body of evidence that could be relied upon to resolve the remaining OAP cases like this one—as well as to evaluate the causation theories presented in the context of the individual test cases. After appellate review of the test case decisions was completed, I oversaw the effort to resolve the remaining open OAP cases. The majority of these cases were dismissed based on petitioners' motions. However, some petitioners elected to proceed with their cases, either on a new theory of causation or based on injuries other than ASD. Most of the OAP petitioners who have continued to press claims for vaccine compensation have presented variations on the theory presented here—that vaccines "significantly aggravated an underlying mitochondrial disorder, resulting in autism-like symptoms."

¹⁰ A "Table" injury is an injury listed on the Vaccine Injury Table, 42 C.F.R. § 100.3, corresponding to the vaccine received within the time frame specified.

Prior to the hearing, petitioner filed a joint submission of the parties, listing the jurisdictional and factual issues upon which they agreed. The parties indicated that “[t]he issue to be decided is whether the vaccinations [A.H.T. received] (either alone or in combination) caused-in-fact her subsequently diagnosed developmental, neurological, or mitochondrial issues.” Joint Submissions at ¶ 7. This joint submission clarifies the injuries for which compensation is sought.

Regardless of how A.H.T.’s condition is characterized, petitioner has the burden to demonstrate by preponderant evidence that a vaccine actually caused or significantly aggravated A.H.T.’s condition.¹¹ For the reasons set forth below, I find that petitioner has failed to do so and thus is not entitled to compensation.

I. Procedural History.

After the short-form petition was filed, A.H.T.’s case, like most other OAP cases, remained on hold until litigation in the test cases was completed.¹² After the resolution of the test cases in 2010, the special masters began the process of determining how the

¹¹ Because the Vaccine Injury Table, 42 C.F.R. § 100.3, lists no injuries for the hepatitis B vaccine (the only vaccine A.H.T. ever received), petitioner cannot avail herself of any presumption in favor of causation. Her burden of proof is the traditional tort burden: she must produce preponderant evidence that a vaccine caused or significantly aggravated A.H.T.’s condition. 42 U.S.C. § 300aa-13(a)(1)(A); *Moberly v. Sec’y, HHS*, 592 F.3d 1315, 1322 (Fed. Cir. 2010) (citing *de Bazan*, 539 F.3d 1347, 1351 (Fed. Cir. 2008); *Pafford v. Sec’y, HHS*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Capizzano v. Sec’y, HHS*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *Althen v. Sec’y, HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005)). *Loving v. Sec’y, HHS*, 86 Fed. Cl. 135, 144 (2009), established a methodology for evaluating a significant aggravation claim. The first three steps require the fact-finder to: (1) determine the vaccinee’s condition prior to administration of the vaccine; (2) determine the vaccinee’s current condition or condition following the vaccine; and (3) decide whether the vaccinee’s condition was significantly worsened after the vaccination. The remaining three steps involve the application of *Althen* in a significant aggravation context, and require the petitioner to produce preponderant evidence of (4) a medical theory causally connecting the significantly worsened condition to the vaccine; (5) a logical sequence of cause and effect demonstrating that the vaccine was the reason for the significant aggravation; and (6) a proximate temporal relationship between the vaccine and the significant aggravation. This methodology has been cited with approval by the Federal Circuit. *W.C. v. Sec’y, HHS*, 704 F.3d 1352, 1357 (Fed. Cir. 2013).

¹² The Petitioners’ Steering Committee [“PSC”], an organization formed by attorneys representing petitioners in the OAP, litigated six test cases presenting two different theories on the causation of ASD. Decisions in each of the three test cases pertaining to the PSC’s first theory rejected the petitioners’ causation theories. *Cedillo v. Sec’y, HHS*, No. 98-916V, 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff’d*, 89 Fed. Cl. 158 (2009), *aff’d*, 617 F.3d 1328 (Fed. Cir. 2010); *Hazlehurst v. Sec’y, HHS*, No. 03-654V, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff’d*, 88 Fed. Cl. 473 (2009), *aff’d*, 604 F.3d 1343 (Fed. Cir. 2010); *Snyder v. Sec’y, HHS*, No. 01-162V, 2009 WL 332044 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff’d*, 88 Fed. Cl. 706 (2009). Petitioners in *Snyder* did not appeal the decision of the U.S. Court of Federal Claims. Decisions in each of the three “test cases” pertaining to the PSC’s second theory also rejected the petitioners’ causation theories, and petitioners in each of the three cases chose not to appeal. *Dwyer*, 2010 WL 892250; *King v. Sec’y, HHS*, No. 03-584V, 2010 WL 892296 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); *Mead v. Sec’y, HHS*, No. 03-215V, 2010 WL 892248 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). The petitioners in each of the three Theory 2 cases did not seek review of the special masters’ decisions.

approximately 4,800 remaining OAP claims would be resolved by ordering each claimant to indicate if he or she wished to proceed or exit the Vaccine Program.

On March 15, 2011, petitioner filed a motion to substitute Mr. Downing as her attorney of record. I granted the motion and, interpreting it as evincing petitioner's intent to proceed with her claim, I ordered her to file an amended petition that asserted the specific basis for her causation claim. Order, issued Apr. 4, 2011. Petitioner complied on September 22, 2011, filing several statements or declarations and some medical records and other evidence along with the petition. See Pet. Exs. 1-6. Over the next six months, petitioner filed additional medical records, statements and affidavits,¹³ and some medical literature.¹⁴ Petitioner filed a statement containing an opinion on causation and the curriculum vitae ["CV"] of Dr. Levinson on February 29, 2012 and a similar opinion and CV from Dr. Phillip C. DeMio on March 12, 2012.¹⁵ See Pet. Exs. 59-60; 62-63. She filed the expert report and CV of Dr. Fran D. Kendall on May 15, 2012. See Pet. Exs. 79-80.

In July 2012, respondent filed her Rule 4(c) report; and the expert reports and accompanying medical literature from Drs. Max Wiznitzer and Shawn McCandless. See Respondent's Rule 4(c) report; Respondent's Exhibits ["Res. Exs."] A-Q. After consultation with the parties, I scheduled an entitlement hearing in Washington, D.C. from February 13-15, 2013. Order, issued Aug. 16, 2012; Pre-Hearing Order, issued Aug. 31, 2012.

Four physicians, Drs. DeMio, Kendall, McCandless, and Wiznitzer, testified in person. Petitioner, Garrick Tipton (A.H.T.'s father), and Mrs. Christy Holt ["Christy Holt"] (A.H.T.'s aunt) also testified in person. I heard telephonic testimony from Mrs. Mary Jo Holt Dunn (A.H.T.'s maternal grandmother), and Ms. Amy Hunter, the doula who assisted with A.H.T.'s birth.¹⁶

Based on testimony at the hearing about the availability of video evidence supporting petitioner's case (see Tr. at 116, 121), I ordered petitioner to file video records of A.H.T. from birth to three years of age. Three DVDs were filed on April 4, 2013 as Pet. Tr. Ex. 3.¹⁷ Post hearing briefs were received from petitioner on May 9, 2013, and from respondent on June 17, 2013. On September 3, 2013, I also filed a medical journal article, N. Wolf & J. Smeitink, *Mitochondrial disorders: a proposal for*

¹³ See Pet. Exs. 73-78.

¹⁴ See Pet. Exs. 67-71.

¹⁵ The filed documents are titled "statements" rather than expert reports, although they do contain opinions on vaccine causation.

¹⁶ Petitioner intended to call Dr. Levinson to testify telephonically, but efforts to reach him were not successful. See Tr. at 284, 290.

¹⁷ Subsequent references to the videos will identify them as Video 1, Video 2, and Video 3. Pertinent provisions will be identified by the date of the recording and elapsed time from the start of the video.

consensus diagnostic criteria in infants and children, *Neurol.* 59(9): 1402-05 (2002) [cited hereinafter as “Wolf & Smeitink, Court Exhibit [“Court Ex.”] I, and provided the parties and their experts an opportunity to comment on the exhibit. See ECF # 90; Pet. Resp. to Court’s Order and Ex., filed on September 30, 2013; Res. Ex. S. This article sets forth the diagnostic criteria ostensibly used by the physician who diagnosed A.H.T. with a mitochondrial disorder.

II. Summarized Medical History.

A.H.T. was born in 2002, following a normal pregnancy. Tr. at 11-12; Joint Submissions at ¶ 2, filed on January 22, 2013. She was delivered at home, with the assistance of a midwife, Juliet Dietsch, and doula, Amy Edwards Hunter. See Petitioner’s Exhibits [“Pet. Exs”] 77, 82 (statements of Amy Edwards Hunter¹⁸ and Juliet Dietsch). A.H.T. had Apgar scores of 7 and 9.¹⁹ *Id.* Both Ms. Dietsch and Ms. Hunter said that A.H.T. was healthy, alert, and nursing well shortly after birth. *Id.*

At her initial visit to her pediatrician, Dr. Rhonda Buttleman, A.H.T. was alert and her physical examination was normal. Pet. Ex. 58, p. 2330.²⁰ A.H.T.’s parents indicated that she was nursing every few hours and was voiding and stooling frequently. *Id.*; Tr. at 109-10 (testimony of Mr. Tipton). Ms. Holt testified that A.H.T. was sleeping 18-20 hours per day and that she had gained 10 ounces since birth. Tr. at 16-17; see *also* Pet. Ex. 58, pp. 2313 (birth weight), 2330 (weight at five days of age).

The only two vaccinations A.H.T. ever received (two hepatitis B vaccinations) were administered before she was six weeks old. She received the first at this initial pediatric visit. Pet. Ex. 58, pp. 2313, 2326, 2330. The documentary evidence and testimony establish that, within days after the first vaccination, A.H.T. developed problems with constipation and that she cried more often and more robustly than many infants. Tr. at 22-23, 56 (Ms. Holt); 129-30 (Mr. Tipton); Pet. Exs. 52, p. 2234; 34, p. 1287. Her sleeping patterns changed and Ms. Holt testified about problems with breastfeeding. See, *e.g.*, Tr. at 20-22, 24, 29, 32, 56, 91-92. These issues are discussed in more detail in Section V, Part B(4), below.

Mr. Tipton did not remember any specific reactions to the second vaccination. He testified that A.H.T. “continued to worsen as time went on,” but stopped short of

¹⁸ Petitioner filed two statements from Ms. Hunter. The first statement was labeled “Statement of Amy Edwards” and filed on September 22, 2011 as Pet. Ex. 3. The second statement was labeled “Statement of Amy Edwards Hunter” and filed on April 16, 2012 as Pet. Ex. 77. The substance of the two statements is the same.

¹⁹ The Apgar score is a numerical assessment of a newborn’s condition (with lower numbers indicating problems), usually taken at one minute and five minutes after birth. The score is derived from the infant’s heart rate, respiration, muscle tone, reflex irritability, and color, with from zero to two points awarded in each of the five categories. See DORLAND’S ILLUSTRATED MEDICAL DICTIONARY (32d ed. 2012) [“DORLAND’S”] AT 1682; NELSON TEXTBOOK OF PEDIATRICS (19th ed. 2011) [“NELSON’S ”] at 536-37.

²⁰ Doctor Buttleman’s records were also filed as Pet. Ex. 4.

saying that she regressed or lost skills. Tr. at 131, 133. Ms. Holt also testified that A.H.T. got worse, but more as a progression of the symptoms she was already experiencing.²¹ Tr. at 37, 63. However, prior to their testimony, A.H.T.'s parents told Dr. John D. Shoffner, the physician who diagnosed her with a probable mitochondrial disorder, that there were no adverse reactions to the second hepatitis B vaccination.²² Pet. Ex. 61, p. 2343.

Over time, some of the problems that first manifested in the days and weeks after A.H.T.'s initial vaccination varied in intensity. The medical records and the testimony of her parents and other family members about the persistence and intensity of these problems were often in conflict with other evidence. What seems clear from the record as a whole is that A.H.T. was a difficult infant and toddler. Behavioral problems continued as she grew older, and by the time she was six years old, they accounted for most of the health care visits and support services rendered. See *generally*, Pet. Exs. 16 (2008 therapy records of Dr. (Ph.D.) Julie Murray, a treating psychologist); 51 (2009 neuropsychological evaluation by Dr. (Ph.D.) Andrew Jones, clinical psychologist); 38 and 54 (2009-12 records from an agency providing behavior analysis and support services); 7, p. 51 (2010 letter from psychiatrist Dr. Arehanna Barry).²³

Notwithstanding any temperament, sleep, feeding, and gastrointestinal issues, A.H.T. appeared to be developing normally for her first 15-17 months of life. See *generally*, Pet. Exs. 52, 58. She gained weight appropriately. See Pet. Ex. 58, p. 2314 (growth chart). She interacted with parents at home and caregivers at her pediatric

²¹ When pressed for a specific symptom that worsened after the second vaccination, Ms. Holt testified that A.H.T.'s bowel movements became either rock hard, or loose and foul-smelling, and that nursing got worse. Tr. at 37. Although she did not attach a specific time frame to onset of loose stools, there is no corroborating, and much contradictory, evidence for any assertion that A.H.T. experienced loose stools in close temporal proximity to the second vaccination. Both the contemporaneous medical records and histories Ms. Holt provided later reflect that A.H.T. suffered from constipation throughout much of her first year of life. See, e.g., Pet. Exs. 34, p. 1287; 28, p. 1088. The first complaint of loose stools or diarrhea does not appear until January 10, 2003, when A.H.T., then nine months old, experienced a bout of enteritis. Pet. Ex. 52, 2233. Thereafter, reports of both diarrhea and constipation were common, although the diarrhea was generally noted in conjunction with an illness or in response to one of the many medical interventions she received. See, e.g., Pet. Exs. 52, p. 2230, 23, p. 239 (reporting diarrhea after treatment with a chelating agent), p. 259 (diarrhea in conjunction with illness (the abbreviation "N/V/D" representing nausea, vomiting, and diarrhea)); 46, p. 2037 (reporting chronic problems with alternating constipation and diarrhea at a January 2005 evaluation); 38, p. 1690 (indicating a drug A.H.T. took caused diarrhea); 19, p. 214 (reporting that dairy products caused diarrhea).

²² Petitioner's Tr. Ex. 1, the intake form for Dr. DeMio (dated August 12, 2005), reflects the two vaccinations, followed by a comment that she had such severe reactions to these two vaccinations that no other vaccines had been administered. *Id.*, p. 3.

²³ This letter merely reflects A.H.T.'s diagnoses; therapy records from Dr. Barry were not provided, although there is evidence that she ordered laboratory testing and an electrocardiogram. See Pet. Ex. 37, pp. 1324-26. Medical records contain conflicting references regarding whether A.H.T. was receiving ongoing psychiatric treatment. See, e.g., Pet. Ex. 7, pp. 54, 67 (Medicaid form from 2010 (dated on p. 67), reflecting continuing treatment by Dr. Berry); 30, p. 1230 (initial note from sleep clinic during same period in 2010 reflecting that A.H.T. had seen a psychiatrist but that she was no longer doing so).

visits. Videos of her taken at one to nine months of age show an alert and interactive infant engaged with toys, household items, and her parents. See *generally* Videos 1 and 2.²⁴ At her regular pediatric visits, she was observed to be developing at a pace appropriate for her age and meeting developmental milestones,²⁵ although she may not have begun walking until 14-15 months of age, a little later than average. See, e.g., Pet Exs. 31, p. 1262 (reporting she began walking at 15 months); 46, p. 2037 (reporting that she began walking at 14 months); *but see* Pet Ex. 52, p. 2229 (15 month well-child visit with notation that A.H.T. had been walking for 2 months).

Neither her first pediatrician, Dr. Rhonda Buttleman, who saw her from five days to about nine months of age, nor the family practice physician, Dr. Richard Hefner,²⁶ who was her primary care provider thereafter, recorded any concerns about her development during this period. See *generally* Pet. Exs. 52, 58. Doctor Hefner, who saw A.H.T. for the first time when she was about five months old for a second opinion on her gastrointestinal problems, observed her while she was crying. He diagnosed her with colic. Pet. Ex. 52, p. 2234. Nevertheless, he referred her to a pediatric gastroenterologist, Dr. Stephen, who diagnosed mild constipation and mild gastroesophageal reflux when A.H.T. was six months old. Pet. Ex. 34, p. 1287.

²⁴ Video 1, from 46:51 (recorded May 18, 2002) through 3:23:22 (recorded October 31, 2002); Video 2, Set 1, from 00:01 (recorded November 23, 2002) through 15:46 (recorded January 3, 2003).

²⁵ The medical records contain notes and marks on developmental checklists reflecting A.H.T.'s development. At about five weeks of age, A.H.T. was "alert" and her general appearance was "AFA," an acronym for "appropriate for age." Pet. Ex. 58, p. 2326. She was holding her head up, startling with loud sounds, grasping fingers, and making noises. *Id.*, p. 2327. At her two month checkup, A.H.T. was smiling, cooing, holding her head up, focusing on people, and holding a rattle. Pet. Ex. 58, p. 2325. At her four month well-child visit, she was described as alert, and she was rolling over, holding her head up, reaching for toys, playing with her hands, looking at a mobile, vocalizing with her parents, and laughing and smiling. Pet. Ex. 58, p. 2323. Doctor Thomas Stephen, a pediatric gastroenterologist, described her as a "well developed, well-appearing young infant, happy, in no distress" when she was six months old. Pet. Ex. 34, p. 1287. At her six month well-child visit, she was sitting with help with no head lag, rolling over, moving toys from hand to hand, reaching for toys, bearing some weight, laughing and babbling, turning to sounds, and making sounds. Pet. Ex. 58, p. 2320. At nine months of age, A.H.T. was pulling up on furniture, sitting by herself, crawling, banging toys, playing patty-cake and peek-a-boo, understanding words such as "no, no" and "bye-bye," starting to feed herself, and having stranger anxiety. *Id.*, p. 2316. She did not yet utter one or two meaningful syllables, and did not respond to her name. *Id.* However, according to Dr. Hefner's assessment, she met all developmental milestones at one year of age, including the use of some words. Pet. Ex. 52, p. 2232. He also found that she met all developmental milestones at 15 months of age: she could stand alone, imitate scribbling, play patty cake, say "mama" or "dada", and take lids off containers. *Id.*, p. 2229. Doctor Wiznitzer testified that A.H.T.'s development was normal through 15 months of age. Tr. at 639-42; see *also* Res. Ex. A at 7.

²⁶ Doctor Hefner's specialty does not appear in his records, but is referred to in the records of clinical psychologist Dr. Laurie Grimes, who noted that Dr. Hefner was a family practice specialist. Pet. Ex. 17, pp. 166, 168.

Aside from a one-page document from Dr. James O'Dell, a naturopath who saw A.H.T. in July 2002,²⁷ there were no records from other health care providers covering A.H.T.'s first 17 months of life.²⁸

Developmental problems were first noted in September 2003 at A.H.T.'s 18 month well-child visit, when Dr. Hefner observed that A.H.T. was not using two-word phrases, indicating a possible language delay. Pet. Ex. 52, p. 2226. In a history taken in May 2004, Ms. Holt reported that her concern about A.H.T.'s speech arose at about 18 months of age as well.²⁹ Pet. Ex. 55, p. 2255. Doctor Hefner elected to take a "wait and see" approach, but by A.H.T.'s next well-child visit six months later when A.H.T. was about two years of age,³⁰ the delay was still evident. Although the records of this visit do not reflect it (see Pet. Ex. 52, p. 2226), Dr. Hefner apparently referred A.H.T. for an evaluation by the state's early intervention program (see *id.*, p. 2225 (records from next visit to Dr. Hefner in August 2004, with the chief complaint listed as "here to discuss therapy recommended [at] 2 yr well baby"))).

The remaining medical treatment and therapy records are extensive, and except when relevant to one of the issues in controversy, are not set forth in detail in this decision. In summary, A.H.T. was seen by many different health care providers, in addition to her primary care provider, Dr. Hefner. These caregivers fall into four

²⁷ See Pet. Ex. 73; see also <http://drjamesodell.com/index.php/about> for information regarding Dr. O'Dell's qualifications and practice. Ms. Holt's journal entries (Pet. Ex. 6, pp. 44-45) also reflect this visit. A naturopathic doctor is one who subscribes to "a drugless system of health care, making use of a wide variety of therapies, including hydrotherapy, heat, massage, and herbal medicine." DORLAND'S at 1233.

²⁸ According to a March 14, 2012 statement, Dr. Sean Brady (a chiropractor who had previously treated Ms. Holt) began treating A.H.T. on June 13, 2002. Pet. Ex. 66 at 2366. Inexplicably, there are no records for such treatment before June 9, 2004, and although Dr. Brady indicated that he had billing and medical coding records establishing the dates of initial and subsequent treatment, the billing and coding records were not filed. His records of A.H.T.'s treatment from June 2004 onward were filed as Pet. Ex. 48. Doctor Brady did not opine on causation in this March 2012 statement; he merely stated that he recalled clearly Ms. Holt's statements that A.H.T.'s problems began shortly after the vaccination that she received at five days of age. Pet. Ex. 66 at 2366-67. Given the lack of contemporaneous records of treatment, I attach little weight to a statement made nearly 10 years after the events in question, particularly as the statement was made after Dr. Brady read Ms. Holt's own affidavit. See *id.* at 2367. There is a journal entry reflecting a consultation with a Dr. Zieve (Pet. Ex. 6, pp. 40-41) from mid-May 2002, but Ms. Holt testified that this was a telephonic consultation. Tr. at 62.

²⁹ In a developmental chronology prepared for A.H.T.'s first appointment with Dr. Kartzinel in June 2007, Ms. Holt reported that she first noticed developmental problems at about 18 months of age. Pet. Ex. 24, p. 464. In a much later history (provided in May 2010), Ms. Holt reported that her concerns about delayed development first arose at around 12 months of age. Pet. Ex. 47, p. 2052 (email intake form completed for Dr. Levinson). She also reported that speech problems were first noted at 18 months of age to Dr. Cecil in December 2011. Pet. Ex. 56, p. 2287. However, she testified that the report from May 2004 about her concerns first arising at 18 months of age was not correct. Tr. at 70.

³⁰ The filed medical records show no health care provider visits between 18-24 months of age. This six-month gap appears to be the longest period A.H.T. went without seeing a health care provider, although it is possible that she saw Dr. Brady during this period. See n.28, *supra*.

categories: therapists addressing specific areas of developmental delay or behavior concerns; several different types of mental health specialists; at least five alternative or complementary medicine providers; and specialists who assessed or treated her for gastrointestinal, urinary, and sleep disorders. Other than Dr. Hefner and Dr. Puri and his associates, none of the health care providers treated A.H.T. over a long period of time.

Aside from the primary care records, the records from the early intervention program provide the evidence prepared closest in time to the events after A.H.T.'s initial hepatitis B vaccination. Through the early intervention program, A.H.T. received Applied Behavioral Analysis ["ABA"] therapy³¹ (which appears to have been termed developmental intervention ["DI"] services),³² speech and language therapy ["ST"],³³ and occupational therapy ["OT"].³⁴ Each of these records supplies some insights into the nature and severity of A.H.T.'s developmental delays and behavioral symptoms at around the time delays became apparent.

³¹ ABA therapy consists of the "application of learning theory based on operant conditioning" and "is the only intervention recommended by the Surgeon General" for ASD. *Dwyer*, 2010 WL 892250, at 272, n.650.

³² No therapy records specifically identified as ABA therapy were filed as a part of the early intervention records, but there are references indicating that A.H.T. received ABA therapy. See, e.g., Pet. Exs. 31, p. 1257 (July 2005 note by Dr. Puri that A.H.T. was "making good progress on ABA therapy"); 24, p. 466 (June 2007 note that she was receiving four to five hours of ABA therapy). The developmental intervention services she received through Carriage House were likely the ABA therapy referred to in these records. See, e.g., Pet. Ex. 39, p. 1818 (progress summary in December 2004 for developmental intervention services rendered since June 2004). Pet. Ex. 25 contains some ABA-type worksheets, but no actual therapy records.

³³ See generally Pet. Ex. 18. The initial assessment and testing for speech and language services took place on May 19, 2004. Pet. Ex. 39, pp. 1822-23. A.H.T., then 26 months old, had the language comprehension skills of a 9-12 month old, and the expressive language skills of a 6-9 month old, with scattered skills in both categories up to the 15 month level. *Id.*, p. 1823. However, the developmental assessment performed two weeks earlier had placed her receptive and expressive language skills in the 12-14 month range. *Id.*, p. 1827.

³⁴ See generally Pet. Ex. 28 and 55. A thorough but concise summary of A.H.T.'s medical history and level of functioning appears in the September 2004 OT assessment. Pet. Ex. 28, pp. 1088-91. The evaluator assessed A.H.T.'s fine and gross motor skills at the 17-18 month level. *Id.*, p. 1090. She was 28 months old at that point. In addition to OT, A.H.T. attended a two-week sensory learning center program at the Therapy Learning Center in Ohio in November 2005, for which no records are available. Pet. Ex. 49, p. 2178 (letter dated Jan 11, 2012, explaining the lack of records and providing the writer's recollection of A.H.T.'s issues). This treatment did not appear to be helpful, as Ms. Holt cancelled a December 2004 OT appointment explaining that A.H.T. had "regressed" since returning from the sensory learning program. Pet. Ex. 28, pp. 1083, 1094. Subsequent occupational therapy records do not appear to be complete, and many of those filed are handwritten and difficult to read, but it appears she received some OT services from Cardinal Hill in 2005-07 and through the school system in 2007-08. See, e.g., Pet. Exs. 27, pp. 630, 705; 16, p. 142. Intensive OT began again in March 2010 and continued into 2011. See generally Pet. Ex. 27. According to testimony at the hearing, A.H.T. was discharged from OT in 2011 at around the time she began treatment for a mitochondrial disorder. Tr. at 117.

She received ST with the early intervention program until she was discharged in March 2005, because early intervention services terminated at three years of age. Pet. Ex. 18, p. 184. She continued to receive ST services, according to her primary care records (see Pet. Ex. 52, p. 2219 (well-child visit at four years of age reflecting improvements with speech therapy)). There are some speech therapy records from Cardinal Hill in 2011. See, e.g., Pet. Ex. 27, pp. 606-23. According to testimony at the hearing, A.H.T. was still receiving ST services. Tr. at 117; See also Pet. Ex. 27, p. 614 (last ST record filed).

A.H.T. began receiving physical therapy ["PT"] services in March 2007, at the recommendation of Dr. Puri. Pet. Ex. 37, p. 1495. She was discharged from PT in February 2008, based on her improved functioning. Pet. Ex. 33, pp. 1285-86. She was re-evaluated in 2009 and received services again until February 2010.³⁵ Pet. Ex. 37, pp. 1356, 1362-63.

Beginning in late 2010, the primary therapy for addressing A.H.T.'s continuing behavior problems was behavioral analysis and ancillary support services from Community Ties and Homeplace Support Services. These problems included defiance, temper tantrums or meltdowns, verbal aggression, and physical aggression towards property, pets, and people. Services continued at least into early 2012. See generally Pet. Exs. 38, 57.³⁶ These very detailed records of A.H.T.'s behavior overlap with the diagnosis and initiation of treatment for a probable mitochondrial disorder and, thus, provide insights into the efficacy of such treatment. She also saw her pediatric neurologist occasionally in 2011 (after more than a year's break in treatment). See Pet. Ex. 31, pp. 1234-41 (2011 records), pp. 1243-45 (prior visit in August 2009). The records from Dr. Puri and his associates also overlap with the period when she was diagnosed and treated for a mitochondrial dysfunction or disorder.

A.H.T.'s treatment by alternative or complementary medical providers began as early as July 2004 when she saw Anne Linden Steele.³⁷ Another treatment facility, the

³⁵ For a brief period beginning in early March 2011, A.H.T. again received PT, but this was due to injuries sustained in an automobile accident. Services were discontinued in April 2011 because she no longer seemed to be in pain. See Pet. Ex. 43, pp. 1869-74 (noting inconsistent reports of pain and not enough objective findings to "legitimate" neck and back pain).

³⁶ The records from these two agencies are in the same format, likely reflecting a name change in the agency rather than two different service providers.

³⁷ Ms. Steele's records do not reflect her specialty, but her website (<http://www.annelindensteele.com/>) does (last visited Oct. 23, 2014). Ms. Holt's journal contains recommendations for treatment by a cranial-sacral therapist (Pet. Ex. 6, p. 45), and a reference to having tried this therapy appears in the treatment history provided at the Carriage House (early intervention) intake interview. See Pet. Ex. 39, p. 1826. There was no evidence discussing what this therapy involved or what specific problems it was intended to address.

Biohealth Centers, was consulted in late 2004 to obtain orders for testing by Great Plains Laboratory.³⁸ Pet. Ex. 76.

The unidentified health care provider who saw A.H.T. at Integrative Health Specialists from March-June 2005 assessed her with “candida” (yeast overgrowth), vitamin and mineral deficiency, and “metal toxicity.”³⁹ A.H.T. was prescribed nystatin (an antifungal agent) and probiotics. She was also chelated with DMSA during this period,⁴⁰ but she developed increased behavior problems during chelation. Pet. Ex. 19, pp. 213-15. Diagnoses included sensory integration disorder, PDD, central nervous system dysfunction, delays in fine motor skills, and expressive and receptive language disorder. *Id.* at 214.

A.H.T. saw three Defeat Autism Now! [“DAN!”]⁴¹ physicians: Dr. DeMio (from September 2005-November 2008),⁴² Dr. Kartzinel (from June-October 2007),⁴³ and Dr. Levinson (beginning in May 2010).⁴⁴ These physicians, along with the provider from

³⁸ Testing by Great Plains laboratory is common in OAP cases. Great Plains laboratories test blood, urine, and stool for many different minerals, parasites, and nutritional markers. See Pet. Ex. 76, pp. 2462-84 (A.H.T.’s test results).

³⁹ It is unclear from these records which “toxic” metals were of concern.

⁴⁰ See *Snyder*, 2009 WL 332044, at *67 n.192. Chelation is the use of chemicals to break the bond formed between some heavy metals and body tissue. Chelation therapy has been approved to reduce lead levels in children and for cases of mercury poisoning. Its use in treating children with ASD remains highly controversial, as there are no controlled studies testing its efficacy and there are significant risks associated with the treatment. DMSA (dimercaptosuccinic acid) is a water-soluble and relatively non-toxic chelating agent. *Dwyer*, 2010 WL 892250, at 103, n.428. DMPS (2, 3-dimercaptopropane-1-sulfonate) is another chelating agent that A.H.T. received. See *Snyder*, 2009 WL 332044, at *177, n.506 (internal citations omitted); see, e.g., Pet. Ex. 23, p. 236 (A.H.T.’s treatment with DMPS by Dr. DeMio).

⁴¹ DAN! physicians subscribe to “biomedical” treatment protocols developed by the Autism Research Institute. These treatments may include chelation and other therapies not vetted as efficacious by controlled clinical studies. *Dwyer*, 2010 WL 892250, at *20, *178. See also Pet. Ex. 60 at 2340 (Dr. Levinson’s CV, listing several lectures on “biomedical” approaches to autism treatment he delivered at Autism Research Institute meetings). Both Drs. Wiznitzer and McCandless characterized Dr. DeMio, Dr. Kartzinel, and Dr. Levinson as “alternative” or “complementary” health care providers. See Res. Exs. A at 4; G at 1. In his testimony, Dr. DeMio discussed DAN!, the Autism Research Institute, its annual conferences, and biomedical treatment and training. Tr. at 265-67, 269. According to Dr. DeMio, the biomedical view of autism considers ASD to be a metabolic, gastrointestinal, immune, and nutritional disorder often caused by environmental toxins, including vaccines and mercury. Tr. at 233.

⁴² Although the last record from Dr. DeMio in Pet. Ex. 23 is dated November 18, 2008 (*id.*, p. 290; Tr. at 247-48), Dr. DeMio began treating her again in August 2012 (see Pet. Ex. 87; Tr. at 247-48).

⁴³ Ms. Holt identified Dr. Kartzinel as a “DAN” doctor when providing an updated client history to Easter Seals in 2007. Pet. Ex. 27, pp. 629-30. According to Dr. Kartzinel’s records, he renewed a prescription for Singulair for A.H.T. in February 2008, but the last treatment record is dated October 29, 2007. Pet. Ex. 24, p. 452.

⁴⁴ According to Ms. Holt, she consulted Dr. Levinson because she wanted to return to the DAN! treatment methods. Pet. Ex. 47, p. 2055.

Integrative Health Specialists, recommended or administered a variety of alternative treatments including chelation, hyperbaric oxygen therapy [“HBOT”], secretin infusions,⁴⁵ intravenous immunoglobulin [“IVIG”],⁴⁶ vitamin and mineral supplements, antifungal and antiviral medications, folinate or folinic acid, methyl B-12, and Actos,⁴⁷ among many others. See *generally* Pet. Exs. 19, 23, 24, 47. In addition to occasional in-person consultations, most consultations with Drs. DeMio, Kartzinel, and Levinson were by telephone or email. *Id.*; see also Tr. at 242-44 (testimony by Dr. DeMio acknowledging that many of the medical consultations regarding A.H.T. were telephonic). A DNA test ordered by Dr. Levinson revealed a single MTHFR mutation (A1298C).⁴⁸ A.H.T. stopped seeing Dr. Levinson in 2011 (see Pet. Ex. 47, p. 2058 (most recent treatment)), as Ms. Holt was “uncomfortable with his office policies.” Tr. at 77-78.

⁴⁵ In controlled studies, secretin was found less effective than a placebo in treating ASD and gastrointestinal symptoms in those with ASD. See *Snyder, 2009 WL 332044*, at *175.

⁴⁶ IVIG infusions are used to treat individuals with immune system deficiencies or dysfunction. “IVIG” stands for intravenous immunoglobulin. Neil M. Davis, *MEDICAL ABBREVIATIONS*, 15th Edition, at 178 (2011). There is no objective evidence that A.H.T. has an immune system problem. Immunoglobulin testing performed by Great Plains laboratory in 2004 showed her IgA level to be mildly elevated and her IgM to be slightly low, but Dr. Puri, who reviewed and commented on these results, did not indicate that the results were of any concern. Pet. Ex. 31, p. 1259. Immunoglobulin testing by Baptist Hospital in 2007 showed results within the reference ranges. Pet. Ex. 15, p. 126. Nevertheless, in 2012 Dr. DeMio began IVIG therapy. Tr. at 220; Pet. Ex. 87, pp. 2558-59.

⁴⁷ Actos (Pioglitazone Hydrochloride) is used in the treatment of type 2 diabetes, acting to decrease insulin resistance. See *PHYSICIANS’ DESK REFERENCE* [“PDR”] (66th ed. 2012), at 2805. There are no tests or diagnostic records showing that A.H.T. had type 2 (or any other type of) diabetes.

⁴⁸ MTHFR stands for methylenetetrahydrofolate reductase, which is a protein involved in getting rid of homocysteine. According to Dr. McCandless, A.H.T.’s MTHFR test result is unimportant. A couple of common polymorphisms had been identified in this MTHFR gene that were once thought to increase the risk of having elevated homocysteine, a risk factor for blood clots. When testing based on this hypothesis began, a lot of people with the altered genes were found, but no increased risk for blood clots or other problems. It has nothing to do with the folate deficiency later found in A.H.T.’s cerebrospinal fluid. Tr. at 602. A polymorphism is a DNA change, but not one that is disease causing or with functional implications. A common polymorphism is one found in more than 1% of the population. Tr. at 600-02.

In addition to treatment by the DAN! physicians, A.H.T. saw a developmental pediatrician, several pediatric neurologists,⁴⁹ several child psychologists,⁵⁰ and a psychiatrist.

A comprehensive neurodevelopmental evaluation was performed in early 2005 at the Weisskopf Child Evaluation Center [“Weisskopf Center”], a part of the University of Louisville School of Medicine Department of Pediatrics. Pet. Ex. 46. Doctor Gail Williams, a developmental pediatrician, diagnosed A.H.T. with a regulatory disorder⁵¹ and with central nervous system dysfunction, as “manifested by toe walking and decreased muscle tone.” Pet. Ex. 46, pp. 2038, 2041, 2045. Like Dr. Grimes, she concluded that A.H.T. did not meet the diagnostic criteria for autism, based on her “better developed social skills” and “clear evidence of joint attention.” *Id.*, pp. 2038, 2041.

⁴⁹ She saw the first pediatric neurologist, Dr. James McKiernan, in August 2004 to determine if she had been experiencing seizures. He concluded that it was “unlikely” she was having seizures. Pet. Ex. 40, p. 1831. She initially saw Dr. Puri, the pediatric neurologist who treated her for the longest period of time, in September 2004, also for possible seizures. He ordered several diagnostic tests for seizures and metabolic disorders. Pet. Ex. 31, p. 1265 (tests ordered). A.H.T. continued to see Dr. Puri, at least into 2011. Testing, including an EEG and MRI, failed to find any evidence of a seizure disorder. See Pet. Ex. 31, pp. 1273, 1275. Much later, some of the “seizure-like” spells were identified as self-stimulatory behavior. See Pet. Ex. 16, pp. 136-37. One of Dr. Puri’s associates, Dr. A.C. Anikumar, saw A.H.T. in July 2007 regarding possible seizures or a movement disorder, but concluded that the movements were most probably behaviorally related and non-epileptic in nature. Pet. Ex. 31, p. 1249. However, Dr. DeMio’s records contain several references to A.H.T. experiencing “extrapyramidal” signs or effects which could possibly be related to seizures (involuntary movements) (abbreviated “EX SXS” on several records), based on viewing videos of A.H.T. in 2006. See, e.g., Pet. Ex. 23, pp. 245, 247-48, 250. A.H.T.’s neurologist apparently viewed the same video records and told A.H.T.’s parents that the videos showed normal child behavior. See *id.*, p. 245.

⁵⁰ These included Dr. (Ph.D.) Grimes, the clinical psychologist who concluded in 2004 that A.H.T. did not meet the criteria for an ASD diagnosis (Pet. Ex. 17, p. 146); Dr. (Ph.D.) Julie Murray, who saw A.H.T. or her parents for nine sessions between July and October 2008 for symptoms of anxiety, obsessiveness, impulsivity, and poor concentration, and for assistance in managing temper tantrums and symptoms of anxiety. Pet. Ex. 16, pp. 133 (initial assessment) and 134-41; Dr. (Ph.D.) Andrew Jones, a clinical and forensic psychologist who administered a battery of tests and, in spite of some concerns about their validity (see Pet. Ex. 51, p. 2195 (expressing concern about “multiple elevated T scores... which were greater than anticipated”), diagnosed her with a bipolar disorder with depressed mood (*id.*, p. 2210)). She also saw Dr. Michael Cecil, a clinical neuropsychologist, in late 2011. He conducted many tests and made recommendations as to educational accommodations and the need for ongoing OT and ST. Pet. Ex. 56, pp. 2286-89.

⁵¹ I was unable to find a clear definition for regulatory disorder, as the diagnosis does not appear in standard medical references such as DORLAND’S or NELSON’S or in either the 4th or 5th editions of the DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS. According to an article posted on the National Institutes of Health website (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2765395/>), “Regulatory Disorders of Sensory Processing (RDSP) constitute a specific diagnostic category in the Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood (DC: 0-3R). . . .Children with regulation disorders exhibit specific symptom constellations in sensory, motor and behavioral domains.” Tr. at 686-87. Doctor Wiznitzer testified that the regulatory disorder diagnosed by Dr. Williams explained A.H.T.’s behavior problems. Tr. at 687-88.

By 2007, Dr. Puri's practice seemed to have accepted a pervasive developmental disorder diagnosis, although it is unclear whether this was based on the history of the diagnosis provided by Ms. Holt or on an independent assessment of A.H.T.'s functioning. See Pet. Ex. 31, pp. 1246 (noting a previous diagnosis of "sensory integration disorder/PDD" in the history section of the office notes in 2007), 1249 (recording diagnoses of pervasive developmental disorder, sensory integration disorder, autistic disorder, and behavioral disorder later in 2007).

In February 2009, when A.H.T. was almost seven years old, Dr. Jones diagnosed her with a bipolar disorder and depression and, according to Dr. Puri, he referred A.H.T. to Dr. Barry. Pet. Exs. 31, p. 1243; 51, p. 2207. In August 2009, Dr. Puri recorded diagnoses of PDD-NOS, bipolar affective disorder, learning disability, central auditory processing disorder, and insomnia. Doctor Puri seemed particularly concerned about A.H.T.'s sleeping difficulty, since lack of sleep "can be a problem in some temperamental children like her." Pet. Ex. 31, p. 1245.

A.H.T. also received care and treatment for several medical issues not directly related to her behavior problems. She had an endoscopy and colonoscopy in the spring of 2007. Pet. Ex. 12, p. 102. She also saw a pediatric urologist in 2008 for frequent urinary tract infections ["UTI"]. Pet. Ex. 14, p. 116.⁵² She saw a pediatric cardiologist, Dr. Roddy McDowell, in 2009, based on a reportedly abnormal electrocardiogram. After additional testing, he concluded that A.H.T.'s heart was structurally normal, in spite of an "innocent heart murmur." Pet. Ex. 13, pp. 105-06. She saw Dr. McDowell one more time in July 2010 when he made a similar assessment. *Id.*, p. 103.

Beginning in June 2010, A.H.T. was evaluated and treated at the Behavioral Sleep Medicine Clinic, a part of the University of Louisville's Pediatric Sleep Medicine Center, where she saw Dr. (Ph.D.) Sarah Honaker, a clinical psychologist, and Dr. Vincent McCarthy. The records from this clinic reflect a significant behavioral component to A.H.T.'s widely varying sleep hours, and a great degree of difficulty in getting A.H.T.'s parents to document sleeping patterns and to implement the recommended changes.⁵³ Ms. Holt sought physiological explanations for A.H.T.'s sleep difficulties, but laboratory testing did not find any physiological problems, according to

⁵² She had previously been seen by or consulted with Dr. Kartzinel and Dr. Hefner, her primary care provider, for such infections. See Pet. Exs. 24, p. 452 (telephonic consultation in October 2007 with Dr. Kartzinel referencing five or six prior UTIs); 52, p. 2216 (sick child visit in February 2008 with Dr. Hefner for a UTI, mentioning one prior UTI in 2005).

⁵³ See Pet. Ex. 30, pp. 1231 (reporting A.H.T. was awake for 26 hours, slept for 6 hours and then awake for another 22 hours; parents unable to keep sleep log); 1228-29 (parents resistant to melatonin use in spite of assurances that it was unrelated to prior nightmares); 1225 (parents inconsistent in sitting with her until she falls asleep and are not sure of times of sleep onset); 1223 (therapist reporting that there were two major barriers to success of therapy, in that parents had great difficulty in waking A.H.T. at the scheduled time and A.H.T. resisted going to bed, and therapist was unsure how well parents enforced bedtime).

the therapist.⁵⁴ *Id.*, p. 1224. A.H.T.'s sleep improved markedly during the therapy. *Id.*, p. 1217.

The sleep center observations by Dr. (Ph.D.) Honaker regarding parental inconsistency in setting and enforcing bedtimes and in seeking physiological explanations for A.H.T.'s sleeping difficulties were mirrored by the behavior analysis specialists who saw her from October 2010 through at least January 2012. After several months of observation of A.H.T. and her caregivers, these analysts developed a plan to change targeted behaviors, which scripted certain daily activities and implemented a "token economy" reward system in which completion of tasks was rewarded by tokens which A.H.T. could redeem weekly for preferred activities or objects. See Pet. Ex. 38, pp. 1690-98. The records reflect numerous concerns by the analysts about A.H.T.'s parents' poor compliance with the behavior modification program.⁵⁵ Over time, both parental compliance and A.H.T.'s behavior improved, although there were peaks and valleys. See Pet. Exs 38, pp. 1750-58; 57, pp. 2309-10.

The medical and therapy records relevant to the factual conflicts and other issues in this case are discussed in more detail below.

III. Expert Qualifications.

Five physicians offered opinions on vaccine causation and other matters in dispute. Three of the experts (Drs. Kendall, McCandless, and Wiznitzer) were well-qualified to offer expert opinions; the other two (Drs. Levinson and DeMio) had experience in treating children with autism and children with mitochondrial disorders, but are best characterized as alternative or complementary medical providers who lacked the academic background, research qualifications, or specialized training important in my assessments of the bases for and reliability of the opinions they offered.⁵⁶ They treated A.H.T. for periods of time far removed from the manifestation of the symptoms after her initial vaccination or the onset of her autistic-like behaviors. I have carefully considered their records as treating physicians and their opinions on causation in light

⁵⁴ Toward the end of the sleep therapy treatment, Dr. Vincent observed that A.H.T had "not been optimally medicated for those diagnoses [referring to issues other than sleep-related] that are medical." Pet. Ex. 30, p. 1221. He also stated: "It is difficult for me to tell whether some of her activities are just totally behavioral in nature or whether there is actually an underlying medical/psychiatric diagnosis." *Id.*, p. 1222.

⁵⁵ See, e.g., Pet Ex. 38, pp. 1773 (parents have not yet implemented task analysis and token economy, resulting in minimal progress in behavioral changes), 1774 (parents have not yet used reinforcement for motivation), 1784 (parents had not taken data requested by behavior analyst and claimed that A.H.T.'s sleep disorder prevented them from implementing most procedures outlined in the behavior plan), 1778 (mom's report that playtime was contingent upon completing home school was contrary to observations of behavioral analyst and parents were inconsistent with keeping data); 1781 (parents not providing tokens at the time of task performance and reinforcing A.H.T.'s escape from and avoidance of tasks), 1793 (parents not recording data).

⁵⁶ According to Dr. McCandless, most of what Dr. Levinson said about mitochondrial function was simply wrong (see Res. Ex. G at 3; Tr. at 588-89) and Dr. Kendall did not appear to place any reliance on Dr. Levinson's opinion, as it was not mentioned at all in her testimony.

of Federal Circuit precedent on the value of treating physicians' opinions. See *Capizzano*, 440 F.3d at 1326 (commenting that treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'") (internal citations omitted). See also *Moberly*, 592 F.3d at 1325 ("Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases.") (citing *Terran v. Sec'y, HHS*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)); *Cedillo*, 617 F.3d at 1339 ("[a] court may conclude that there is simply too great an analytical gap between the data and the opinion proffered") (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (additional internal citations omitted)); *Lalonde v. Sec'y, HHS*, 746 F.3d 1334, 1337-38 (Fed. Cir. 2014) ("In Vaccine Act cases, petitioners must proffer trustworthy testimony from experts who can find support for their theories in medical literature in order to show causation under the preponderance of the evidence standard."); *Snyder v. Sec'y, HHS*, 88 Fed. Cl. 706, 745 n.67 (2009) (emphasizing that a statement of a treating physician is not "sacrosanct" and can be rebutted).

The Federal Circuit has upheld the special masters' use of *Daubert* and summarized the four *Daubert* factors as "(1) general acceptance in the scientific community, (2) whether the theory has been subjected to peer review and publication, (3) whether the theory can and has been tested, and (4) whether the known potential rate of error is acceptable." *Cedillo*, 617 F.3d at 1339 (citing *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 593-94 (1993)); see also *Andreu v. Sec'y, HHS*, 569 F.3d 1367, 1379 (Fed. Cir. 2009). The Federal Circuit also approved the use of the *Daubert* factors in evaluating an expert's "reliability" as well as their "methodology." *Cedillo*, 617 F.3d at 1339.

In this case, Drs. Levinson and DeMio's status as treating physicians adds little to the reliability of their causation opinions, which largely consisted of conclusory statements. With regard to the logical connection between vaccination and injury, these particular treating physicians are no more percipient as witnesses about what actually transpired after the vaccinations than any other physician who testified in this case. Moreover, nothing in *Capizzano* requires special masters to give weight to the opinions of treating doctors who espouse "junk science," and who treat children based on unproven hypotheses, with drugs with no known efficacy against the medical conditions presented,⁵⁷ and without test results to warrant the speculative diagnoses proffered.⁵⁸

⁵⁷ In ordering tests, Dr. DeMio recorded a number of diagnoses, including static encephalopathy, metabolic derangement, metabolic error, glycemic disorder, autoimmune disease, and hypothyroidism. See, e.g., Pet. Ex. 37, pp. 1533-35, 1577, 1591, 1665. Other than static encephalopathy, these were all new diagnoses unsupported by the medical testing ordered.

⁵⁸ Doctor DeMio ordered many standard laboratory tests on a monthly basis between February 2006 and June 2007, in spite of repeated results within reference ranges. See generally Pet. Exs. 23; pp. 293-370; 37, pp. 1534-1665; 42, pp.1836-67. He also ordered tests that were less routine. He had a standing order for a comprehensive metabolic panel and complete blood count ["CBC"] with differential and platelets, on a monthly basis. Pet. Ex. 37, p. 1533. Other tests ordered included plasma amino acids, red blood cell elements, urine toxic metals, various virus antibodies, stool parasites and bacteria, thyroid,

See *Capizzano*, 440 F.3d at 1325-27. See also *Dwyer*, 2010 WL 892250, at *116, 141 (criticizing the practitioners and researchers who convinced parents of the efficacy of various specious treatment methods for their children with ASD). Both Drs. DeMio and Levinson prescribed treatments of dubious efficacy, ordered tests with results that conflicted with their hypotheses, and made diagnoses unsupported by the evidence. I have not entirely rejected their observations about A.H.T., but I cannot credit their statements about the connection between A.H.T.'s vaccination and her subsequent medical and behavioral problems.

However, I have fully credited the records of the treating physicians, Drs. Buttleman and Hefner, who saw A.H.T. during her first year of life and who treated her for irritability and constipation, and diagnosed colic.

The four physicians who testified at the hearing offered opinions regarding symptoms A.H.T. allegedly displayed after the vaccinations and whether these were symptoms that suggested a mitochondrial regression had occurred. Although they were not percipient witnesses, their testimony about the likelihood of the events described is a factor in the factual findings set forth in Section V, Part C, below. The primary contributions of the experts were in explaining mitochondrial disorders, the distinction between primary mitochondrial disorders and secondary mitochondrial dysfunction, and explaining the evidence and conflicting opinions surrounding A.H.T.'s diagnosis and vaccine causation.

The witnesses' training and experience that bear on their qualifications to testify as experts and on the weight I accorded their testimony are set forth below, along with some observations and impressions regarding their testimony.

A. Petitioner's Experts.

All three of petitioner's experts opined that the hepatitis B vaccination was responsible for the symptoms A.H.T. displayed after vaccination. All three stated that

myelin antibodies, and fecal metals, among many others. Most results were entirely within reference ranges, but occasionally, a few individual results would be slightly high or low. See, e.g., Pet. Ex. 23, pp. 364 (all red blood cell elements within reference range, except selenium), 356 (urine toxic metals all within reference range), 345 (CBC and metabolic panel with nearly all results within reference ranges), 320 (comprehensive metabolic panel with results all within reference ranges); 24, pp. 378-79 (viral panel, stool culture, and thyroid testing all within reference ranges). Most of these laboratory reports were from Doctors' Data, a laboratory seen with some frequency in records from OAP cases, and one with some difficulties with licensing agencies. See *Dwyer*, 2010 WL 892250, at *182 n.687. Although Dr. DeMio testified that he saw a lot of immune and metabolic issues in A.H.T. on testing (Tr. at 211-12), he did not point to specific tests that demonstrated those problems. He testified that she had "issues eventually with organisms like yeast and viruses." *Id.* Like Dr. DeMio, Dr. Levinson ordered many laboratory tests (see Pet. Ex. 47, pp. 2059-2107, 2129-43). With the exception of some elevated white blood cell counts and a positive streptococcus antibody test, all the results on the traditional laboratory tests were within the reference ranges, including the comprehensive metabolic panel. *Id.*, pp. 2140-43. Testing by Geneva Diagnostics encompassed a toxic element clearance profile, completed on June 17, 2010 (Pet. Ex. 47, pp. 2134-39), and a nutritional evaluation completed on June 28, 2010, assessing oxidative stress, organic acids, amino acids, essential fatty acids, and toxic and nutrient elements (Pet. Ex. 47, pp. 2059-86).

A.H.T. had a mitochondrial disorder or dysfunction which was aggravated by her hepatitis B vaccination, but their theories about how the vaccination did so varied considerably. Their backgrounds and qualifications were likewise quite divergent as well.

1. Doctor Levinson.

Doctor Levinson graduated from the University of Miami School of Medicine, and completed a residency in psychiatry. Pet. Ex. 60 at 2339. He did not list any publications on his CV, although the CV included a reference to his dissertation on the use of valerian root as a sleep aid. According to his CV, he has lectured on the “biomedical” treatment of autism and gastrointestinal issues in autistic patients, as well as on “detoxification” and dietary interventions. He has also appeared in several television programs on subjects as diverse as reversing aging, autism, and heavy metal poisoning. *Id.* at 2340-41. According to his February 2012 statement, he regularly treated patients “with mitochondrial disease, metabolic disorders, and immune-system related conditions” and “frequently lecture[d] on mitochondrial disorder[s] and the potential for environmental and biological triggers of this condition.”⁵⁹ Pet. Ex. 59 at 2336.

From the filed records, it is difficult to determine what diagnoses informed his treatment of A.H.T., as his records from 2010 and 2011 do not reflect a diagnosis. He referred A.H.T. to Dr. Shoffner for mitochondrial disorder testing about a year after Ms. Holt completed his intake form. In his February 2012 statement, Dr. Levinson mentioned his treatment of A.H.T. for a mitochondrial disorder and her improvement on such treatment, but he did not indicate the nature of the treatment, when it began, or what constituted improvement or how it differed from the treatment he provided prior to her diagnosis. See Pet. Ex. 59 at 2336-37.

His February 2012 statement was conclusory in nature. He did not explain his reasoning or point to anything that supported the opinions he expressed regarding diagnosis and causation. These were serious deficiencies, given his lack of any training in immunology, oxidative stress, or mitochondrial disorders, matters about which he opined.

2. Doctor DeMio.

⁵⁹ Doctor McCandless expressed skepticism about Dr. Levinson’s qualifications to lecture about mitochondrial disorders, pointing out three specific statements in Dr. Levinson’s causation opinion “that demonstrate a lack of understanding of mitochondrial biology and physiology.” Res. Ex. G at 3. He added in testimony that these three statements were not supported by solid, underlying research. Tr. at 588. He explained that most people who treat children with mitochondrial diseases “often see some deterioration associated with viral illnesses and fever,” but to opine why this happens or to attribute it happening to a vaccination in a five-day old was simply speculation. Tr. at 589.

Doctor DeMio testified as both treating physician and expert, although precisely what qualified him as an expert in either mitochondrial disorders or the causes of autism spectrum disorders remains elusive. He graduated from medical school at Case Western Reserve University. Pet. Ex. 63, p. 2358. He is board certified in emergency medicine. Tr. at 226. He has no formal specialized training in metabolic diseases or in any of the several areas (pediatrics, immunology, neurology, or gastroenterology), in which he proffered opinions. Tr. at 227-28. His only publications involved chapters on arthritis, gout, inflammation, and nutrition in an integrative medicine textbook. Pet. Ex. 63, p. 2360.

He did partial residencies in pathology and internal medicine, followed by a three-year residency in emergency medicine, all in the Cleveland, OH area. Tr. at 183-84. As a part of his emergency medicine residency, he received some pediatric training. Tr. at 226-27; Pet. Ex. 63, p. 2359. After completing his residency in 1989, he worked briefly in Massachusetts, before returning to Cleveland's Mount Sinai hospital as a part-time faculty member. He also worked at emergency medicine departments in two other hospitals and in their residency training programs. Tr. at 185-86. None of his appointments during this period were full-time faculty or clinical positions at any one institution. Tr. at 186-87. He also maintained a private medical practice in which he offered nutritional treatments as an alternative to drugs. Tr. at 188.

At the time of his testimony, he held no faculty appointments, although he had privileges at several hospitals. Tr. at 228. He currently treats patients with immune dysfunction, metabolic disorders, mitochondrial disorders, developmental problems, behavior and mood issues, and cognitive dysfunction diagnosed "by other people who basically aren't doing much, if any, medical treatment for them." Tr. at 188-89, 230. The majority of his patients are children with developmental disabilities, including ASD, obsessive compulsive disorder ["OCD"], attention deficit hyperactivity disorder, dyspraxia, apraxia, mitochondrial dysfunction, and mitochondrial disease. Mitochondrial dysfunction patients comprised from a quarter to a third of his patients over the last nine years. Tr. at 194-95. His clinical practice is a "cash office," which does not directly bill medical insurers for the care rendered. Tr. at 229-30.

He serves as the Chief Medical Officer of the U.S. Autism and Asperger's Association (Tr. at 190) and has assisted the Autism Research Institute with their "think tanks" and meetings (Tr. at 191). He is the founder and executive director of the American Medical Autism Board, which he described as "the board certified by medical doctors who do the kind of treatment that several of us out there are doing" (Tr. at 192), presumably referring to biomedical approaches to the treatment of autism. He acknowledged that this board is not recognized by the American Board of Medical Specialties. Tr. at 231.

Much of Dr. DeMio's testimony involved broad, general statements, even when he was discussing his own treatment of A.H.T. In describing that treatment, he used medical terminology vaguely and indiscriminately. For example, he testified regarding

his treatment of A.H.T. that: “then there’s methylation⁶⁰ and some other metabolic support that we did. Methylation’s one of the metabolic things that we do, and so we added in a lot of those treatments.” Tr. at 213. He “found [A.H.T.] to have accumulated a lot of metal toxins,” but did not indicate which metals were toxic or how he knew that they were at toxic levels.⁶¹ *Id.* The tests initially performed for various metals were all within the reference ranges. See, e.g., Pet. Ex. 23, pp. 328, 350, 356. One later urine test, which was performed after chelation began, showed one slightly elevated result for tin, but no results were significantly above the reference ranges.⁶² *Id.*, p. 348. Although he testified that he found many immune and metabolic issues as the result of the testing he ordered for A.H.T. (Tr. at 211-12), he did not point to any specific tests that demonstrated these issues. He found her gastrointestinal system was not “to the balance that we want and we also found issues eventually with organisms like yeast and viruses” either based on tests or “clinically,” but once again, he did not point to specific tests. Tr. at 213.

He was equally vague about how A.H.T. responded to his “biomedical” treatments. He testified that:

She definitively had responses, and a lot of them were very good, and then she ended up getting some upheavals I call them. Many people call them side effects, things that showed she was able to respond to those. . . .Some of them for a few months would really help her a lot to kind of impress the speech therapist that she was able to learn better. . . a lot of [her symptoms of OCD, cognitive function, and focus] got better, and some of them either got worse or she shifted over to some other things, so she had had hallucinations or some very intense preoccupations.

Tr. at 214.

To summarize, I did not find his testimony reliable in general or useful in resolving either the factual disputes or causation questions. Although Dr. DeMio had

⁶⁰ “Methylation” is defined chemically as the addition of methyl groups to a substance. DORLAND’S at 1152. I doubt that this was what Dr. DeMio meant. It is likely that he was referring to the methyl B 12 (methylcobalamin) treatments he ordered during his early treatment of A.H.T. Testing by Geneva Diagnostics encompassed a toxic element clearance profile, completed on June 17, 2010 (Pet. Ex. 47, pp. 2134-39), and a nutritional evaluation completed on June 28, 2010, assessing oxidative stress, organic acids, amino acids, essential fatty acids, and toxic and nutrient elements (Pet. Ex. 47, pp. 2059-86). I note that problems in methylation of DNA and methylcobalamin treatments were discussed in the Theory 2 test case decisions (see, e.g., *Dwyer*, 2010 WL 892250, at *140-42) as a part of the oxidative stress aspects of the mercury causation theory, a theory rejected in each of the Theory 2 OAP test cases.

⁶¹ On cross-examination, Dr. DeMio acknowledged that a section of his website discussed his belief that one of the major causes of the “autism epidemic” is mercury and aluminum in vaccines. Tr. at 232-33.

⁶² As chelation is performed to remove metals such as lead and mercury from the body, increases in urinary levels of metals susceptible to chelation is expected. This does not mean that toxic levels were present in the body prior to chelation. *Snyder*, 2009 WL 332044, at *176-78; Pet. Ex. 23, p. 348.

treated A.H.T.,⁶³ I gave little weight to his testimony about the events after the vaccination as the testimony was based primarily on what was reported to him by A.H.T.'s parents, years after the events in question. As for his opinions regarding their credibility and ability as historians (see Tr. at 203), I had the opportunity to assess these matters for myself. Unlike Dr. DeMio, I carefully reviewed every medical record filed and noted that Ms. Holt's recitations of A.H.T.'s medical history varied over time, and some of the matters she reported were inexplicably absent from the contemporaneous records.⁶⁴ See, e.g., n.30, *supra*. On at least one occasion, Mr. Tipton's reports seemed calculated to mislead health care providers about A.H.T.'s medical history. See Pet. Ex. 43, p. 1876 (screening form signed by Mr. Tipton in which he falsely reported that A.H.T. had received the chickenpox vaccine and was up to date on immunizations).

⁶³ Doctor DeMio began treating A.H.T. about three years after the events in question.

⁶⁴ For example, after reviewing the early pediatric records during cross-examination, Dr. Kendall acknowledged that the normal growth and development described in the primary care records through nine months of age were inconsistent with the testimony of A.H.T.'s family members. Tr. at 388-89.

3. Doctor Kendall.

Doctor Kendall, a biochemical geneticist and mitochondrial disease specialist, obtained her medical degree from the New Jersey Medical School. Tr. at 291; Pet. Ex. 80 at 2504.⁶⁵ She completed a residency in pediatrics, followed by a fellowship in genetics and metabolism at Boston Children's Hospital and Harvard Medical School, and then a research fellowship in genetics and metabolism at Tufts. Tr. at 291-92; Pet. Ex. 80 at 2504. Both fellowships involved an active clinical practice in patients with suspected or known genetic and metabolic disorders. The research fellowship involved work in a mitochondrial research laboratory as well. Tr. at 292. After her fellowship, she began a mitochondrial disorders program at Boston's Children's Hospital which focused on the diagnosis, care, and management of mitochondrial disease patients. Tr. at 295. She has been treating patients with mitochondrial disorders for 22 years and is board certified in biochemical genetics. Tr. at 293, 298. Although Dr. Kendall trained as a pediatrician and had been board certified in pediatrics at one time, her certification was not current, and she did not see pediatric patients for treatment other than that related to mitochondrial disease. Tr. at 298-300, 332-33.

She has held academic appointments at both Harvard Medical School and Emory Medical School as a geneticist in the pediatrics department. Tr. at 293-94. She currently teaches and lectures at symposiums, at Emory University Nursing School, and annually at the United Mitochondrial Disease Foundation's symposium. She has a hospital appointment at Children's Healthcare of Atlanta as a clinical geneticist. Tr. at 295. However, her primary work is in an outpatient setting, in her role as President, Virtual Medical Practice, where she manages patients with a known diagnosis, evaluates patients for mitochondrial disease, and provides second opinion consultations throughout the world as the "virtual" part of the practice. Pet. Ex. 80 at 2505; Tr. at 295, 298-99. She also evaluates patients being considered for enrollment in clinical trials. Tr. at 299.

Doctor Kendall's CV listed three research interests: inborn errors of metabolism; the pathophysiology of multisystem problems in disorders of mitochondrial energy production; and the efficacy of clinical treatment in disorders of mitochondrial energy production. Pet. Ex. 80 at 2505. There were eight journal articles listed as "Original Reports" on her CV, Pet. Ex. 80, but only one of them explicitly involved mitochondrial disorders. *Id.*, p. 2509. However, she testified that her most recent publication (which did not appear on Pet. Ex. 80, her CV) was a review article on mitochondrial disease and diagnostics. Tr. at 296-97. The CV also listed "Reviews," which appeared to include book chapters and journal articles, including one on testing in mitochondrial disorders and one entitled "Bridging the Gap between ASD and Mitochondrial Disease."

⁶⁵ Doctor Kendall testified that this CV was out of date and indicated that she would provide a copy of the new one. Tr. at 297. An updated CV was never filed.

Pet. Ex. 80, at 2509.⁶⁶ She did not indicate that she was a peer reviewer or editor for any professional publications.

Unlike Dr. DeMio, Dr. Kendall possessed the requisite qualifications to opine about mitochondrial disorders. The reliability and credibility problems posed by Dr. Kendall's testimony did not concern her qualifications to opine about mitochondrial disorders, but rather her lack of familiarity with the medical records regarding A.H.T.'s growth, development, and treatment during the relevant periods, and her evasiveness in answering my questions as well as those from opposing counsel.

Her lack of familiarity about the medical records was somewhat unusual for an expert witness testifying in the Vaccine Program. She was unsure what diagnostic criteria Dr. Shoffner used (Tr. at 324-25), although it was clearly identified in the diagnostic report. Pet. Ex. 61, pp. 2349-50. She was unable to recall when A.H.T. manifested some of the symptoms upon which the diagnosis was based. See Tr. at 310. When asked if she had reviewed A.H.T.'s medical records from her first year of life, Doctor Kendall replied that she was "assuming" that she did. Tr. at 339. She could not recall if fever was mentioned in the medical records as a symptom occurring after A.H.T.'s vaccination. Tr. at 341-42. She could not recall when A.H.T. was diagnosed with hypotonia. Tr. at 344. She could not recall when A.H.T. started having autistic-like behaviors. Tr. at 345. She could not recall when A.H.T. began displaying symptoms of dysautonomia (temperature instability),⁶⁷ nor did she recall how often this symptom occurred. Tr. at 345-46. She believed that the medical records reflected A.H.T. suffered from fatigue, but could not identify a particular time frame when fatigue was reported as a problem. Tr. at 348. She testified that the medical records described A.H.T. as lethargic after her vaccination (Tr. at 339-40), but that description does not appear in any contemporaneous record. After reviewing the early pediatric records during cross-examination, Dr. Kendall acknowledged that the normal growth and development described in the primary care records through nine months of age were inconsistent with the testimony of A.H.T.'s family members. Tr. at 388-89. Her lack of preparation for testimony was disappointing.

Additionally, Dr. Kendall avoided giving straight answers to straightforward questions. When asked whether a neonate with primary mitochondrial disease would likely have normal growth and weight gain, she replied, "[t]hey can." When pressed to indicate if such growth and weight gain would be expected, she responded "it depends on the patient." She was similarly evasive in answering questions regarding motor and intellectual development in a neonate with a primary mitochondrial disease, responding again, "it depends on what their clinical presentations are." Tr. at 348. These tautological answers were not informative about what is generally or typically seen in

⁶⁶ The CV listed "abstracts" separately. Pet. Ex. 80 at 2510. In general, they appeared to be the abstracts of the journal publications listed earlier.

⁶⁷ Doctor Kendall's report indicated that dysautonomia, including temperature instability, was a possible symptom of mitochondrial disease. Pet. Ex. 79 at 2500; see *also* Tr. at 308-09.

such patients. This evasiveness, coupled with the lack of support for some aspects of her opinion, caused me to question whether her testimony was entirely reliable.

Her testimony provided details on her theory of vaccine causation that her expert report lacked. The portion of her report addressing causation (Pet. Ex. 79 at 2496-97) was very short, only about two paragraphs long, and was based on two cited journal articles, one of which was largely a case report, discussing autistic regression in children with diagnosed mitochondrial disorders. As Dr. Kendall admitted on cross examination, A.H.T. did not experience autistic regression in the classic sense of losing “speech and those type of things,” and she agreed that there were many differences between the children described in the studies and A.H.T.’s presentation. Tr. at 356; 357-58.

When asked about support for specific aspects of her theory of causation, she avoided a direct answer, as exemplified by the following exchange:

Q: What other literature are you relying on for your theory?

A: As I indicated, some of the other articles that talk about temperature.

Q: Can you be more specific?

A. They are noted in some of the other articles.

Q: Nothing was filed with your report, so I’m just - -

A: No, I understand. I’m just mentioning it based on the questions that you’re posing, and it’s coming up, so that’s what I’m saying.

Q: But you did not submit anything to support your theory, is that correct?

A. I did not submit those articles, no.

Tr. at 358. She clarified that not all the articles she cited in her report were actually filed as evidence. Tr. at 360. The failure of petitioner to file supportive evidence for her opinions, particularly after Dr. McCandless challenged her reliance on other literature she claimed was supportive of her opinions (see Res. Ex. G at 4), was troubling.

B. Respondent’s Experts.

With regard to A.H.T.’s symptoms after vaccination and the likelihood that they occurred as described by the witnesses, I accorded greater weight to the testimony of respondent’s two experts. Both were currently board certified in pediatrics, displayed familiarity with the contemporaneous records, gave careful attention to the testimony of A.H.T.’s parents and fact witnesses, and provided reasons for their conclusions. Both Drs. Wiznitzer⁶⁸ and McCandless were far better prepared to discuss A.H.T.’s medical

⁶⁸ During his testimony, Dr. Wiznitzer indicated that he did not have Dr. Hefner’s records at the time he wrote his expert report (Res. Ex. A), thus explaining why his comments in that report about A.H.T.’s development ended at nine months of age, when she stopped seeing Dr. Buttleman. Res. Ex. A at 7; Tr. at 670. Also, on cross-examination, petitioner’s counsel noted that Dr. Wiznitzer’s report referred to A.H.T.’s birth as occurring in a hospital. See Tr. at 691-92. I note that the filed medical records do not include any records regarding A.H.T.’s home birth; Dr. Buttleman’s records do not mention where A.H.T. was born; and Dr. Puri, A.H.T.’s pediatric neurologist, referred obliquely to a hospital birth. See generally Pet. Exs. 58 (Dr. Buttleman’s records); 31, p. 1262 (recording “vaginal delivery and was home with the

records than Dr. Kendall. With regard to neurological issues, including encephalopathies in general, I found Dr. Wiznitzer to be the most qualified and reliable witness. Although he displayed the unfortunate tendency of sparring with opposing counsel, particularly with respect to hypothetical questions, his responsiveness to my questions distinguished him from Dr. Kendall. Of the two mitochondrial disease experts, Dr. McCandless was the better witness, and his opinions were better supported than hers. His explanations were clear and he genuinely tried to answer questions, rather than to dodge them.

1. Doctor McCandless.

Doctor McCandless holds three board certifications: pediatrics, clinical genetics, and clinical biochemical genetics. After completing medical school and a residency in pediatrics, he practiced pediatric medicine for five years. He then completed a clinical genetics residency at Case Western Reserve University in Cleveland, Ohio. Tr. at 414. This was followed by a faculty position in clinical genetics at the University of North Carolina. He later returned to Cleveland for a fellowship in clinical biochemical genetics. Tr. at 413-14.

In his current positions at Rainbow Babies and Children's Hospital and Case Medical Center, he evaluates and cares for patients who have, or are suspected to have, biochemical genetic disorders. Tr. at 414. He is also involved in outpatient care for the same disorders. He is the medical director of a Prader-Willi syndrome clinic and of the Center for Human Genetics. He diagnoses and treats children and adults with mitochondrial disorders. He has been caring for such patients for the last 17 years. Tr. at 414-16.

Doctor McCandless holds a faculty appointment at the Case Western Reserve School of Medicine, where he teaches genetics to medical students and graduate students, and serves as the director of the residency training program in medical genetics. Since 1996, his teaching has focused primarily on inborn errors of metabolism, some general genetics, and mitochondrial diseases as a part of the biochemical genetics program. He is a member of several professional societies, including the American Academy of Pediatrics, is a fellow of the American College of Medical Genetics, and a member of the board of directors for the Society for Inherited Metabolic Disorders. Tr. at 416-17. He lectures about mitochondrial disorders at the medical school, and developed the program on mitochondrial disorders for a national meeting of the American College of Medical Genetics and the Society for Inherited Metabolic Disorders joint session.

His research has focused primarily on fatty acid oxidation disorders, with fewer publications in the area of respiratory chain disorders. Tr. at 418. He is the principal site investigator for a multicenter clinical trial of coenzyme Q-10 therapy for children with

mother in a few days). I thus do not consider this incorrect statement regarding A.H.T.'s birth location as a dereliction on Dr. Wiznitzer's part.

mitochondrial disorders. His research laboratory uses mouse models to try to understand how mitochondrial dysfunction leads to symptoms and how to better treat those symptoms. He is involved in several clinical trials related to the treatment of urea cycle disorders and drug trials to treat phenylketonuria and other lysosomal storage diseases. Tr. at 419.

Doctor McCandless has testified as an expert witness twice for plaintiffs and once for a defendant in courts other than the Vaccine Program. This was his first appearance as a witness in a Vaccine Act case. Tr. at 421-22.

Although not lengthy, his opinion (Res. Ex. G) was well-written and well-reasoned. The primary discrepancy in his opinion—stating that Dr. Shoffner diagnosed a possible, rather than a probable, mitochondrial disorder—is not inaccurate, just incomplete. Because Dr. Shoffner’s records regarding A.H.T. were filed as a part of three different exhibits (Pet. Exs. 26, 47, and 61) and Dr. Shoffner apparently changed his diagnosis between August 1 and August 10, 2011, without any reference to the earlier diagnosis, much less an explanation for the change, Dr. McCandless apparently missed the later diagnosis of a probable mitochondrial disorder. I find this oversight understandable, particularly as there was no additional testing conducted by Dr. Shoffner between the two visits that would account for the change in diagnostic category.

2. Doctor Wiznitzer.

After graduating from medical school, Dr. Wiznitzer completed a three year residency in pediatrics at what is now Cincinnati Children’s Hospital, followed by a year-long fellowship in developmental pediatrics at the Cincinnati Center for Developmental Disorders. Tr. at 619. He then completed a three year fellowship in child neurology at the University of Pennsylvania and an additional two year fellowship at the National Institutes of Health on disorders of higher cortical function in children. Tr. at 619-20. He is board certified in pediatrics, neurology (with special qualifications in child neurology), and neurodevelopmental disabilities. Tr. at 620.

At the time of the hearing, he was an associate professor of pediatrics, neurology, and international health at Case Western Reserve University School of Medicine, and teaches at the nursing and medical schools. Tr. at 620-21. His primary clinical appointment is as a child neurologist at Rainbow Babies and Children’s hospital. His clinical responsibilities there include services at the inpatient unit, outpatient clinical practice, the epilepsy service and teaching residents. His responsibilities also include administration of research grants, including one involving autism treatments. Tr. at 621.

He is a member of and holds positions in several relevant professional organizations, including teaching and course development as a fellow of the American Academy of Neurology [“AAN”], where he has presented courses or lectures on ADHD, autism, and pediatric behavioral neurology. He is part of an AAN task force charged with developing a position paper on interventions in autism. Tr. at 621-22. He is a

member of the executive committee of the American Academy of Pediatrics [“AAP”] and serves as that organization’s liaison to the executive committee of the Council on Children with Disabilities. He is a member of the autism subcommittee of the AAP and a member of various AAP working groups, including one on neuromotor examinations in children. Tr. at 622. He chairs a task force dealing with dyspraxia, a developmental coordination disorder. Tr. at 646. He is also a member of the Child Neurology Society and the International Society for Autism Research. Tr. at 622-23.

Doctor Wiznitzer is a member of the editorial boards of two professional journals. He is a peer reviewer on a regular basis for medical journals dealing with pediatrics, neurology, and other specialties. Tr. at 623. As a member of the Brighton Collaboration, an international organization dealing with vaccine safety, he has helped to develop definitions for various conditions to help in standardizing studies into adverse events after vaccination. Tr. at 623. He also develops questions for various medical certification examinations. Tr. at 624.

He has diagnosed and treated children with ASD and other developmental disabilities for about 25 years. He has conducted research into and has numerous peer reviewed publications, including journal articles, book chapters, and abstracts, on the topics of autism (including co-morbid conditions such as tuberous sclerosis), ADHD, and other developmental disabilities. Tr. at 624-25. He treats children with mitochondrial dysfunction and disorders in his clinical practice. He refers children with suspected mitochondrial disorders to the genetics department and the mitochondrial team for testing and diagnosis. Tr. at 625.

In addition to his clinical, teaching, writing, and research responsibilities, Dr. Wiznitzer devotes about four to five hours per week to litigative consultations. Although he primarily reviews cases for respondent in the Vaccine Program, he has recommended compensation in some of those cases, and has supported claims of his own patients for compensation. Tr. at 625-26. He has testified frequently on behalf of respondent in the Vaccine Program. Doctor Wiznitzer was offered as an expert in pediatric neurology and developmental disabilities, without objection. Tr. at 626-27.

IV. The Causation Theories Presented.

A. Mitochondrial Disorder, Disease, and Dysfunction.

Neither party filed much background information about mitochondrial disorders in general. The comprehensive literature review filed by petitioner, D. Rossignol & R. Frye, *Mitochondrial dysfunction in autism spectrum disorders: a systematic review and meta-analysis*, MOLEC. PSYCHIATRY, 17: 290-314 (2010), Pet. Ex. 71 [hereinafter “Rossignol & Frye, Pet. Ex. 71”], did not discuss the wide variety of mitochondrial disorders, focusing more on the co-morbidities in mitochondrial dysfunction, mitochondrial disease, and ASD, and the relative rates of various clinical findings. Some of the various clinical phenotypes, such as Alper and Leigh syndromes, were mentioned in C. Verity, et al., *The clinical presentation of mitochondrial diseases in*

children with progressive intellectual and neurological deterioration: a national, prospective, population-based study, DEV. MED. & CHILD NEUROL., 52: 434-40 (2010).⁶⁹ As this study focused on patients with progressive disease, it did not provide information on the wide variety of other mitochondrial disorders.

Mitochondrial disease can present in a wide variety of ways, according to Dr. McCandless. Tr. at 435. He added that “it has been said that mitochondrial dysfunction can cause almost any symptom in any part of the body at almost any time, which to a certain extent is true.” *Id.* However, “mitochondrial diseases tend to present in some very characteristic ways [which are] usually related to the tissue that’s most involved, and those are the tissues that use the most energy.” *Id.* Doctor Kendall explained that “there are subtypes of mitochondrial disease that are clearly defined [that] are descriptive of a group of clinical features that are seen over and over again and often in constellation with a specific gene defect or a specific biochemical feature,” but that most patients do not fall into a “well-categorized subtype.” Tr. at 349. She testified that A.H.T. does not fit into one of these subtypes. Tr. at 349-50.

Initially, petitioner claimed that A.H.T. has a mitochondrial *disorder*, one which was “significantly aggravated” by A.H.T.’s initial hepatitis B vaccination. Petition, ¶¶15-16. This claim appears to have been modified by petitioner’s post-hearing brief. Drawing from the headings in the brief, petitioner claims that A.H.T. has mitochondrial *dysfunction* (Petitioner’s Post-Hearing Brief [“Pet. Br.”] at 1-3), which was vaccine induced (*id.* at 3-10), entitling her to compensation (*id.* at 10-13). Likewise, Dr. Kendall’s expert report claimed that A.H.T. has a mitochondrial disorder, but in questioning Dr. Kendall, petitioner’s counsel primarily asked about “mitochondrial dysfunction.” For example, Dr. Kendall testified that A.H.T. had probable mitochondrial *dysfunction* (Tr. at 328-29), but her report referred to “clinical features and biochemical and enzymatic data in support of a mitochondrial *disorder*.” (Pet. Ex. 79 at 2497) (emphasis added).

The terms used to characterize A.H.T.’s condition varied throughout the post hearing brief, suggesting that petitioner thinks the terms mitochondrial disorder and dysfunction are interchangeable.⁷⁰ They are not. The distinction is significant, in that while respondent conceded that A.H.T. has laboratory evidence of some moderate mitochondrial dysfunction, respondent contends that such dysfunction is not responsible for A.H.T.’s clinical symptoms, and that it is unlikely A.H.T. has a mitochondrial disorder

⁶⁹ Hereinafter cited as “Verity, Res. Ex. K” or as the “PIND study” (Progressive Intellectual and Neurological Deterioration). Witnesses referred to this study either as “Verity” or “PIND.”

⁷⁰ Petitioner’s post hearing brief uses the terms mitochondrial “dysfunction” and “disorder” interchangeably throughout. See, e.g., header using “Mitochondrial Dysfunction” at 1; “mitochondrial disorder” at 1; citations to testimony about “mitochondrial dysfunction” at 2-3; citations to articles discussing mitochondrial disease at 3. I note that even Dr. DeMio agreed that the terms “mitochondrial disease” and “mitochondrial dysfunction” have different meanings. Tr. at 262-63.

or disease.⁷¹ Tr. at 471-501, 565-66; Respondent's Post-Hearing Brief ["Res. Br."] at 18-19. *Id.*

The most helpful information concerning the distinction between mitochondrial disorders and mitochondrial dysfunction came from Dr. McCandless. He defined primary mitochondrial disease as "a set of clinical abnormalities that directly result from mitochondrial dysfunction." Res. Ex. G at 2. In primary mitochondrial disease, there is evidence that the mitochondria do not function normally and there is a measurable clinical effect of the dysfunction. Tr. at 423, 564-66.

In testimony, Dr. Kendall defined a primary mitochondrial disorder as one "in which there is an alteration in a gene that alters a protein that is directly involved in energy production." Tr. at 396-97. In essence, she asserted that a defect in either mtDNA or nDNA is necessary to have a primary mitochondrial disorder or disease. Tr. at 397-98. Doctor McCandless agreed that the defect had to be one that "leads to a protein in the mitochondria that's not doing its job properly and that leads to the dysfunction," but he did not require that the defect be genetic. Tr. at 428. In a primary mitochondrial disorder, "the basic underlying problem is the mitochondrial structure or function is wrong from the beginning," leading to symptoms of mitochondrial disease. Tr. at 429.

According to Dr. McCandless, secondary mitochondrial defects exist when some other process causes dysfunction of the mitochondria, leading to symptoms. Tr. at 429. When dysfunction of the mitochondria is observed in a laboratory setting, there must be some evidence that the dysfunction also causes an identifiable clinical finding or symptom before the patient can be characterized as having a mitochondrial disease or disorder. Res. Ex. G at 2; Tr. at 428. In testimony, he clarified that one can infer from *in vitro* (laboratory) testing of tissue to what may happen *in vivo*, but there still must be some evidence of dysfunction in the body. This evidence may be test results or some clinical symptomology. He pointed to hypoxia or rotenone (a fish poison) as examples of an outside agent that could produce mitochondrial dysfunction. Tr. at 428-29.

Most of the few studies filed in this case focused on individuals with diagnosed mitochondrial disorders, rather than individuals with some evidence of mitochondrial dysfunction. Thus, the applicability of these studies to someone with mitochondrial dysfunction, rather than a mitochondrial disorder, is questionable. Additionally, although A.H.T. has been diagnosed with a probable mitochondrial disorder, the evidence supporting that diagnosis rests on the presence of certain symptoms, about which there are significant factual disputes. This may explain petitioner's shift in focus from mitochondrial disorder to mitochondrial dysfunction in petitioner's post hearing brief. And, as it is more difficult to establish how a vaccine can trigger a genetic condition

⁷¹ The parties' witnesses agreed that the terms "mitochondrial disorder" and "mitochondrial disease" were interchangeable. Tr. 264 (DeMio); 428 (McCandless). Doctor McCandless also testified that it is very important to clarify what people mean when they use the terms "disease," "disorder," and "dysfunction" in discussing mitochondrial problems. Tr. at 426-27.

present since birth, the focus on dysfunction rather than disorder eases, to some extent, petitioner's burden to prove that a vaccination can, more likely than not, be responsible for A.H.T.'s symptomology.

B. The Theories.

The causation theory identified in the amended petition—that mitochondrial disease can be aggravated by an outside event—builds on an observed characteristic of mitochondrial disorders that is not particularly controversial, even if it has not been well studied or documented. That is, the condition of individuals with mitochondrial disorders often worsens over time. This may occur gradually, or there may be abrupt regressions or decompensations that result in illness and/or the inability to perform motor or cognitive tasks once mastered. Pet. Ex. 79 at 2494; Res. Ex. A at 8; Res. Ex. G at 2; Tr. at 444-46, 588.

These regressions may occur without any apparent cause or may be temporally related to events such as viral or febrile illness, anesthesia, dehydration, surgery, and the use of some drugs, such as HIV medications and statins. Pet. Ex. 79 at 2494; Res. Ex. G at 4; Tr. at 392-93, 398, 572, 588-89, 608-09. Some of those who experience decompensation or regression return to baseline, some plateau, and in many, the loss of skills signals a downward spiral in the progression of mitochondrial disease. Unfortunately, many mitochondrial diseases are relentlessly progressive and ultimately fatal. Res. Ex. G at 2-3; see also Verity, Res. Ex. K at 435, 439 (noting that mortality rates of children with mitochondrial disease enrolled in this study were high, with 40 of the 112 children enrolled in the study beginning in 1997 having died by 2008).

In certain types of mitochondrial or metabolic disorders, there is a measurable physiological response that causes the decompensation. In individuals with urea cycle disorders, an illness (or dehydration due to an illness) may produce an excess of ammonia in the body, termed "hyperammonemia," resulting in a metabolic decompensation. See J. Kingsley, et al., *Immunizations for Patients with Metabolic Disorders*, PEDIATRICS, 118(2): e460-70 (2006), filed as Pet. Ex. 70, at e464 (hyperammonemic states are produced by breakdown of muscle tissue during periods of anorexia, such as may be seen in ill children) [hereinafter "Kingsley, Pet. Ex. 70"]; T. Morgan, et al., *Vaccines are not Associated with Metabolic Events in Children with Urea Cycle Disorders*, PEDIATRICS 127: e1147-53 (2011) [hereinafter "Morgan, Res. Ex. I" or the "Morgan study"] at e1148 ("children with [urea cycle disorders] are at high risk of devastating metabolic decompensation in the setting of acute childhood illnesses"). See also Tr. at 502-03 (Dr. McCandless discussing vaccinations in children with urea cycle disorders and the Morgan study).

Decompensation or regression occurs in other types of mitochondrial or metabolic disorders as well as in urea cycle disorders. A correlation has been drawn between metabolic stressors, such as illnesses and surgery, and periods of regression in these patients, based on a temporal relationship between such stressors and a regression or decline in health. This relationship has not been well documented, but it

appears to be generally accepted as a causal one. Res. Ex. G at 4; Tr. at 502-03. Fever, in particular, has been recognized as a stressor that can possibly aggravate a mitochondrial disorder, although fever in the absence of an illness has not been systematically studied. Tr. at 352, 392, 572; Pet. Ex. 61, pp. 2347-48. Several of the filed medical journal articles discussed the connection between fever, febrile illness, and decompensation. However, Dr. McCandless testified that it was the underlying illness, and not merely the febrile response to it, that was responsible for the deterioration. Tr. at 512-13, 572-73.

The lack of both specificity and strength in the association between illness and decompensation or regression has contributed to the uncertainty about the causal mechanism—that is, what is it about a fever or illness that causes the loss of skills? Not all individuals with mitochondrial disorders experience periods of decompensation with such stresses, and many experience such periods of decompensation even in the absence of metabolic stress.⁷² The same patient may experience an illness and lose skills, but handle the next several illnesses without any apparent regression. Tr. at 445-46, 590-91. The nature of the underlying mitochondrial disorder, the specific manifestation in a particular individual, the type of illness, and the nature of the regression are all factors affecting the response of a patient with a mitochondrial disorder to an illness. Whether the regression persists is also quite variable among and within the various types of mitochondrial disorders.⁷³

Both Drs. Kendall and McCandless testified about some of the theories regarding the causal mechanism for decompensation or loss of skills. Tr. at 352-53, 444-45. Petitioner's theory that a vaccine can cause onset of a dormant or underlying mitochondrial disease or cause long-lasting mitochondrial dysfunction was presented primarily by Dr. Kendall. This theory extends what is generally accepted about mitochondrial disorders in three specific ways. First, petitioner contends that an external event can trigger *onset* of a mitochondrial disorder that would otherwise have remained dormant, not simply cause regressions or loss of skills in individuals with a diagnosed or, at least suspected, mitochondrial disorder. Second, petitioner claims that a *vaccine*, not just an illness, can exacerbate, aggravate, or trigger this onset or cause mitochondrial dysfunction. Third, petitioner claims that this aggravation can cause the manifestation of symptoms, not only shortly after vaccination, but new symptoms

⁷² To illustrate the frequency of illness or regression, Dr. McCandless testified that observations over a period of several years of 100 hypothetical children with confirmed mitochondrial disease would show that somewhere between 40-60% of them would get sicker and stay sick longer than their siblings without mitochondrial disease when confronted with a cold or influenza, and that they would return to baseline more slowly than their siblings. Of those who got sicker, less than ten would have a severe or significant deterioration. Some of these might not return to baseline. However, not all illnesses would produce this effect of being sicker for longer, even in the small percentage of children who experienced a severe deterioration with illness. Tr. at 590-93. The response to illness may be cyclic, occurring several times in one year, and then not occurring at all in subsequent years. Tr. at 593-94.

⁷³ For example, Dr. Kendall testified that, in individuals who present with a mitochondrial encephalopathy, some improve, 20-30% experience severe progressive deterioration, and the remainder are stable with periodic ups and downs. Tr. at 338.

manifesting many months later. Petitioner attributed A.H.T.'s post vaccination irritability and constipation to aggravation of her mitochondrial disorder or causation of mitochondrial dysfunction, signaling some form of brain injury, and also contended that the behavioral symptoms and developmental delays that manifested more than 15 months later were likewise the result of this injury.

The medical witnesses petitioner presented did not agree on the specific nature and mechanism of the damage. During the hearing and in her post hearing brief, petitioner advanced Dr. DeMio's theory that ongoing "brain inflammation" was responsible for A.H.T.'s symptoms. The "brain inflammation" theory ostensibly incorporated most of Dr. Kendall's theory that a vaccination can trigger an underlying mitochondrial disorder, producing a loss of skills. However, Dr. DeMio also claimed that the initial insult of the hepatitis B vaccine produced inflammation in A.H.T.'s brain and this inflammation was responsible for A.H.T.'s early and later symptoms. Yet a third theory was proposed by Dr. Levinson—that A.H.T.'s symptoms were the result of oxidative stress as the result of the interaction of her underlying mitochondrial disorder and the immunological stress of the hepatitis B vaccine. This theory was not explicitly argued in the post hearing brief, but petitioner quoted a portion of Dr. Levinson's statement regarding this position in her post hearing brief. Pet. Br. at 10. Each of these theories, along with some of the evidence provided by respondent, is discussed in more detail below.

1. Doctor Kendall's Theory.

Doctor Kendall's expert report provided few details on her theory of causation. The portion of Pet. Ex. 79 that addressed causation was very short, only two paragraphs long. *Id.* at 2497. She referenced two medical journal articles as the support for her assertions.⁷⁴ When examined carefully, neither article provided substantial support and one contradicted her assertion that vaccines alone could cause or trigger a decompensation in a patient with a mitochondrial disorder.

Her testimony provided some of the details that her expert report lacked. She testified that A.H.T. had an underlying mitochondrial disorder, that the hepatitis B vaccination was "an immunological trigger" for her fever (Tr. at 352), which stressed her system, "outstrip[ped] the body's ability to develop energy for functionality" and primarily led to damage to her central nervous system. (Tr. at 353).

In terms of timing, she pointed to symptoms that developed between hours to days after the vaccination. Tr. at 353-54. Her theory accounting for the observed

⁷⁴ Petitioner's Ex. 69, which was also filed as Res. Ex. P, is primarily a case report. J. Poling, et al., *Developmental Regression and Mitochondrial Dysfunction in a Child with Autism*, J. CHILD NEUROL., 21(2): 170-72 (2008) [hereinafter "Poling, Pet. Ex. 69"]. Doctor Shoffner, the physician who diagnosed A.H.T. with a probable mitochondrial disorder, was one of the co-authors of this case report. The second journal article was filed as Pet. Ex. 68 and Res. Ex. Q: J. Shoffner, et al., *Fever Plus Mitochondrial Disease Could be Risk Factors for Autistic Regression*, J. CHILD NEUROL., 25 (4): 429:34 (2010) [hereinafter "Shoffner, Pet. Ex. 68"].

temporal link between illnesses and deterioration or regression in mitochondrial disease was based on the increased energy demands that such illnesses or stressors place on the body and the inability of impaired or defective mitochondria to meet those increased energy demands. Brain and muscle tissue require high levels of energy, and when illness increases the demands, the supply available to brain and muscle is reduced, resulting in lost motor and cognitive skills, among other symptoms. Tr. at 301, 303-04, 352.

This theory could account for the observation in Wolf and Smeitink, Court Ex. I, at 1402, that the presenting symptom in children with mitochondrial disorders is often neuromuscular in nature. However, it does not account for deterioration observed without an identifiable triggering event.

The specific mechanism of an energy deficit to account for clinical deterioration is less well accepted than the fact that regressions do occur. See Res. Ex. G at 4 (Dr. McCandless stating that the “strength and mechanism of any such association are not at all clear”); Tr. at 556-57 (discussing Dr. Kendall’s theory, another theory, and his opinion that both might contribute to diminished energy production in the mitochondria, along with other factors as yet unknown). Nevertheless, in this decision, I will assume, *arguendo*, that Dr. Kendall’s increased energy demand mechanism is correct. The difficulty comes in finding evidence, other than her very cursory opinion and testimony (Dr. Kendall’s direct examination, including establishing her qualifications to opine, encompassed only about 40 pages of testimony), to support the other contested aspects of her opinion.

a. Can a Dormant Mitochondrial Disorder Be Triggered by an External Event?

Doctor Kendall was unequivocal in stating that a vaccination does not cause alteration in a “genetic blueprint” or alter “the functionality of . . . protein structure.” Tr. at 334. She testified that an individual can “harbor either DNA changes or the propensity for these diseases and not exhibit them from the time of birth, for example.” Tr. at 303. Although she did not explicitly testify that an external trigger is *required* for an underlying mitochondrial disorder to manifest, she appeared reasonably certain that A.H.T.’s disorder was so triggered. Tr. at 352-54.

Other than Dr. Kendall’s opinion, there is little evidence in this record to suggest that a metabolic stressor can *trigger* a dormant or unrecognized mitochondrial disorder. The anecdotal evidence linking stress to a regression is based on what mitochondrial disease specialists have seen in their own patients (*see, e.g.*, Tr. at 557), necessarily implying that the mitochondrial disorder was already diagnosed or strongly suspected (*see also* Verity, Res. Ex. K, at 436 (reporting that 33 of the 112 participants diagnosed with mitochondrial disease had experienced an exacerbation of their condition “in association with fever or minor illness”)). Doctor McCandless testified that he could not recall any patient who was normal and then experienced a sudden decompensation (“crash and burn”) due to illness. Tr. at 608-09.

Relying on the anecdotal experience of one of her patients and Pet. Exs. 68-69, Dr. Kendall claimed that an event such as an illness could trigger a previously unrecognized mitochondrial disorder. She described an asymptomatic teenager who developed symptoms of a mitochondrial disorder (progressive muscular manifestations) after a severe case of influenza. Later, genetic testing disclosed a previously unsuspected mtDNA deletion syndrome. Tr. at 302-03. However, mitochondrial disorders can manifest at virtually any point in life, as Dr. Kendall acknowledged (see Tr. at 302-03), and thus this temporal relationship could be due to coincidence alone.

The Poling case report, filed as Pet. Ex. 69, was weak support for an external event acting as the trigger for a mitochondrial disorder. Doctor Poling, the lead author of Pet. Ex. 69, wrote the report about the experience of his infant daughter.⁷⁵ The child reportedly experienced symptoms of a developmental regression within 48 hours of a DTaP vaccination and more symptoms within five to 15 days of a measles vaccination administered at 19 months of age. Poling, Pet. Ex. 69, at 2 (factual presentation). The onset of neurological symptoms was within the periods for a DTaP Table encephalopathy (72 hours) and a measles Table encephalopathy (five to 15 days). See 42 C.F.R. § 100.3(a)(II)(B) and (a)(III)(B)(2011) (Vaccine Injury Table identifying encephalopathy as an associated injury for DTaP and measles vaccines and setting forth the time periods required). The child was eventually diagnosed with both autism and a mitochondrial disorder. Poling, Pet. Ex. 69, at 3.

Even though the Poling claim was compensated, a published decision in the case indicates that compensation was based on the presence of a Table injury, in which entitlement to compensation is legally presumed. *Poling v. Sec'y, HHS*, No. 02–1466V, 2011 WL 678559, at *1 (Fed. Cl. Spec. Mstr. Jan. 28, 2011) (fees and costs decision, noting that the case was compensated as a Table injury). Such a decision cannot be precedential under any circumstances, as decisions issued by special masters and judges of the Court of Federal Claims constitute persuasive, but not binding, authority. (*Hanlon v. Sec'y, HHS*, 40 Fed. Cl. 625, 630 (1998)), and certainly not in a case

⁷⁵ The familial relationship was not disclosed by Dr. Poling in the case report. Disclosure of possible conflicts of interest is expected when submitting a medical journal article for publication. Conflicts of interest are a matter to be considered when applying *Daubert*. In its opinion on remand in *Daubert*, the Ninth Circuit considered whether the matters an expert proposed to testify about flowed from research conducted independently of involvement in the litigation in question, noting that this factor provides objective proof that the research was conducted for scientific purposes. *Daubert v. Merrell Dow Pharmaceuticals*, 43 F.3d 1311, 1317 (9th Cir. 1995); see also *Exxon Shipping Co. v. Baker*, 128 S. Ct. 2605, 2626 n.17 (2008) (declining to consider research funded in part by a party to the litigation). The familial connection, and the fact that a vaccine injury claim for the child's injuries was compensated, were mentioned in a commentary on the Verity study, Res. Ex. K. See M. Sharrard, *Clinical presentation of mitochondrial diseases in children with progressive intellectual and neurological deterioration*, DEV. MED. & CHILD NEUROL., 52: 407-08 (2010) [hereinafter "Sharrard, Res. Ex. J"]. Sharrard stated that the child in this case report was described by her father as having "developed autistic features after vaccination and a subsequent febrile illness, and was later found to have a mitochondrial disorder." *Id.* at 407. Sharrard also indicated that the vaccine injury claim was successful. *Id.* I also note that Drs. Rossignol and Frye disclosed their potential conflict of interest in the article filed as Pet. Ex. 71.

involving a different vaccine (one without any associated Table injury), a different clinical presentation, and different timing.⁷⁶

As Dr. McCandless observed, information acquired through experience in which a causal connection between two events is inferred can be misinterpreted as proof of that causal connection. Tr. at 593. See *Paluck v. Sec'y, HHS*, 104 Fed. Cl. 457, 475 (2012) (noting that although “case reports ‘do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value’.... ‘case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.’” (quoting *Campbell v. Sec'y, HHS*, 97 Fed. Cl. 650, 668 (2011)); *Bast v. Sec'y, HHS*, No. 01–565V, 2012 WL 6858040, at *24, *28 (Fed. Cl. Spec. Mstr. Dec. 20, 2012), motion for rev. denied, 117 Fed. Cl. 104 (2014) (discussing the limited value of case reports); *THE REFERENCE MANUAL ON SCIENTIFIC EVIDENCE*, Federal Judicial Center, 2011(3d ed.) at 724 (noting that in determining medical causation, case reports “are at the bottom of the evidence hierarchy,” largely because they lack controls and thus do not provide the level of information or detail found in epidemiologic studies; nevertheless, they “may be the first signals of adverse events or associations that are later confirmed with larger or controlled epidemiological studies.”) *Id.* at 475. “[S]ome courts have suggested that attempts to infer causation from anecdotal reports are inadmissible as unsound methodology under *Daubert*.” *Id.* at 217 n.14 (citing *McClain*

⁷⁶ In the recent Federal Circuit decision in a mitochondrial disorder case, *Paluck v. Sec'y, HHS*, No. 2014–5080, 2015 WL 2403354, at *8-9 (Fed. Cir. May 20, 2015), the panel relied to some degree on the Poling case study in reversing the special master’s decision denying compensation. The panel also found that the special master and respondent had conceded the plausibility of the petitioner’s causation theory in *Paluck*. The Poling case settlement itself cannot be viewed as a concession that vaccines can trigger or aggravate mitochondrial disorders. Because the Vaccine Injury Table represents a blend of science and policy (*Shyface v. Sec'y, HHS*, 165 F.3d 1344, 1352-53. (Fed. Cir. 1999) (quoting legislative history acknowledging that the Table may provide compensation to some whose injuries are not vaccine-caused); *Shifflett v. Sec'y, HHS*, 30 Fed. Cl. 341, 345 (1994) (observing that Congress designed the Vaccine Injury Table to be “overinclusive.”); a settlement of a Table injury case cannot be viewed as a concession of Prong 1 of *Althen* in every case involving the same vaccine and injury. Rather, the Table makes actual causation irrelevant when an injury meets all the Table criteria. *Quinn v. Sec'y, HHS*, No. 90-0884V, 1992 WL 183197, at *6-7 (Fed. Cl. Spec. Mstr. July 15, 1992) (when the Table injury criteria for encephalopathy are met, the fact that the vaccine in question has never been shown to cause the injury resulting in the encephalopathy is irrelevant). And, even if a case meets the Table injury criteria, respondent may still defend on the basis of a factor unrelated, but only if the “factor unrelated” is not an idiopathic or unknown cause. § 13(a)(2)(A); *Snyder v. Sec'y, HHS*, 553 Fed.Appx. 994, 999-1000 (Fed. Cir. 2014) (presumption of causation in a Table encephalopathy case rebutted by a factor unrelated—evidence of genetic disorder known to cause seizure disorders). Moreover, a concession by respondent in one case does not constitute a concession in another, as science and medicine are not immutable, and evidence filed in one case may not be filed in another case. For example, a concession that the measles vaccine can cause an encephalopathy occurring within five to 15 days of a vaccination is not a concession that it can do so at times shorter or longer. *Shyface*, 165 F.3d at 1351 (quoting the legislative history of the Vaccine Act asserting that a similarity to conditions or time periods in the Table would not be sufficient to demonstrate vaccine causation). Here, respondent’s expert conceded that regression or decompensation had been observed to occur in conjunction with febrile or viral illness in those with mitochondrial or metabolic disorders. He did not concede that such events occurred in conjunction with a vaccination or that such illnesses could trigger or aggravate an underlying mitochondrial disorder or dysfunction.

v. Metabolife Int'l, Inc., 401 F.3d 1233, 1244 (1st Cir. 2005) (additional internal citations omitted).

Another study reported the “onset of clinical symptoms [seizures in both] was temporally associated with vaccination” in two of the 112 children in the study, which looked at children with severe progressive neurological impairments. Verity, Res. Ex. K (the PIND study) at 436. The authors noted that there was some evidence of a fever in one child and the other was febrile on admission and had evidence of a Norwalk viral infection at the time of onset. *Id.* at 436. However, the authors drew no conclusions regarding any role of vaccination, illness, or fever in the activation or triggering of the disorders.

No other evidence that illness could trigger a dormant mitochondrial disorder appears in this record.⁷⁷

b. Vaccination or Vaccination with Fever as a Triggering or Aggravating Event.

Assuming *arguendo* that a dormant mitochondrial disorder can be triggered, activated, or exacerbated by illness, can a vaccine, with or without fever, perform the same function as an illness?

Doctor Kendall’s opinion that a vaccination alone can exacerbate or trigger mitochondrial disease (see Tr. at 342-43 (testifying that when she was a biochemical geneticist in training, the fact that immunizations can cause “metabolic decompensations” was “pounded into us”)) represents a significant extension from what is generally accepted about the causes of such decompensations.⁷⁸ Doctor McCandless agreed that sometimes in training, students are told that they should be careful about giving vaccines to those with mitochondrial disorders, but added that there was no evidence to support that caution, and that “we’re probably doing a disservice to our trainees by saying that.” Tr. at 502. He noted that those with urea cycle disorders are prone to metabolic decompensations, and the only study to look at the relationship between vaccinations and decompensations in those with urea cycle disorders found no

⁷⁷ Doctor McCandless testified that “[i]n the laboratory, there’s all kinds of things you can do to samples to make the mitochondrial function abnormal.” Tr. at 567-68. However, the context of this testimony indicates that he was not referring to the trigger or activation of a primary mitochondrial disorder, but rather an external factor affecting the functioning of the mitochondria, causing a secondary mitochondrial problem. He explained that muscle biopsies performed on children with neurological injuries such as cerebral palsy often disclose “subtle abnormalities of mitochondrial dysfunction that in the final interpretation we don’t believe are the primary cause of their neurological disease . . . and so we believe that that is because there’s some secondary effect on the mitochondrial function.” Tr. at 569-69.

⁷⁸ Triggering a decompensation or regression in a previously asymptomatic individual is not necessarily the same as causing or triggering the loss of skills in a person in whom a mitochondrial disorder has already manifested.

evidence of any causal relationship.⁷⁹ He testified that he was unaware “of any evidence that would support a vaccine directly causing a decompensation and deterioration in an underlying mitochondrial disorder,” although he would not say it was impossible. Tr. at 505.

With the exception of a brief statement about the Poling case by the CDC director (who plays no role in Vaccine Act proceedings and whose specialty as a physician was not identified) filed as Pet. Ex. 83, there was no other evidence in this record that a vaccination alone, unaccompanied by a fever, could trigger the onset of clinical symptoms of a mitochondrial disorder.⁸⁰

According to Dr. McCandless, there is no evidence that a mitochondrial disease or a metabolic illness can be triggered or exacerbated by the hepatitis B vaccine. Tr. at 501-02. He indicated that the possibility that one could be was a topic of discussion, referring to the Shoffner and Poling articles (Pet. Exs. 68 and 69), but that “it’s not because those of us who actually do it are that worried about [it].” Tr. at 502.

Vaccination accompanied by a fever, as opposed to vaccination alone, seemed to play a more central role in Dr. Kendall’s causation theory, because, as she testified, there was more support for fever causing such regressions and there was support in *in vitro* studies⁸¹ for increased temperature adversely affecting mitochondrial function. Tr. at 303-04. The presence of fever helped explain why the theory of increased energy demands would apply to A.H.T.’s case and why the hepatitis B vaccination was the triggering event for her subsequent symptoms. See Tr. at 335 (testifying that the vaccination caused fever); 342, 352 (fever is a stressor in metabolic disorders); 343, 352 (unfiled *in vitro* studies associating heat with diminished energy production in mitochondria); 352-53 (damage as a result of the lack of energy producing central nervous system symptoms within hours to days).

Although this chain of events fits Dr. Kendall’s theory about the role of increased energy demands, there was little evidence to support her assertion that vaccination alone could activate or worsen a mitochondrial disorder. At best, there were articles mentioning the *possibility* that vaccines could exacerbate disorders involving inborn

⁷⁹ Doctor McCandless referenced the Morgan study, Res. Ex. I, for this point. Tr. at 503. He acknowledged on cross examination that this was a small study, like the others filed in this case, and characterized it as a pilot study, not a definitive one. Tr. at 516-17. He disagreed with petitioner’s counsel that the study showed a disproportionate number of adverse events (hyperammonemic episodes) after hepatitis B vaccinations than other vaccinations. Tr. at 518-22. He supported the conclusion of the study’s authors that additional research on vaccine safety in children with a variety of inborn errors of metabolism should be performed. Tr. at 521-22.

⁸⁰ Petitioner’s post hearing brief began with a quote from the former Director of the Centers for Disease Control and Prevention, Dr. Julie Gerberding, filed as Pet. Ex. 83, commenting on the Poling case. Pet. Br. at 1. The commentary was prefaced by Dr. Gerberding’s statement “I don’t have all the facts because I still haven’t been able to review the case files myself.” Pet. Ex. 83 at 2519.

⁸¹ None of these studies were filed. Tr. at 343.

errors of metabolism.⁸² The one study filed that actually examined the role of vaccination in metabolic decompensations contradicted her position that vaccines caused decompensations.⁸³

Even the support for vaccination accompanied by a fever as an aggravating event was scant. The Poling case report noted the presence of a fever. And, as the title of the Shoffner case study suggested, fever was a prominent factor in the causation analysis postulated by Dr. Shoffner. Doctor Kendall identified both of these articles as supportive of her opinion that the hepatitis B vaccine was responsible for A.H.T.'s condition. See Pet. Ex. 79 at 2497 (citing to the Shoffner and Poling articles in stating that A.H.T.'s "exposure to the [h]epatitis B vaccination aggravated a pre-existing condition with subsequent onset of clinical symptoms and regression" and noting that this process was "documented and reported by several groups, noting a precedent for this association"). I note the overlap of Dr. Shoffner as an author of both of the articles Dr. Kendall cited in support of her opinion, suggesting that the "several groups" cited were actually part of the same group.

The Shoffner article, Pet. Ex. 68, was not supportive of Dr. Kendall's opinion that a vaccine alone could trigger onset of a mitochondrial disorder. This very small study looked retrospectively at 28 patients with co-morbid diagnoses of autism and mitochondrial disease. Pet. Ex. 68 at 429. About 61% (17 of 28) of the children studied were said to have experienced an "autistic regression" ("defined as the loss of developmental skills that included speech, receptive skills, eye contact, and social interests in individuals")—a higher percentage of regression than commonly reported in those with ASD. *Id.* at 430. The authors also reported that 12 of the 17 children experienced an autistic regression within two weeks of a febrile episode. *Id.* Vaccination, without any associated fever, was not associated with regression. *Id.* at 431.

⁸² See, e.g., Kinsley, Pet. Ex. 70. The authors conducted a literature review to find recommendations for or against vaccination of children with specific types of inborn errors of metabolism. In most disorders, the full schedule of vaccinations was recommended, albeit with the caution to closely monitor for fever in some. See *id.*, Tables 1-4. Live viral vaccines were the only contraindicated vaccines and then only in those children with severe combined immunodeficiency disorders. *Id.*, Table 1.

⁸³ Morgan, Res. Ex. I, was a retrospective investigation to determine if children with urea cycle disorders had an increased risk of hyperammonemic episodes after vaccination. Patients with such disorders "typically experience recurrent hyperammonemic episodes (HAEs) during periods of excessive protein intake or catabolic stress. *Id.* at e1148. Petitioner quoted another sentence from this description of the rationale behind the study in her post hearing brief at 3: "Immunizations may mimic infections, causing similar, typically milder inflammatory and metabolic responses." Morgan, Res. Ex. I at e1148. However, this was a statement of the hypothesis being tested in the study, not the conclusions drawn from the evidence found. The authors found no evidence to support the hypothesis that childhood vaccine exposure triggers HAEs in children with [urea cycle disorders]." *Id.* at e1151. Hepatitis B was among the vaccines administered to the study population. *Id.* at e1149. The authors concluded that these results likely had reassuring implications for other medically vulnerable children, but recommended additional research focusing on vaccine safety with other inborn errors of metabolism, including mitochondrial disorders. *Id.* at e1152.

Doctor McCandless characterized the Shoffner study authors as saying that vaccines can cause inflammation, which in turn can cause autistic regression. Tr. at 503-04. He thought this hypothesis merited additional study, but that the Shoffner and Poling papers Dr. Kendall relied upon did not “really prove what they claim or purport to be proving. And, if you read them carefully, they’re not really claiming [a causal association].” Tr. at 504.

Aside from Dr. McCandless’ criticisms, I note that the Shoffner study relied upon a very small sample, making it difficult to assign it much weight.⁸⁴ Additionally, the lack

⁸⁴ In recent Vaccine Act cases, Federal Circuit judges have expressed concern about special masters’ reliance on small studies involving rare events, perhaps because the studies may not be sufficiently powered to detect the events being studied. *Paluck*, 2015 WL 2403354, at *8-9 (finding that the special master erred in determining a period of onset for symptoms of neurodegeneration using only articles and a case study containing very few participants, but relying on the Poling and Shoffner studies as evidence supporting *Althen’s* first prong); *Koehn v. Sec’y, HHS*, 773 F.3d 1239, 1243 (Fed. Cir. 2014) (questioning the special master’s reliance on a study insufficiently powered “to produce statistically significant results”). The “power” of a study to detect events is one factor in determining how much weight to give such studies. Reference Manual on Scientific Evidence, Federal Judicial Center, 2011(3d ed.) at 218-19. The concern about small studies expressed by the Circuit judges is one shared by special masters. However, in the traditional toxic tort case, plaintiffs rarely prevail without epidemiological evidence showing a relative risk (odds ratio) of 2 or greater, both to establish general causation (the “can it cause?” query) and that the toxic substance is more likely than not the responsible agent in the case at bar (the “did it cause?” query) by preponderant evidence. *Id.* at 217 n.14 (citing *McClain v. Metabolife Int’l, Inc.*, 401 F.3d 1233, 1244 (11th Cir. 2005) (additional internal citations omitted)). Toxic tort cases are very similar to Vaccine Act cases in the scientific subject matter, the lack of definitive proof of a substance’s effects on the human body, and in the application of the preponderant evidence standard. Unlike toxic tort litigation, a study involving an odds ratio of 2 or greater is rarely, if ever, seen in contested Vaccine Act causation in fact cases. Respondent routinely concedes causation or settles at close to full value in cases where the epidemiology is far less definitive. Cases involving influenza vaccine and Guillain Barré syndrome do not have epidemiology showing a relative risk greater than 2, but the vast majority of such cases are settled. See, e.g., *Jones v. Sec’y, HHS*, No. 14-1007V, 2015 WL 2359064, at *1 (Fed. Cl. Spec. Mstr. Apr. 23, 2013) (typical of settlements routinely seen in influenza-Guillain Barré cases). Respondent has agreed to settle cases where the available proof of vaccine causation is even lower. See, e.g., *Tompkins v. Sec’y, HHS*, No. 10-261V, 2013 WL 3498652, at *2 (Fed. Cl. Spec. Mstr. June 21, 2013), *motion for rev. denied*, 117 Fed. Cl. 713 (2014) (recounting the procedural history of the execution of a settlement agreement in the case (rendered void by the death of the vaccinee from unrelated causes)). *Tompkins* later proceeded to hearing on petitioner’s causation in fact claim, and in the subsequent decision, I ruled that petitioner had failed to produce preponderant evidence, based in part on the epidemiological evidence regarding both influenza and tetanus vaccines and the lack of a causal association of the tetanus vaccine with Guillain Barré syndrome.

In a Program where *Daubert* is not used to exclude evidence or experts, causation of rare conditions is often alleged, and there is little evidence on general and specific causation other than opinions. Special masters often discuss the evidence filed and relied upon by a party as a part of their statutory mandate to consider the record as a whole. They may accept less definitive epidemiology as some support for a causation opinion, but rarely does a special master rely upon epidemiology alone. Evidence from small studies may be the only evidence available to support or undercut an opinion on causation. When there is no support for a causation theory other than the expert’s own *ipse dixit*, a judge in another court may refuse to admit the testimony (*Joiner*, 522 U.S. at 146) (citing *Daubert*, 509 U.S. at 589), but a special master is not similarly constrained by the federal rules of evidence. In the OAP test cases, the special masters heard evidence from the petitioners on theories that other state and federal courts refused to admit, based on *Daubert* and *Frye v. United States*, 293 F. 1013 (D.C. Cir. 1923). See *Blackwell v. Wyeth*, 971 A.2d 235 (2009); *Doe v. Ortho-Clinical Diagnostics, Inc.* 440 F. Supp. 2d 465

of explanation of the methodology used makes reliance on the study problematic. The Shoffner paper did not clearly indicate when mitochondrial disease was diagnosed in the patients; thus, it is impossible to determine if the autistic regression occurred prior to or after the onset of mitochondrial disorder symptoms or diagnosis. See Tr. at 598 (Dr. McCandless commenting that the article did not explain how or when the mitochondrial disorder diagnosis was made). The Shoffner study did not reflect whether the regression was reported contemporaneously, was pulled from later histories in the participants' medical records, or was elicited from interviews of the study participants' parents.⁸⁵ It appears from comments about the group with fever that either a records review or some form of interview was conducted.⁸⁶ Shoffner, Pet. Ex. 68, at 431.

The authors of the Shoffner study acknowledged some limitations themselves. They "did not investigate changes that could be important in the induction of regression such as dehydration, hypoglycemia, decreases in substrate ability to oxidative phosphorylation, and other metabolic abnormalities such as fatty acid oxidation

(M.D. N.C. 2006); *Redfoot v. B.F. Ascher & Co.*, No. C 05-2045 PJH, 2007 WL 1593239 (N.D. Cal. June 1, 2007).

I emphasize that I am not requiring epidemiological evidence in this (or any other) case, but I must consider the epidemiological evidence the parties filed as part of the statutory requirement to consider the evidence as a whole. When two well-qualified experts testify contradictory to one another on vaccine causation, support (or lack thereof) in the scientific literature is one factor identified in *Daubert* itself as a matter to consider in deciding if the expert testimony is reliable. *Daubert*, 509 U.S. at 596; see also *Caves v. Sec'y, HHS*, 100 Fed. Cl. 119, 133-34 (2011) (an expert may testify without medical literature support the opinion, but such experts are rarely persuasive)

⁸⁵ In the OAP test cases, considerable doubt about the validity of later-reported regressions was noted, particularly in view of the widespread information about the purported link between MMR vaccines and onset of autistic symptoms or loss of skills. *Dwyer*, 2010 WL 892250, at *36, n.163, *169; *Snyder*, 2009 WL 332044, at *44, *137. In my own experience as a special master, with close to 1700 autism cases on my docket, I have read medical records of many children who reportedly experienced an autistic regression at a particular time, usually proximate to a vaccination, as reported in a later history, the petition, or affidavits. When the contemporaneous medical records and histories more proximate to the events in question were examined, the regression, if any, did not occur as reported in the vast majority of cases. Conflation of events to place their occurrence close in time to a possible cause has been quite common in the OAP cases, although, with rare exceptions, it does not appear that the conflation was deliberate. See *Hodges v. Sec'y, HHS*, 9 F.3d 958, 961 (Fed. Cir. 1993) (noting that Congress contemplated the special masters would use their accumulated expertise in the field of vaccine injuries to judge the merits of individual claims). Using parental recall to establish that a regression occurred instead of contemporaneous medical records reporting such a regression is a significant flaw in the methodology. Based on the information provided in the Shoffner paper, Pet. Ex. 68, it is impossible to determine what the authors relied on to determine that a regression had occurred in close temporal proximity to a febrile episode.

⁸⁶ The reference to the degree of fever includes the qualifier "as reported by parents," which could mean interviews as a part of the study, a review of contemporaneous records, or a review of later histories in the medical records. However, the authors also commented that the "precise fever duration was difficult to ascertain because patients were usually managed in the home." Shoffner, Pet. Ex. 68, at 431. This comment suggests that the presence or absence of fever around the time of regression was based on parental recall.

dysfunction.” Shoffner, Pet. Ex. 68 at 432. The authors also commented: “In our patients with mitochondrial disease and autism spectrum disorders, the vaccines did not appear related to the neurological regression.” *Id.* Thus, this article is a thin reed upon which to hang Dr. Kendall’s opinions that vaccines, with or without fever, can trigger onset of a mitochondrial disorder or cause mitochondrial dysfunction.

c. Logical Connection and Timing.

Moving from theory to the logical connection between vaccination and onset of A.H.T.’s symptoms, Dr. Kendall testified that A.H.T.’s irritability and inconsolability were evidence that she experienced “some encephalopathy, some altered neurological change” after the vaccination Tr. at 329-30, 334-35. She did not explain how this encephalopathy could be followed by apparently normal growth and development, with onset of behavioral symptoms many months later. On cross examination, she acknowledged that irritability and inconsolability were non-specific symptoms that could be caused by factors other than an encephalopathic event. Tr. at 336. In response to my questions, she agreed that they might represent symptoms of colic, rather than an encephalopathy reflecting some brain injury. Tr. at 383.

Her conclusion that the vaccination triggered or otherwise activated A.H.T.’s underlying mitochondrial disorder appeared to focus on the lack of any other explanation for her symptoms. When asked if A.H.T.’s “reaction to the [h]epatitis B vaccination was the triggering event for this child that caused her to become symptomatic,” she testified that “certainly there does not seem to be any other mechanism in place, and what I mean by that is there’s no other documented illness, there’s no other documented trigger, and there certainly seems to be no period of normalcy, as was kind of explained in detail by a lot of the questions posed to [A.H.T.’s] parents and other witnesses. So, yes, it appears that that was an aggravating event for her.” Tr. at 330-31. The lack of any other cause and a presence of a temporal connection are not sufficient to establish that the vaccine was responsible, either separately or together. See *Lalonde*, 746 F.3d at 1341 (“a temporal correlation alone is not enough to demonstrate causation”) (citing *Moberly*, 592 F.3d at 1323); *Hibbard v. Sec’y, HHS*, 698 F.3d 1355, 1366 (Fed. Cir 2012) (rejecting the assertion that lack of any other identified cause can demonstrate vaccine causation, even when the vaccine in question has been associated with the injury claimed and the temporal relationship is appropriate).

Although Dr. Kendall did not specifically testify that the autistic-like symptoms and developmental delays that A.H.T. demonstrated 15-17 months after vaccination were also caused by activation of the underlying mitochondrial disorder, the last two paragraphs of her expert report so indicate. Pet. Ex. 79 at 2497; see also Tr. at 329-30. Because these symptoms occurred so long after the vaccination, they must derive from an injury that occurred shortly after the vaccination in order to find the vaccination responsible, based on her “hours to days” testimony on timing. Whether this is the result of the “activation” or triggering of the mitochondrial disorder or of some damage

(see Tr. at 330) caused by the initial activation was not set forth clearly in testimony or expert report.

Appropriate timing, like the rest of Dr. Kendall's causation theory, is based on the Poling and Shoffner articles. However, there are many significant differences between the facts of A.H.T.'s case (even accepting the facts relied upon by petitioner and Dr. Kendall) and those of the Poling child and the children discussed in the Shoffner article. Not only were there differences in the timing of onset (A.H.T.'s autistic-like symptoms occurred long after the vaccination) and the strength of the mitochondrial diagnosis, both articles discussed "autistic regression," and Dr. Kendall agreed that A.H.T. did not experience an autistic regression at any point. Tr. at 350-55; see also Res. Ex. G at 2 (Dr. McCandless discussing Dr. Kendall's reliance on these two journal articles and noting that the medical records show no deterioration in A.H.T.'s neurological status, loss of developmental milestones, or any plateau in A.H.T.'s neurological development).

2. Brain Inflammation Theory.

Petitioner's reliance on the brain inflammation theory discussed by Dr. DeMio did not become clear until late in the hearing. During his cross-examination of Dr. Wiznitzer, Mr. Downing attempted to clarify petitioner's causation theory. He initially indicated that the hepatitis B vaccine produced systemic inflammation, based on the presence of the fever. Tr. at 678-81. In response to a clarifying question by Dr. Wiznitzer, Mr. Downing indicated that brain inflammation was a necessary part of the theory. Tr. at 682. It does not appear that brain *inflammation* was part of Dr. Kendall's theory (or a part of the medical literature upon which Dr. Kendall's theory was based). The term "brain inflammation" was never used by Dr. Kendall in her testimony. The closest she came to talking about inflammation of any kind was in response to a question:

Q: Dr. Kendall, is it biologically possible for an immunological or inflammatory trigger to aggravate an underlying latent mitochondrial issue to the point where the individual becomes symptomatic?

A: Yes.

Tr. at 303. However, the causal mechanism she identified as causing the injury was not inflammation itself; it was inability of the defective mitochondria to cope with increased stress, causing some unspecified form of damage. Tr. at 352-53. Some of the stressors that she identified as possible triggers of a mitochondrial regression, which included surgery and certain drugs, would be unlikely causes of brain inflammation.

The "brain inflammation" theory has its roots in the testimony of Dr. DeMio, but it was not explicitly raised in his February 2012 statement. In that statement, he commented that he had treated A.H.T. for numerous medical problems, "including those of the central nervous system, metabolism, the immune system, and the gastrointestinal system." Instead of the term "brain inflammation," he opined more generally that she had "brain damage." Pet. Ex. 62 at 2356. However he did not offer any theory as to

how the brain damage occurred. He merely described the temporal relationship as “an appropriate time course.” *Id.* at 2357. In view of the alleged regression when A.H.T. was one week old and onset of ASD-type symptoms at around 18 months of age, some further explication of the lengthy temporal relationship was necessary.

Doctor DeMio’s statement paid lip service to the mitochondrial disorder diagnosis by attributing improvement in the many problems he identified (“abnormally low ability to do intellectual tasks, . . . abnormal thinking . . . cannot function normally in settings with family and peers, . . . abnormal gait, . . . abnormal play and social interactions, . . . abnormal obsessions, . . . abnormal oppositionality”) to the “mitochondrial treatment” she received. Pet. Ex. 62 at 2356-57 (setting out four bullet points, each concluding that some aspect of A.H.T.’s medical issues had improved with mitochondrial treatment). However, his earlier opinions and treatment of A.H.T. had focused on the inflammation caused by toxins and presumed immune issues that are central to a biomedical approach to treating autism symptoms,⁸⁷ and mitochondrial treatments such as those A.H.T. received would not likely improve either inflammation or immune system problems. Indeed, as the two mitochondrial specialists acknowledged, the available treatment for mitochondrial disorders does not improve symptoms of those disorders in most cases. Tr. at 375-77, 460-61; see also Pet. Ex. 61, pp. 2347-48.

Doctor DeMio likewise adopted the mitochondrial disorder diagnosis, but the adoption was perfunctory. Tr. at 217 (stating that he agreed with the diagnosis). He devoted far more of his testimony to his position that the initial vaccination caused encephalopathy and brain damage that was inflammatory in nature or immune-based. He testified: “I mean, she had brain damage, and I’m convinced there was inflammation there, and I still am because the treatment that we’ve done [has] been helpful for her.” Tr. at 224. He stated that there was “no doubt in my mind” that A.H.T. had brain inflammation and was “close to 100-percent sure that’s what happened with her. I think it’s a part of her encephalopathy. She has immune dysfunction and cognitive dysfunction, and so part of that I think really speaks to that issue of inflammation at the level of the brain.” Tr. at 246. He later testified that “I think she has OCD from immune dysfunction that causes autoimmunity to the brain, including brain inflammation.” Tr. at 252. He added that she had metal toxicity as well, based on testing and clinical symptoms. *Id.* He also testified that her “immune system’s pretty sick.” (Tr. at 220).⁸⁸ The immune system references may explain his 2012 use of IVIG in treating A.H.T. about a year after her diagnosis and the subsequent initiation of treatment for a mitochondrial disorder. As IVIG is used in treating autoimmune, inflammatory, or immune system problems, rather than mitochondrial disorders, his use of it in treatment

⁸⁷ His early treatment of A.H.T. focused on chelation for toxic metals, suspected autoimmune problems, and treatment with an antiviral drug (Valtrex) for presumed immune problems. See Pet. Ex. 23, p. 236-37.

⁸⁸ Although Dr. DeMio testified that he saw a lot of immune and metabolic issues in A.H.T. on testing (Tr. at 211-12), he did not also point to specific tests that demonstrated those problems. He testified that she had “issues eventually with organisms like yeast and viruses” and had “accumulated a lot of metal toxins.” *Id.*

likely reflected his continuing focus, not on mitochondrial dysfunction, but on immune dysfunction.

Doctor McCandless took issue with the brain inflammation theory. Although the irritability A.H.T. displayed could be consistent with brain inflammation, most mitochondrial encephalopathies do not have a great deal of inflammation associated with them. Tr. at 456.

3. The Oxidative Stress Theory.

Because he did not testify, Dr. Levinson's opinions are drawn only from his February 2012 statement. His opinion, which postulated that A.H.T. had an immune and inflammatory response to the initial vaccination, producing oxidative stress on the mitochondria (Pet. Ex. 59 at 2), is not precisely the theory presented at the hearing. Nevertheless, petitioner quoted a portion of his statement in her post-hearing brief. Pet. Br. at 10.

Doctor Levinson attributed the "central nervous symptoms" A.H.T. displayed to the initial vaccination, and I have considered his opinion in my decision on causation, in spite of its similarity to the oxidative stress caused by mercury theory advanced and rejected in the Theory 2 OAP cases. See, e.g., *Dwyer*, 2010 WL 892250, at *115.

Like Dr. DeMio, Dr. Levinson's opinions conformed to what he was told by A.H.T.'s parents. He opined that the hepatitis B vaccine caused A.H.T. to have a fever, that "mitochondria are the major generators of body heat" and the "inflammatory and immune response" produced by the vaccination was a "catalyst in the development of mitochondrial disorder" by virtue of the oxidative stress caused by the vaccination. Pet. Ex. 59 at 2337. He stated that "it is more likely than not that the vaccination . . . provoked an immune and inflammatory response [which] served as an environmental trigger providing excessive oxidative stress to the mitochondria. This led to [A.H.T.] manifesting central nervous system symptomology as a direct result of a vaccine-induced mitochondrial dysfunction." *Id.*

Although the oxidative stress in the OAP test cases was alleged to have been caused by a mercury-based preservative in some vaccines, rather than by the vaccines themselves, the source of the stress was unimportant in the theory presented. The purported causal relationship between oxidative stress and ASD was thoroughly debunked by the true experts on oxidative stress called by respondent. See, e.g., *Dwyer*, 2010 WL 892250, at *115. Doctor Levinson provided no medically or biologically plausible, much less probable, explanation of how oxidative stress could cause or trigger either an underlying mitochondrial defect or autism-like symptoms themselves. In terms of timing, he indicated that a fever could be produced "immediately following immunization," and implied that the fever caused mitochondria to become "extremely active," with the inflammatory and immune response to the vaccination becoming the catalyst for A.H.T.'s mitochondrial dysfunction. Pet. Ex. 59 at 2337.

Neither of the two mitochondrial disease specialists provided any real support for the oxidative stress theory. Doctor Kendall discussed *oxidative phosphorylation* (OXPHOS) with regard to the electron transport chain activity in the mitochondria (see, e.g., Tr. at 318, 343, 352), but she never even hinted that “oxidative stress” played a role in mitochondrial disorders.

Doctor McCandless probably provided the most support for Dr. Levinson by acknowledging that fever can cause increased energy consumption, which results in “increased flux through the system,” which is one definition of oxidative stress. Tr. at 515. The other definition, increased production of reactive oxygen species, is not an effect of fever. *Id.* Clearly, Dr. McCandless did not accept that this increased flux of metabolites through the respiratory chain could be responsible for a mitochondrial disorder or cause mitochondrial dysfunction, as he indicated that many things cause such increased metabolic stress, including “eating a meal [and] breathing air pollution.” Tr. at 513-14.

Doctor McCandless also explained that the use of coenzyme Q10, a powerful antioxidant, prescribed to treat some mitochondrial disorders, is not evidence that such disorders are caused by oxidative stress. He commented that it is rarely effective in treating mitochondrial disorder patients, other than those who have a specific Q10 deficiency. Tr. at 465-66. Testing performed on A.H.T. did not disclose a Q10 deficiency. Pet. Ex. 26, pp. 522-24.

C. The Lack of Factual Predicates.

Although some of the problems with petitioner’s theories are addressed above, the factual disputes in this case are so substantial that I turn first to resolving the facts in dispute before applying *Althen* and *Pafford* to determine if petitioner has met her burden to prove that A.H.T.’s hepatitis B vaccinations were the but-for cause and a substantial factor in her initial symptoms and subsequent ASD-like behaviors. *Shyface*, 165 F.3d at 1352-53.

V. Resolution of Factual Conflicts.

The causation theories summarized above are based on certain predicate facts concerning A.H.T.’s symptoms and diagnosis. An expert’s opinion is only worth as much as the facts upon which it is based. *Dobrydnev v. Sec’y, HHS*, 566 Fed.Appx. 976, 982-83 (Fed. Cir. 2014) (citing *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993)); *Fehrs v. United States*, 620 F.2d 255, 265 (Ct. Cl.1980).

In this section, I set forth the evidence, identify conflicts, and make findings of fact. Where necessary, I explain the rationale for the factual findings, and discuss the effect of these factual findings on the causation opinions.

A. Introduction and Legal Standards.

Determining what happened after A.H.T.'s vaccinations and what symptoms of a mitochondrial disorder or dysfunction that she actually displayed involves resolving the same issues present in many Vaccine Act cases: the contemporaneously created medical records differ from the testimony and affidavits of parents, family members, and others on several points.

Two general legal principles guide the resolution of conflicts between contemporaneous records and later-adduced evidence. The first is that the absence of a reference to specific symptoms in a medical record does not conclusively establish the absence of symptoms during that time frame. See, e.g., *Murphy v. Sec'y, HHS*, 23 Cl. Ct. 726, 733 (1991), *aff'd*, 968 F.2d 1226 (Fed. Cir. 1992) (“[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance” (citation omitted)).

The second principle addresses the degree of reliance commonly accorded to contemporaneous records. Special masters frequently accord more weight to contemporaneously-recorded medical symptoms than those recounted in later medical histories, affidavits, or trial testimony. “It has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.” *Murphy*, 23 Cl. Ct. at 733 (citation omitted); see also *Cucuras v. Sec'y, HHS*, 993 F.2d 1525, 1528 (Fed. Cir. 1993) (medical records are generally trustworthy evidence). Memories are generally better the closer in time to the occurrence reported and when the motivation for accurate explication of symptoms is more immediate. *Reusser v. Sec'y, HHS*, 28 Fed. Cl. 516, 523 (1993). Inconsistencies between testimony and contemporaneous records may be overcome by “clear, cogent, and consistent testimony” explaining the discrepancies. *Stevens v. Sec'y, HHS*, No. 90-221V, 1990 WL 608693, at *3 (Fed. Cl. Spec. Mstr. Dec. 21, 1990).

The factual findings set forth below are drawn from the testimony and other evidence with these legal principles in mind. For the reasons stated, I place more weight on the contemporaneously created records, medical histories, and other documents created closer in time to the events in controversy than on the testimony of A.H.T.'s family members and friends.

The facts in controversy primarily concern whether A.H.T. experienced a fever after her initial vaccination; the nature and diagnostic significance of other symptoms arising after vaccination; and whether A.H.T. truly had the symptoms relied upon in diagnosing her probable mitochondrial disorder. The parties disagree whether A.H.T. had such symptoms to the requisite degree or, indeed, at all.⁸⁹

⁸⁹ In her post hearing submission, petitioner asserted that Dr. Kendall identified “15 different subjective and objective criteria” of a mitochondrial disorder present in A.H.T. Pet. Br. at 1-2. See also Tr. at 300-01, 307-24, 376. However, this section of my decision addresses the presence or absence of the conditions used by Dr. Shoffner to arrive at a diagnosis of a “probable mitochondrial disorder” in August 2011, rather than those referenced by Dr. Kendall as possibly related to such a disorder. Because

It is petitioner's contention that A.H.T. had a febrile response to her initial hepatitis B vaccination. The fever activated an underlying mitochondrial disorder, triggering the onset of temperament changes, sleeping difficulties, problems with breastfeeding, and gastrointestinal dysfunction. Later alleged manifestations of the triggered mitochondrial dysfunction include developmental delay and behavioral problems variously diagnosed as sensory integration disorder, regulatory disorder, and ASD.

I discuss the evidence regarding the early problems that are alleged to have been caused by the hepatitis B vaccination in Part B, and make factual findings in Part C. I address the mitochondrial disorder diagnosis and related factual issues in Part D, followed by the factual findings in Part E.

B. Evidence of Symptoms Arising Shortly After Vaccination.

Petitioner and Mr. Tipton asserted that, shortly after the initial hepatitis B vaccination, A.H.T. had a fever, changed her sleeping patterns, began to arch her back and cry inconsolably, experienced constipation, and developed problems with nursing.⁹⁰ Tr. at 20-24, 57-58 (Ms. Holt); 129-30 (Mr. Tipton). Petitioner's primary expert, Dr. Kendall, referred to these reported changes as a "regression," although she seemed somewhat equivocal about that characterization during her testimony. See Tr. at 350-51, 380-81; *but see* Tr. at 457-58 (Dr. McCandless finding no evidence in the medical record of a regression). Some of these changes are well-documented. Others are not.

In contrast to Dr. Kendall's characterization of the reports of behavioral changes, both Drs. Wiznitzer and McCandless testified that a baseline for feeding and sleeping in an infant takes days to a few weeks to establish, and that the changes from the relatively calm and placid course of the first few days after birth to the much more difficult infant after the first week was part of A.H.T.'s transition from the intrauterine to the extrauterine environment, and that the changes did not constitute a regression. Tr.

mitochondrial disorders can produce very diverse symptoms in many body systems, the intensity or nature of the symptom is significant when considering a mitochondrial disorder diagnosis. For example, Dr. McCandless contrasted the constipation often experienced by children (and particularly those children with restricted eating patterns and developmental delays—a description applicable to A.H.T.) with the severe gastrointestinal motility problems that suggest a mitochondrial disorder. Tr. at 553. Thus, Dr. Kendall's recitation of a laundry list of symptoms that might be consistent with a mitochondrial disorder is not particularly helpful in establishing a diagnosis for A.H.T.

⁹⁰ Mr. Tipton, Mrs. Dunn, and Mrs. Christy Holt also described a change in A.H.T.'s eye contact within a few days after the vaccination, indicating that she was looking off into the distance, and not focusing on those holding her. See, e.g., Tr. at 91; 109, 114, 163, 168, 170. However, Dr. Wiznitzer, a board certified pediatrician and pediatric neurologist, testified that a newborn cannot turn her head and localize to a sound and that good eye contact does not develop until one to three months of age. Tr. at 628. Doctor McCandless, a board certified pediatrician, testified that newborns do not fix their eyes on something and follow movements. Tr. at 452. In view of this un rebutted expert testimony, I have accorded little weight to the family members' observations regarding any change in eye contact shortly after the initial vaccination.

at 451-53, 547-49, 627-28, 652. Doctor Wiznitzer explained that a newborn's reactions to life outside the womb evolve over the first few weeks of life, and that the changes in A.H.T. were normal aspects of this transition and attributable to the colic⁹¹ diagnosed by all three of the physicians who saw her in the first six months of her life. Tr. at 627-29. Doctor McCandless expressed similar opinions. Tr. at 451-53, 548; Res. Ex. G at 2.⁹²

I first set forth the evidence supporting petitioner's claims, followed by contemporaneous documentation, histories, and medical opinions.

1. Testimony and Affidavits.

Both Ms. Holt and Mr. Tipton were present at the pediatric visit on April 4, 2002, when the initial hepatitis B vaccine was administered. Mr. Tipton testified that they discussed the hepatitis B vaccine with Dr. Buttlemann, who told them that the vaccine was safe and that A.H.T. might run a fever, which could be treated with Tylenol. Tr. at 111.

According to Ms. Holt, A.H.T. "slept hard" the day of the vaccination, was warm to the touch⁹³ and ran a "low grade" fever, which Ms. Holt defined as a fever between 100-102° Fahrenheit.⁹⁴ She was "very groggy" and did not wake periodically to nurse as she had before the vaccination; Ms. Holt described her as "lethargic." Tr. at 19-21. Mr. Tipton indicated that she was running a "low-grade" fever shortly after the vaccination, slept for a very long period of time, and screamed "bloody murder" when she did wake up. Tr. at 111-13. Mrs. Dunn testified that she received a telephone call from Ms. Holt a few days after the vaccination, reporting worries about A.H.T.'s fever. Tr. at 90. According to Ms. Holt and Mr. Tipton, the fever persisted for several days following the vaccination. Pet. Exs. 1 at ¶ 7-9; 2 at ¶ 7-9; Tr. at 20-22, 27, 125-26.

⁹¹ Infantile colic is "benign paroxysmal abdominal pain, usually in the first three months of life." DORLAND'S at 383. It can produce long periods of intense, inconsolable crying. *Id.*

⁹² Petitioner's counsel did not precisely object to this testimony, but did express his opinion he was being "ambushed," in that this opinion was not expressly stated in Dr. Wiznitzer's report, Res. Ex. A. Tr. at 653-56. As Dr. McCandless had made the same point in his expert report (Res. Ex. G at 3), petitioner's counsel was not being sandbagged with a new theory. I indicated at the time of the comment that Dr. Kendall and Dr. McCandless were both trained as pediatricians, and could be called to contradict Dr. Wiznitzer's testimony if his assertions were truly in controversy. Neither was recalled to testify.

⁹³ The description "warm to the touch" also appears in ¶ 7 of both Ms. Holt's and Mr. Tipton's affidavits, which were filed in September 2011. Pet. Exs. 1, 2. The affidavits do not mention a specific temperature or even that A.H.T.'s temperature was taken. *Id.*

⁹⁴ Just a few moments later, Ms. Holt testified that she "did not recall" A.H.T.'s exact temperature, but was sure she had a fever. Tr. at 21. She could not recall the highest temperature A.H.T. had. Tr. at 53. She and Mr. Tipton were taking A.H.T.'s temperature initially by placing the thermometer under her arm, but were not sure they were doing it correctly. By April 9, they were taking her temperature rectally. Tr. at 52-53. Mr. Tipton testified that the initial temperature reading from A.H.T.'s armpit was close to 100°. Tr. at 113.

Ms. Holt testified that the day and evening of the vaccination, A.H.T. required stimulation to stay awake while nursing. She described A.H.T.'s eyes as "glazed and unfixed." Tr. at 20. The lethargy continued into the following day, when A.H.T. had several extended family members visit. Tr. at 21-22; 54, 56; 91.

A.H.T.'s parents testified that the Saturday night after the vaccination, she began frantic, inconsolable crying, with high pitched screaming that lasted the entire night, and did not stop until Sunday. Tr. at 22-23, 56. Ms. Hunter testified that Ms. Holt called her and reported the screaming, but she was not specific about when the telephone call occurred. During the telephone call, she could hear A.H.T. screaming in the background. Tr. at 145.

Mrs. Christy Holt's account differs from those of A.H.T.'s parents and grandmother. She testified that she visited A.H.T. shortly after the vaccination. In contrast to the somnolence described by A.H.T.'s parents, she described A.H.T. as very fussy and uncomfortable. Tr. at 161. She did not recall A.H.T. running a fever, but remembered that she was very upset and could not be consoled. *Id.* She also described a very high-pitched, loud, and constant scream (Tr. at 162).

A.H.T.'s parents and family members testified that her inconsolable crying and screaming persisted for months. Tr. at 63, 91-92, 102-03, 145. When asked if Dr. Buttleman had ever observed the inconsolable crying at an office visit, Ms. Holt indicated that car rides seemed to put A.H.T. to sleep, intimating that A.H.T. was not screaming during her office visits with Dr. Buttleman. Tr. at 82.

According to Ms. Holt and Mr. Tipton, A.H.T.'s sleep pattern never returned to the 18-20 hours per day she slept before the vaccination. Ms. Holt described A.H.T. as being awake 17-18 hours per day, with brief catnaps accounting for the remaining hours, and requiring hours of swinging and rocking to get her to sleep at all. Tr. at 24, 32; see *also* Tr. at 91-92 (testimony of grandmother, Mrs. Dunn, regarding poor sleep and inconsolable crying).

Ms. Holt testified that, despite thinking that something was seriously wrong on Saturday evening, they did not take A.H.T. to the emergency room because Dr. Buttleman had told them to call her before going to the emergency room.⁹⁵ Tr. at 57-58. Mrs. Dunn also felt that something was wrong at some point, but could not recall encouraging A.H.T.'s parents to take her to the hospital. Tr. at 98.

Ms. Holt also described A.H.T. as having problems with latching on to the breast that she had not displayed prior to the vaccination. Tr. at 22-23. She explained that A.H.T. would simply mouth or gum the breast, but did not have a secure latch. Tr. at 23, 34. However, on cross-examination, Ms. Holt testified that A.H.T. was able to nurse

⁹⁵ Ms. Holt also testified that A.H.T. experienced jerking episodes that would awaken her and that these episodes also occurred during fits of screaming. She indicated this was a reason she did not take A.H.T. to the emergency room. Tr. at 57-58.

to get the “foremilk,” but had difficulty in “taking in” the “hind milk” (Tr. at 54-55), suggesting that the problem was not an inadequate latch, but perhaps the length of time nursing. She reported that between A.H.T.’s April 15 and May 9 visits to Dr. Buttleman, the problems with nursing worsened. Ms. Holt was leaking milk and A.H.T. was spitting up. Tr. at 32; see *also* Tr. at 33-34 (Ms. Holt describing her own training as a doula, which included observation of an appropriate latch). Ms. Hunter, the doula, described in her April 2012 affidavit that in “one of her calls,” Ms. Holt reported problems with A.H.T. latching on to the breast and being “sleepy when nursing.” Pet. Ex. 77, p. 2486.

Ms. Holt testified that she called Dr. Buttleman several times about these concerns. Tr. at 21, 26-27; see *also* Tr. at 115 (Mr. Tipton describing two calls to Dr. Buttleman). According to Ms. Holt, one of the calls took place within 24 hours of the vaccination and another occurred on April 9, 2002 (five days after the vaccination). A later call concerned a chest rash, her low grade fever, and the lack of sleeping. Tr. at 21, 27. Mr. Tipton described the initial call as occurring when they noticed the fever, shortly after the vaccination. Tr. at 112. He testified to a second call when she began screaming, which began when she awoke from the long period of sleeping after the vaccination, sometime on Saturday night. Tr. at 113, 115.

According to both parents, Dr. Buttleman recommended Tylenol during the calls. Tr. at 26, 54, 115. On one of the calls, Dr. Buttleman told them not to call unless they had taken A.H.T.’s temperature before calling her. Tr. at 54, 112. Ms. Holt also called again on April 12, primarily because A.H.T. had not had a bowel movement for a week. Tr. at 27-28. She described Dr. Buttleman as being unconcerned. Tr. at 29. This contrasts with Ms. Holt’s later testimony that at the April 15 visit, Dr. Buttleman told her that she needed to know if A.H.T. went for four days without a bowel movement. Tr. at 31. It also conflicts with Ms. Holt’s journal,⁹⁶ which described telephonic contact with a nurse at Dr. Buttleman’s office, rather than Dr. Buttleman herself. Pet. Ex. 6, p. 36.

2. Contemporaneously Prepared Documents.

Ms. Holt’s and Mr. Tipton’s testimony about A.H.T.’s behavior after her initial vaccination tracks closely with the symptoms Dr. Levinson relied upon in his February 23, 2012 statement. See Pet. Ex. 59 at 2336-37. However, their testimony and affidavits and those of family and friends conflict with contemporaneous records and histories provided closer in time to the events in question. Medical records and Ms. Holt’s journal (Pet. Ex. 6) reflect contemporaneous reports of constipation and other symptoms of colic (inconsolable crying and gas) soon after the initial vaccination, but

⁹⁶ Ms. Holt kept a notebook or journal, filed as Pet. Ex. 6, in which she wrote periodically. It is not always in chronological order although entries were generally made chronologically, according to Ms. Holt’s testimony. Tr. at 81-82. In most cases, there are entries on one page, followed by a blank page, likely representing the back side of the page on which the prior entry was made. Ms. Holt also testified that she might occasionally tear out a page to write a note to someone. Tr. at 82. Portions of some pages appear to have been “blacked out” by covering them with an unlined piece of paper. See, e.g., Pet. Ex. 6, pp. 39-40.

most of the other symptoms were either not discussed at all in the journal or the medical records or mentioned in a context different from the testimony about them.

Ms. Holt's journal entries soon after A.H.T.'s birth included questions and concerns about her own condition.⁹⁷ These early entries also document A.H.T.'s soft fontanelles, gastrointestinal discomfort, the availability of homeopathic remedies for colic, and the relationship between the diet of a nursing mother and gassy discomfort in the baby.⁹⁸ Pet. Ex. 6, pp. 32-33. It is silent about concerns regarding fever, somnolence, lethargy, sleeplessness, jerking, or problems with A.H.T.'s nursing ability or latching.

The journal also reflected questions for Dr. Buttleman and summarized a telephone consultation on April 12, 2002 (eight days after the initial vaccination), but does not contain entries for any of the other telephone calls about which Mr. Tipton and Ms. Holt testified. Pet. Ex. 6, pp. 35-36. The questions included the schedule for vaccination, travel concerns, "Mylicon⁹⁹ for gas," a breastfeeding schedule, and the lack of bowel movements since the evening of April 5. *Id.*, p. 35. Notes that were apparently made after the telephone consultation with Dr. Buttleman's nurse on April 12 reflect information about how to treat constipation with rectal stimulation and use of glycerin suppositories. Pet. Ex. 6, p. 36. Once again, there were no indications of concern about A.H.T. having problems latching on when nursing, sleeplessness, or fever.¹⁰⁰

The journal entries on or around April 12 reflected Ms. Holt's interest in alternative medicine and general concerns about vaccinations and other health interventions. An undated journal entry following the entry for a postpartum visit from the midwife on April 12 contained comments about specific vaccines, followed by an entry reading "delayed schedule is better" and "exemption form (religious)." The

⁹⁷ Entries made on April 11-12, 2002 concerned symptoms of mastitis (a breast infection), bleeding due to too much activity, and recovery from the birth process. Pet. Ex. 6, pp. 32-33. The only entry regarding breastfeeding referred to Ms. Holt leaking milk and the advice she received at a post-partum visit on April 12 with Ms. Dietsch (the midwife), that it "should stop within 1 week hopefully." *Id.*, p. 33. The notebook entry for April 11, 2002, discusses a call or visit from the doula, Amy Hunter, who apparently recommended a Dr. Baird for "alternative treatment." See also Tr. at 29, 145.

⁹⁸ An entry on April 12, 2002, apparently made during or after the postpartum visit with Ms. Dietsch, the midwife, reads: "pay attention to what I'm eating because it can make her gassy. massage her belly clockwise circles, massage gas thru so she can pass it easier," followed by several other lines with suggested treatment for "colic," including homeopathic remedies available at a health food store. Pet. Ex. 6, p. 33.

⁹⁹ Mylicon is an over-the-counter treatment for gas in the stomach or intestines. See, e.g., PDR (66th ed. 2012) at 1667.

¹⁰⁰ The first physician's record in which Ms. Holt specifically described problems with A.H.T.'s ability to "latch on" was in her May 2010 communication to Dr. Levinson. Pet. Ex. 47, p. 2055. She had mentioned that A.H.T. stopped breastfeeding "properly" to Dr. Kartzinel in 2007. Pet. Ex. 24, p. 464.

hepatitis B vaccine was not one of the vaccines mentioned.¹⁰¹ Pet. Ex. 6, p. 34. This journal entry also mentioned several over-the-counter supplements and the advice “1st few weeks don’t expect much.” *Id.* Ms. Holt testified that these vaccine-related entries involved research she was doing in order to decide whether to follow a delayed or regular vaccination schedule. Tr. at 59.

On April 15, 2002, A.H.T. returned to Dr. Buttleman for her two to four week checkup. Listed as one of the reasons for the visit was “trouble with” bowel movements. Pet. Ex. 58, p. 2328; Tr. at 30-31. A.H.T. was taking Mylicon,¹⁰² and bowel movements/voiding and crying/colic were marked on the checkup sheet as areas of concern. Constipation and using rectal stimulation and “babylax” (presumably referring to a baby laxative) to treat it were discussed. Pet. Ex. 58, pp. 2328-29. A.H.T. was alert and her physical examination was normal. *Id.*, p. 2328. She was responding to sound, holding her head up, and fixating on faces. *Id.*, p. 2329. A.H.T. was nursing for 10 minutes on one side every two to four hours. *Id.* She was sleeping for four hours at a time.¹⁰³ These notes did not reflect any concern about a vaccine reaction, fever, problems latching onto the breast, or sleeplessness. The office visit notes are consistent with Ms. Holt’s journal entry on April 15, 2002. See Pet. Ex. 6, p. 37.

A.H.T. had her one month checkup with Dr. Buttleman on May 9, 2002. The form reflected “worried about stomach.” The entry for weight is difficult to read,¹⁰⁴ but reflects she weighed over nine pounds, a gain of about a pound and a half in the three weeks since the prior visit. Pet. Ex. 58, p. 2326. She was nursing for five to 10 minutes every

¹⁰¹ As there were two more hepatitis B vaccinations in the three-shot series, the lack of any mention of a severe and persistent reaction to the initial vaccination here is significant.

¹⁰² Ms. Holt’s testimony was that she was told to use Mylicon at this visit, as gas was causing A.H.T.’s arching back, crying, and fussiness at nursing. Tr. at 31. However, the record reflected that she was already using Mylicon. Pet. Ex. 58, p. 2328.

¹⁰³ I interpret the handwritten notation “4 hrs” on Pet. Ex. 58, p. 2329, as reflecting the longest period of unbroken sleep, rather than the total hours of sleep in a day. I base this interpretation on my experience in reading hundreds of medical records for newborns and infants in over nine years as a special master. These records invariably reflected the longest period of unbroken sleep. I cannot recall any record that reflected a total period of sleep (which would have to be computed by adding all the many naps and nighttime sleep to arrive at a total). Any pediatrician who was informed that a newborn’s total sleep in a 24 hour period was just four hours would have been concerned, as the infant would have been sleeping far less than the norm. See NELSON’S at 47 (reflecting that the total sleep for a newborn averages between 10-19 hours out of 24; that breast fed infants sleep between one and three hours between feedings, with longer periods at night; and that extremely fussy/difficult to console infants are likely to have medical issues, with colic and reflux as examples of such issues). I also note that the time periods listed for sleep increased over time (four to five hours in May 2002, four to six hours in July 2002, six to seven hours in October 2002, to “through the night” in December 2002), consistent with an infant developing increasing periods of sleep consolidation through the first year of life. Pet. Ex. 58, pp. 2316, 2320, 2323, 2325.

¹⁰⁴ The entry clearly reflects a weight of nine pounds, and some indecipherable number of ounces. Pet. Ex. 58, p. 2326. The weight curve chart at p. 2314 reflects that a girl weighing nine pounds at one month of age would be at the 50th percentile on the curve.

three to four hours. Pet. Ex. 58, p. 2327. A.H.T. was still experiencing problems with constipation, as the checkup form reflected the use of glycerin suppositories. There was a check mark over the “Crying/colic” line, and based on the testimony and the medications A.H.T. was taking, it likely reflects that she was experiencing both. *Id.*, p. 2327. A.H.T. received her second hepatitis B vaccination at this visit. Pet. Ex. 58, pp. 2313, 2326. This was the last vaccination A.H.T. ever received.¹⁰⁵

Another journal entry on May 15, 2002, also reflected Ms. Holt’s continuing vaccine research. Pet. Ex. 6, p. 40; see *also* Tr. at 62-63. Under the name “Dr. Zieve,”¹⁰⁶ Ms. Holt made references to the advantages of nursing and a directive to “educate yourself as to aspects of [infectious disease].” There were also references to “chronic diseases due to obsession w/eliminating infectious diseases,” “cancer higher in those who have not been allowed to have high fevers,” “expose kids to diseases, then treat w/vitamins and homeopathic remedies,” and ended with a notation that “one large dose of Vit[amin] A gets rid of any virus.” Pet. Ex. 6, pp. 40-41. Ms. Holt’s notes also reflected the comments: “mumps/rubella easy diseases to treat,” and “difficult to believe in most studies.” Her notes on vaccination concluded with a list of various means of obtaining exemptions to vaccines. Pet. Ex. 6, p. 41. What is notably absent is any indication of questions or concerns about A.H.T. adversely reacting to either of the vaccines she actually received.

A.H.T.’s two month well-child visit took place on May 30, 2002. A note at the top of the form indicates: “per parents, no vaccines at this time.”¹⁰⁷ Pet. Ex. 58, p. 2324. Although the form reads “no complaints,” A.H.T. was still taking medications for colic, indicating ongoing problems. She weighed at least 10 pounds, a gain of about one pound that month.¹⁰⁸ *Id.* She was nursing for 10 minutes every two to three hours, and

¹⁰⁵ Ms. Holt testified that she had concerns about A.H.T. receiving this second vaccination, but permitted the vaccination because she wanted to believe that A.H.T.’s problems were due to colic. Tr. at 35-36. She also intimated that Mr. Tipton wanted A.H.T. to get vaccinated. Tr. at 37. However, Mr. Tipton testified that he was concerned about A.H.T. receiving the second hepatitis B shot, but that Dr. Buttleman talked them into it. Tr. at 130-31.

¹⁰⁶ In three weeks between A.H.T.’s one and two month well-child visits, Ms. Holt’s notebook contains an entry dated May 15 that reads “continue nursing at night,” along with the name “Robert Zieve/Ziev.” Pet. Ex. 6, p. 38. Ms. Holt testified that he was someone she spoke to on the phone, but she did not recall how she found him or the nature of his specialty. Tr. at 62-63.

¹⁰⁷ Ms. Holt’s journal entry for May 30, 2002 contains notes about vaccine safety. Pet. Ex. 6, p. 42. These notes read: “MMR doesn’t relate to autism[.] 2 kids w/ reactions[.] pertussis-hosp for week[.] tetanus-die[.] meningitis-hosp 2 wks/death[.] chemically engineered. DTP most usually causes reactions[.] Prevnar not required[.] very purified. Amer Acad of Ped website[.] CDC[.] high fevers caused by viruses, not by the diseases we’re vaccinating against.” The notes likely reflect the discussion with Dr. Buttleman about vaccinations at A.H.T.’s two month well-child visit. See Tr. at 35 (testimony by Ms. Holt that Dr. Buttleman discussed vaccine safety with her).

¹⁰⁸ This weight check is reflected on the growth chart, placing A.H.T. between the 25th and 50th percentiles. Pet. Ex. 58, p. 2314.

was also receiving prune juice. Pet. Ex. 58, p. 2325. She was described as fussy and sleeping for up to four to five hours. *Id.*

At this visit, Dr. Buttleman discussed expressing milk rather than nursing, “to try to get on schedule.” *Id.* at 2324. This entry suggests that the problem was not nursing per se, but more that A.H.T. had not established a regular schedule for sleeping and eating.¹⁰⁹ In contrast, Ms. Holt testified that Dr. Buttleman was concerned about A.H.T. not getting enough breast milk and told her to stop trying to nurse and to feed bottled breast milk. Tr. at 78-79. However, the medical record does not reflect any concern about A.H.T.’s weight gain.

Ms. Holt’s journal does not reflect any concerns about weight gain. An undated note (which is the only note in the journal between the notes from the May 30 visit with Dr. Buttleman and a July 25 visit to the naturopathic doctor) mentioned options for treating A.H.T.’s ongoing gastrointestinal issues. The notes reflected the amount of Mylicon to use with each feeding, the possibility A.H.T. may be experiencing “heartburn type of pain,” a possible switch to a soy based formula based on a milk allergy, feeding A.H.T. only every three hours, pumping and storing breast milk, and instructions to call back “next” Thursday. It indicates “doing great → stay w/Isomil [.] treat her as reflux. . . .silent reflux → doesn’t always spit up [.] Zantac.” Pet. Ex. 6, p. 43. Given the reference to Zantac,¹¹⁰ a medication A.H.T. was taking at the time of her next visit to Dr. Buttleman on July 29, 2002, this note may have reflected a phone call to Dr. Buttleman, matters discussed at the May 30 visit, or a visit to another physician. The note likely summarized the office visit with Dr. Buttleman, given the comments about “doing great” (which likely reflect that the advice came from a health care provider who had recently seen A.H.T.), the advice about pumping and storing breast milk (which was referenced in Dr. Buttleman’s notes), and the advice to call back “next” Thursday, which would be a week after the Thursday, May 30 visit.

A.H.T. saw Dr. O’Dell, a naturopathic physician whom Ms. Holt had previously consulted on nutritional issues, on July 25, 2002. Pet. Ex. 73; Tr. at 79. The one-page record also contains the web address for the National Vaccine Information Center (NVIC), a resource for information on vaccine refusal rights and vaccine side effects.¹¹¹ Pet. Ex. 73.

¹⁰⁹ This suggestion may also reflect a concern about how much milk A.H.T. was receiving during nursing, as bottle feeding expressed milk allows for a more accurate assessment of intake. However, given that A.H.T. fell between the 25% and 50% range for weight (and at the 25% mark for length) between two and nine months of age, it does not appear that there were any acute concerns about her nutritional status at her early well-child visits. See Pet. Ex. 58, p. 2314 (growth chart).

¹¹⁰ Zantac is an over-the-counter medication used to treat reflux. PDR (66th ed. 2012), at 1408.

¹¹¹ NVIC describes its mission as being “dedicated to the prevention of vaccine injuries and deaths through public education and to defending the informed consent ethic in medicine.” <http://www.nvic.org/about.aspx>.

Ms. Holt's journal entry referencing the Dr. O'Dell visit indicated that A.H.T. "definitely" had a milk allergy, and that the hepatitis B vaccine could have "played a role" by "mess[ing] w/her liver." He apparently recommended that A.H.T. avoid all dairy, switch from a milk-based formula to a particular soy formula, and treatment with "friendly bacteria." Doctor O'Dell informed Ms. Holt that he did not vaccinate his own children. Pet. Ex. 6, pp. 44-45.

At A.H.T.'s four month checkup, which occurred four days after the appointment with Dr. O'Dell, "no complaints" was written on the form, followed by a dash and the word "stomach." The word following "stomach" is not decipherable. Doctor Buttleman discussed stretching out feedings and starting rice cereal. Pet. Ex. 58, p. 2322. A.H.T. was sleeping four to six hours at a stretch. *Id.*, p. 2323.

In late August 2002, A.H.T. returned to Dr. Buttleman for a "problem" visit, one not associated with the regular schedule at which developmental milestones were recorded. Doctor Buttleman discussed diet and bowel movements with Ms. Holt and diagnosed A.H.T. with constipation. In addition to using glycerin suppositories, Dr. Buttleman directed Ms. Holt to "push juices." Pet. Ex. 58, p. 2321. A.H.T. weighed over 13 pounds. *Id.*

At A.H.T.'s six month well-child visit in early October 2002, she weighed 14 pounds, 10 ounces, more than double her birth weight.¹¹² She had a runny nose for several days before the visit, and her father reported that she was not on any medications, suggesting that her colic had resolved. If she was taking the supplements recommended by Dr. O'Dell, her father did not report them. Pet. Ex. 58, p. 2319. The guidance was to start "table/finger" food and get A.H.T. on a schedule. *Id.*, pp. 2319-20. The checkup sheet reflected that she was taking four to five ounces of formula and was sleeping six to seven hours at a stretch. *Id.*, p. 2320.

Two entries pertaining to sleep appear in Dr. Buttleman's records in November and December 2002, when A.H.T. was about nine to ten months old. At the November visit, A.H.T. was ill with otitis media, and one of the listed symptoms was "not sleeping," but in context, it appears to refer to a symptom of illness rather than a chronic condition. Pet. Ex. 58, p. 2318. The December well-child visit notes reflected a discussion about A.H.T.'s diet, a recheck for her previous otitis media, and the presence of a cough. The notes also reflect that A.H.T. was sleeping "through the night." *Id.*, pp. 2315-16. This was her last visit to Dr. Buttleman.

In January 2003, Dr. Hefner became A.H.T.'s primary care provider. Her first documented bout of diarrhea is referenced in Dr. Hefner's notes from January 2003, in conjunction with enteritis. She was noted to have had an early history of constipation,

¹¹² Petitioner's post hearing brief indicates that A.H.T. stopped seeing Dr. Buttleman at five months of age, attributing the change in physicians to Dr. Buttleman's refusal to listen to parental concerns. Pet. Br. at 7. The reference to timing is incorrect, as A.H.T. continued to see Dr. Buttleman until December 2002, when A.H.T. was about nine months old.

which was described as “better.” Pet. Ex. 52, p. 2233. In August 2003, he noted that A.H.T. had experienced “frequent bouts” of diarrhea, presumably referring to several visits between January and August 2003. Pet. Ex. 52, p. 2228; see Pet. Ex. 52, p. 2229-31. He recommended dietary changes. Pet. Ex. 52, p. 2228.

3. Video Records.

Video recordings document the behavior of A.H.T. and her caregivers during discrete periods of time during the first few weeks after vaccination. Although I recognize that video recordings may represent periods of “good behavior” because parents may not record the baby during more difficult times, the recordings in this case are devoid of any statements indicating the behavior recorded is unusual or atypical. Contrary to Mr. Tipton’s assertions at the hearing (Tr. at 116, 121), they do not support the testimony about A.H.T.’s problem behavior in the days and weeks after vaccination.

A video clip of approximately five minutes was recorded beginning at 8:54¹¹³ on Friday, April 5, 2002, the day after the initial vaccination. Rather than documenting the extended lethargy, somnolence, and difficulty in waking reported by her parents for that day, the clip reflected A.H.T. sleeping, opening her eyes without stimulation, crying slightly (with a voice in the background saying “wet diaper”), and Mr. Tipton holding her, during which she stopped crying. She returned to sleep shortly thereafter. Video 1, at 12:53. No comments were made about any extended period of sleep, and the reaction to her awakening treated it as routine. The next day (Saturday, April 6, 2002, the day when A.H.T. was reported to continue an extended period of sleep), a video clip of approximately 11 minutes showed A.H.T. awakening without stimulation, yawning, receiving a diaper change, and being bathed (generating some crying but no shrieking or screaming). She was alert while being wrapped in a blanket after the bath. On Sunday, April 7, the only video clip for that day was a short clip showing A.H.T. sleeping. *Id.* at 25:40. The Saturday and Sunday video clips did not reflect either the extended somnolence or the non-stop screaming her parents reported.

On Tuesday, April 9, a video of approximately six minutes documented a visit, possibly by A.H.T.’s grandmother. A.H.T. was in a bouncy seat, and was not fussing or crying. There was a background comment of “strong little girl.” About eight minutes into the video, A.H.T. began to cry, but she stopped crying when she was nursed. In a short clip less than a minute long from Wednesday, April 10, someone remarked at about 5 PM that A.H.T. had been up since 2:45 PM. Video 1, at 35:03. There was no indication that this was unusual or that she was having difficulty sleeping.

The next clip was recorded on April 26, 2002. A.H.T. was in her swing, and appeared alert. Video 1, at 46:00. The next recording was from May 18, 2002, about nine days after the second vaccination. A.H.T. played in her crib, appeared alert and happy, and made sounds. *Id.* at 46:51. This video is consistent with Dr. Buttleman’s records of A.H.T. at the two month well-child visit. Another short clip filmed about six

¹¹³ These times represent the time elapsed from the start of the video.

days later showed A.H.T. playing with her father. She was alert and not crying. *Id.* at 50:26.

In summary, the video showed A.H.T. to be awake on Friday, April 5 and Saturday, April 6, 2002. No comments on the video suggested that these periods of wakefulness were occurring in the context of an extended hard sleep. Video records also documented periods over the next few weeks when she was awake, interactive, and not crying. Throughout the video, she appeared to behave like a normal infant, not one who had suffered an encephalopathic event.

4. Histories in Medical or Treatment Records.

There are no other contemporaneous records concerning A.H.T.'s condition within a few weeks of her hepatitis B vaccinations. However, there were some histories provided by A.H.T.'s parents as they sought treatment for her gastrointestinal difficulties and during early intervention evaluations that bear on the matters in controversy. I note that all these histories were given at a time after Ms. Holt's July visit to Dr. O'Dell, who had attributed A.H.T.'s symptoms to her hepatitis B vaccinations.

The history provided closest in time to the events described is from A.H.T.'s first visit to Dr. Hefner on September 11, 2002, when she was about five and one half months old. The chief complaints at this visit were listed as "difficult [bowel movements]. crys alot (sic), inconsolable, ↓ sleeping, ↓ naps, since 1 wk old." Pet. Ex. 52, p. 2234. She was reported to take four to six ounces of formula every three hours and was gaining weight. Like Dr. Buttleman, Dr. Hefner attributed A.H.T.'s symptoms to colic. *Id.*

Similar complaints were voiced when A.H.T. saw a pediatric gastroenterologist in October 2002 at about six months of age. The history reflected episodic "inconsolable crying" a week after birth, with difficult bowel movements beginning two-three weeks later. Poor sleep was noted, but there was no "significant arching or food refusal." Pet. Ex. 34, p. 1287.

The next histories were given after A.H.T. was referred for early intervention services in the spring of 2004. The Carriage House developmental examination contained the history that she was "unhappy since about one week of age." Pet. Ex. 39, p. 1826. Ms. Holt reported that she had attributed A.H.T.'s crying to colic at that time, but now had concerns about A.H.T.'s "emotional status." *Id.* The speech and language assessment contains a history of having had words "come and go" from her vocabulary "since birth." *Id.*, p. 1823.

A history taken in May 2004 reflected that A.H.T. had problems with colic-like behavior and difficulty sleeping during her first year. She would cry "nonstop" or until she vomited. She would then become quiet and start jerking. Ms. Holt also reported a history of difficulty with bowel movements. Pet. Ex. 55, p. 2255.

Breastfeeding difficulties were also discussed, with Ms. Holt reporting that the difficulties involved “overproduction of milk” (which would account for Ms. Holt’s complaints about leaking milk) and biting or yanking at the breast. Pet. Ex. 55, p. 2256. The biting and yanking complaints are consistent with a report to Anne Linden Steele in July 2004 that “nursing was awful at 2 months” (Pet. Ex. 41, p. 1832) and to an occupational therapist in September 2004 that A.H.T. “did not nurse well and would bite and yank her head to the side” but did well on the bottle (Pet. Ex. 28, p. 1088).

In an OT assessment performed in September 2004, Ms. Holt reported to the therapist that A.H.T. “screamed nonstop” during her first year of life. She also reported that at two weeks of age, she went 17 hours without sleeping, and would only sleep in her swing. Pet. Ex. 28, p. 1088. Night terrors were reported “since she was an infant.” Ms. Holt indicated that, since A.H.T. was able to walk, she would get out of bed two or three times a week while screaming and would run around without acknowledging her parents’ presence. At the beginning of 2004, she was sleeping 11-12 hours per day, but at the time of the assessment, A.H.T. was sleeping only three to four hours per night, and required several hours to fall asleep, in spite of the lack of a daily nap. *Id.* The history of biting and yanking her head during breastfeeding was repeated. Symptoms of “intestinal spasm” and reflux at two months of age were listed, and she was reportedly unable to produce bowel movements during her first year of life without rectal stimulation. *Id.* Although other medical records had not indicated any persistent problems with diarrhea, outside of bouts associated with an illness, Ms. Holt reported “recurrent diarrhea.” *Id.*

A.H.T.’s first neurology evaluation took place in August 2004. A history of “screaming episodes” since she was seven days old was provided. She was also reported as waking up wild-eyed and crying in the middle of the night since she was six months of age. Reflux, constipation, and diarrhea were also reported. Pet. Ex. 40, p. 1830.

A second neurologist, Dr. Puri, noted in September 2004 that she would not go to sleep without being held or watching TV. Pet. Ex. 31, p. 1262. The clinical psychologist who tested A.H.T. for autism in October 2004 noted that during the period from August through October 2004 the family was “struggling with significant sleep disturbance” (Pet. Ex. 17, p. 144); a report borne out by the OT records (see, e.g., Pet. Ex. 55, pp. 2267, 2276, 2279). By February 2006, A.H.T.’s sleeping problems had apparently improved, as Dr. Puri noted that she had “some difficulty falling asleep,” but that she remained asleep once she fell asleep. Pet. Ex. 31, p. 1254. A somewhat dissimilar history was recorded by Dr. DeMio, also in February 2006, noting that her sleep was “poor,” but he also noted long sleep latency. Pet. Ex. 23, p. 243.

The first reference in the medical records to A.H.T. suffering a fever after her initial vaccination was not made until May 18, 2011, more than nine years after the

vaccination.¹¹⁴ This report was made at A.H.T.'s initial visit to Medical Neurogenetics, Dr. Shoffner's practice. See Pet. Ex. 47, p. 2121.

5. Experts' Opinions Regarding Post-Vaccination Symptoms.

The physicians' testimony regarding the likelihood that the symptoms after vaccination occurred as A.H.T.'s parents and other family members described focused on two symptoms: the loss of ability to latch onto the breast and the likelihood that A.H.T. experienced a febrile reaction to her initial vaccination. They also testified about whether there were alternate explanations for A.H.T.'s uncontested symptoms of irritability, crying, and constipation beginning shortly after the initial vaccination. Petitioner's position is that the post vaccination symptoms occurred as she and Mr. Tipton described, that A.H.T.'s fever was the trigger for activating an underlying mitochondrial disorder, and that the other symptoms she displayed were consistent with an encephalopathic event, if not a full-blown mitochondrial encephalopathy. Pet. Br. at 11-12.

Both Drs. DeMio and Kendall accepted the testimony provided by A.H.T.'s parents and other friends and family at face value. Assuming both the presence of fever and the loss of the ability to latch onto the breast, Dr. Kendall testified that a vaccine could cause a fever in a neonate (Tr. 343-44, 352),¹¹⁵ that loss of ability to latch onto the breast was evidence of a neurological problem (Tr. at 340-41), and that the irritability, changes in sleeping, constipation, and general temperament in A.H.T. after the vaccination were consistent with a mitochondrial decompensation or regression (Tr. at 322, 344). Doctor Kendall also testified that the temperature regulation system in a

¹¹⁴ In his February 2012 statement (Pet. Ex. 62), Dr. DeMio recounted the symptoms reported by A.H.T.'s parents at their first visit with him in 2005. Fever of any type is not mentioned. *Id.* at 2356. Nevertheless, in response to a leading question, he testified that A.H.T.'s parents had mentioned a fever after the hepatitis B vaccination at their initial meeting. However, fever is not mentioned as a reaction anywhere on the intake form, Pet. Tr. Ex. 1.

¹¹⁵ Although not discussed by any of petitioner's witnesses, petitioner filed a very short medical journal article describing a records review of fevers in neonates in 1991 and 1992 at an Israeli hospital. See N. Linder, *et al.*, *Unexplained fever in neonates may be associated with hepatitis B vaccine*, Arch Dis Child Fetal Neonatal Ed., 81:F206-07 (1999), filed as Pet. Ex. 67. The authors noted that fever was the most common report of an adverse event after hepatitis B vaccination of neonates, with reports of fever in 1% to 3.7%. They then compared the number of neonates who experienced a fever, but this number was not based on records of temperatures. Rather, they used discharge diagnoses of "temperature regulation diseases" or the administration of intravenous antibiotics. Because the hepatitis B vaccine was not administered in Israel until 1992, the researchers looked at records from 1991 and 1992. The incidence of unexplained fevers was slightly more than twice as high (0.6%) in 1992 as it was in 1991 (0.28%). *Id.* Doctor McCandless testified that this study had what he called a "fatal methodological flaw," in that the investigators knew the answer to the question of whether there were more fevers in the year hepatitis B vaccine was administered to the neonates than the prior year at the time they began the study. Tr. at 511, 576-78. Furthermore, the "P" value selected guaranteed that the difference between the two years would be statistically significant. See Tr. at 578-79. This retrospective study did not account for other factors that could affect fever in neonates in the two years examined, such as the rate of communicable illnesses in the general population, or changes in hospital protocols for reporting and treating febrile illnesses.

neonate is not as functional as in older infants (Tr. at 343-44) and that vaccines in general could produce fever (Tr. at 352). She also thought that tactile assessments that a child felt “warm” were a reliable indicator that the child had a fever. Tr. at 343.

Doctor DeMio believed A.H.T.’s parents were accurate historians, and that their testimony was consistent with what they reported to him at their initial visit with him in 2005. However, he was unsure if he had ever reviewed A.H.T.’s early pediatric records. Tr. at 203, 238, 244.

Doctor Wiznitzer was clearly quite skeptical about Ms. Holt’s claim that A.H.T. lost the ability to latch onto the breast. He testified that the loss of this ability necessarily implied the loss of the ability to suck and thus to take in adequate nourishment. Tr. at 656-58. The testimony and other evidence that A.H.T. gained weight, maintained appropriate percentiles in weight, height, and head circumference, and produced adequate urine were, according to Dr. Wiznitzer, inconsistent with losing the ability to latch onto the breast. Tr. at 633-35, 638, 656-58. He noted that A.H.T. gained weight without unusually frequent feedings, based on the parents’ reports to Dr. Buttleman of how often and how long she was nursing. Tr. 689. He believed that the difficulties Ms. Holt encountered in nursing were consistent with nursing a child with colic and a regulatory disorder. Tr. at 687-88. Rather than having an “inadequate latch,” Dr. Wiznitzer attributed the problems in breastfeeding to A.H.T.’s “difficult” temperament. Tr. at 686-89.

Doctor Kendall attempted to explain how the loss of ability to latch could exist simultaneously with normal weight gain, by indicating that frequent feeding could compensate for a poor latch or other inability to feed. Tr. at 340-41. As the record is devoid of evidence that A.H.T. was being fed at more frequent intervals, her testimony on this point is not relevant. She noted a “little bit of a drop off in” A.H.T.’s weight at around four months of age. Tr. at 384. However, by that time, A.H.T. was being bottle-fed formula and Ms. Holt testified that A.H.T. did fine on the bottle. Tr. at 37, 79. Thus, this aspect of Dr. Kendall’s testimony is also irrelevant.

Doctor Wiznitzer noted that the contemporaneous medical records did not reflect any report of fever after the initial hepatitis B vaccination. He found this significant, as there is a heightened degree of concern when a fever in excess of 100.4-100.6°F is present in a neonate, as it may reflect symptoms of sepsis, a serious and sometimes fatal infection in a neonate. Tr. at 629-30; Res. Ex. A at 8. He referenced two excerpts from pediatric textbooks for this assertion. See Res. Ex. D, an excerpt from the American Academy of Pediatrics’ *TEXTBOOK OF PEDIATRIC CARE*, Ch. 181; *Fever*. This excerpt states:

Because of the difficulty in determining, based solely on the degree of fever, whether an infant younger than 2 to 3 months is at a low or high risk for bacterial disease (septicemia has occurred even in infants who have low grade fevers), evaluation should be prompt and thorough whenever a fever of at least 100.4° F (36° C) exists[the] evaluation should

generally include a complete physical examination [and testing of blood, urine and possibly stool and cerebral spinal fluid].

Id. at 3 (using the CM/ECF generated page numbers). See *a/so* Res. Ex. C, a one-page excerpt from NELSON’S regarding management of acute illnesses, which states: “Many would agree that a sepsis work-up is indicated in the febrile child younger than 1 mo and possibly younger than 3 mo.”

On cross examination, Dr. Wiznitzer acknowledged that fever is a common reaction to some vaccinations, but he added that there is little evidence that the hepatitis B vaccine causes fever. Tr. at 660-62. He agreed that the vaccine monograph¹¹⁶ (Pet. Tr. Ex. 2) indicated that fever had been reported after hepatitis B vaccination in about 10% of recipients, but he explained that fevers are uncommon in neonates, and the monograph did not separately assess fevers in the two age groups studied, adolescents and infants. Tr. at 662-64. Doctor McCandless also expressed doubt that the hepatitis B vaccine caused fever, although he stated that it was not impossible for it to do so. Tr. at 510-12.

With regard to the other symptoms A.H.T. allegedly displayed after the initial vaccination, respondent’s experts did not contest that A.H.T. experienced persistent crying, slept less, was constipated, arched her back, and had episodic jerking. All of these symptoms were reported to one of her primary care providers, the pediatric gastroenterologist she saw at about six months of age, or were otherwise reflected in Ms. Holt’s journal. However, respondent did dispute that the vaccination caused these symptoms. Respondent’s experts attributed the problems in breastfeeding, persistent crying, difficulty in sleeping, back arching, and constipation to the colic diagnosed by both primary care providers and the pediatric gastroenterologist. Res. Ex. A at 9, Tr. at 629, 631-32. Doctor Wiznitzer provided un rebutted testimony that the “jerking awake” that A.H.T.’s parents described is common in infants during the first few months of life. Tr. at 633. He also testified that there was no evidence of lethargy in A.H.T.’s records during the first year of her life. Tr. at 632-33. I concur with his conclusion regarding the absence from the records, notwithstanding Dr. Kendall’s assertion that the records reflected lethargy.

C. Factual Findings Regarding Post-Vaccination Symptoms.

I have carefully considered the record as a whole in arriving at the factual findings set forth below.

¹¹⁶ Petitioner labeled this document as a “monograph.” It appears to include the same type of information commonly found in the package inserts accompanying vaccines, which include all reported adverse events following vaccination. However, listing adverse events does not constitute an admission that the vaccine was causal. See *Werderitsh v. Sec’y, HHS*, No. 99-319V, 2005 WL 3320041, at *8 (Fed. Cl. Spec. Mstr. Nov. 10, 2005) (“[a] report or information submitted by a licensed manufacturer . . . does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect”); see also *Christiansen v. Sec’y, HHS*, 08-244V, 2012 WL 6766650 (Fed. Cl. Spec. Mstr. Nov. 13, 2012).

1. Gastrointestinal Symptoms and Growth.

(a) The advent of problems with constipation and colic within a few days of the initial hepatitis B vaccination is well-established by both testimony and medical records. Problems with constipation persisted, but lessened by about six months of age.

(b) Chronic or frequent diarrhea did not occur at a point close in time to A.H.T.'s initial or second hepatitis B vaccination.

(c) A.H.T. maintained a weight curve between the 25th and 50th percentiles until nine months of age.

(d) She fell off her weight curve between nine and 18 months of age, in conjunction with several bouts of diarrhea. Her weight dropped to the 5th percentile at one year of age, but rebounded to the 20th percentile at 15 months of age.

(e) It is possible that A.H.T. developed chronic diarrhea at some point after 18 months of age, but if so, it is not documented by contemporaneous records, which reflected bouts of diarrhea in conjunction with certain types of food and some medical interventions.

2. Irritability and Crying.

(a) A.H.T. cried more often and more robustly after her initial hepatitis B vaccination than she did before it. A.H.T. was, as an infant, difficult to console.

(b) The record as a whole does not support a finding of the “non-stop” crying in the first year of her life about which her parents and family members testified.¹¹⁷ Rather, A.H.T. displayed the episodic crying reported to the pediatric gastroenterologist in October 2002.

(c) Based on her symptoms, Dr. Hefner diagnosed colic, a diagnosis also made by Dr. Stephen and Dr. Buttleman. I accept their diagnosis as correct. That diagnosis accounted for the inconsolable crying reported and observed, as well as the gastrointestinal complaints. Infants with colic cry robustly and are difficult to console.

(d) By six months of age, the colic symptoms had eased. However, A.H.T. displayed some problems involving crying, tantrums, and general unhappiness during the remainder of her first year of life and thereafter. She was resistant to efforts to get her on a regular schedule for eating.

¹¹⁷ The medical and video records establish that there were times when she appeared happy and calm, and the extent of her play and interaction skills as recorded during well-child visits indicate that she could play and interact with parents or other caregivers. I cannot reconcile the testimony that she cried nearly all of her waking hours with this other evidence.

3. Alterations in Sleeping Patterns.

(a) Prior to her initial vaccination at five days of age, A.H.T. likely slept much of the day, with brief periods of alertness and interaction, including periods when she nursed. The periods of sleeping prior to her vaccination may well have been 18-20 hours per day, consistent with the sleeping patterns of many neonates.

(b) The reports that A.H.T. slept nearly continuously and was difficult to rouse in the two days after her initial vaccination¹¹⁸ are not supported by contemporaneous records, and are contradicted at least in part by the video evidence. I find that she did not experience significant lethargy and that she was not difficult to arouse in the day or two after the vaccination, even if she slept more than the 18-20 hours a day she had slept prior to the vaccination.

(c) A.H.T. slept less after one week of age than the 18 to 20 hours per day she slept previously. However, I do not accept A.H.T.'s parents' testimony that her total sleep per day amounted to just four or five hours daily for an extended period of time.¹¹⁹

(d) A.H.T. napped less frequently and for shorter periods of time after her initial vaccination than she did before it, and at some point during her first 18 months, she stopped napping entirely. However, the periods of unbroken sleep described in the medical records increased over time, consistent with the normal sleep patterns of infants. Contrary to A.H.T.'s parents' testimony, I find that the reports of length of sleep in Dr. Buttlerman's records reflect the longest period of unbroken sleep, rather than the total amount of sleep in a day.

(e) During infancy, A.H.T. experienced difficulty in falling asleep and often slept in her swing.

(f) At six months of age, she developed night terrors. However, by nine months of age, she was sleeping through the night.

(g) At the time of her referral for early intervention services, she had poor sleep habits, delayed sleep onset, and did not nap, but she slept through the night. Additional sleeping problems developed during her early intervention therapies.

(h) Problems with sleeping may have persisted thereafter, although the records and other evidence are not clear for how long or when, or whether the problems were periodic or episodic. Sleep problems became so severe in 2010 (when A.H.T. was eight years old) that she was treated at a pediatric sleep clinic.

¹¹⁸ A.H.T. received the vaccination on Thursday, April 4, 2002.

¹¹⁹ In this regard, I note that a history taken in August 2004 reported that on one day early in infancy she was awake for 17 consecutive hours. This report strongly suggests that this was an unusual occurrence, rather than a common one.

4. Breastfeeding.

(a) A.H.T. breast fed well initially, but after she developed colic, breastfeeding became more difficult. Nevertheless, she took in adequate nourishment exclusively (or nearly exclusively) from breastfeeding through two months of age, as evidenced by her weight gain and place on the weight curve.

(b) A.H.T. was receiving prune juice by bottle prior to the cessation of breastfeeding. A.H.T. had no problems with bottle feeding, which likely contributed to Dr. Buttleman's suggestion that Ms. Holt feed breast milk by bottle.

(c) A.H.T. was nursing for appropriate periods and frequency as reported at well-child visits through two months of age.

(d) A.H.T. stopped nursing regularly at about two months of age, but contrary to Ms. Holt's testimony, I find that the change to bottle feeding of breast milk and then to various formulas was not due to a problem with A.H.T.'s ability to "latch on" to the breast. Rather, it represented at least three problems: getting A.H.T. on a regular schedule, overproduction of milk, and A.H.T. biting and yanking on the breast.

(e) Ms. Holt stopped breastfeeding at about two months of age and eventually switched A.H.T. to formula at around four months of age, after about two months of bottle-feeding pumped breast milk.

5. Fever.

Unlike the crying, gastrointestinal discomfort, sleeping, and feeding issues, there are no contemporaneous records that support even part of petitioner's claims that A.H.T. developed a fever of several days duration after the initial hepatitis B vaccination. In the absence of medical or other contemporaneous records,¹²⁰ I looked for circumstantial evidence tending to make the occurrence of the event in question more or less likely. The weight of the evidence is against a finding that A.H.T. experienced a post-vaccination fever.

Ms. Holt and Mr. Tipton's testimony differed as to how high the fever was, how long it lasted, and when and how many calls were made to Dr. Buttleman.¹²¹ Moreover, Mrs. Christy Holt, who visited A.H.T. nearly every day during this time period, could not recall any expressions of concern about fever. Tr. at 161, 171-72.

¹²⁰ Petitioner's expert, Dr. Kendall, agreed that there was no mention of fever after vaccination in the medical records. See Tr. at 341-42.

¹²¹ I note that petitioner, who bears the burden of proof in this off-table case, could have asked me to compel Dr. Buttleman to testify, prepare an affidavit, or answer interrogatories concerning her recollections of telephonic contact, how telephonic contacts were documented by her practice, and whether she considered the presence of fever in a neonate sufficiently serious so as to occasion an office or emergency room visit. Petitioner did not make such a request.

More significantly, however, the April 12 call to Dr. Buttleman's nurse regarding constipation and colic is documented in Ms. Holt's journal, but fever was never mentioned. Additionally, in spite of Ms. Holt's testimony about her level of concern regarding the dramatic changes in A.H.T.'s behavior, there are no references to these changes in the journal, while much more mundane issues are referenced. Ms. Holt made notes about a telephonic consultation with Dr. Buttleman's office regarding constipation between the visits when A.H.T. was five days and two weeks of age, and I find it significant that no such notes were made about a fever after vaccination.

Ms. Holt's journal is reflective of a person concerned about health questions. Her actions are those of a person willing to make unconventional health care decisions, as reflected in her rejection of the recommendation to induce labor made by her obstetrician and her choice of a home birth attended by a midwife. She wrote down questions for her health care providers and advice she received. The journal reflects concerns about side effects of vaccination and even the need for vaccinations at all, but is silent about ill effects from the vaccinations A.H.T. actually received.

I thus find it unlikely that A.H.T.'s parents would have deferred to Dr. Buttleman regarding A.H.T.'s second vaccination in light of the reactions to the first vaccination that they described. This capitulation to Dr. Buttleman is even more unlikely in view of the comments in the journal and Ms. Holt's testimony that she had "researched" a number of vaccines and how to obtain vaccine exemption between the first and second hepatitis B vaccinations.

Moreover, if Dr. Buttleman had been notified, as A.H.T.'s parents testified that she was, even as late as the next well-child visit, I am confident that she would have reflected a febrile reaction in her notes and, at a minimum, included advice about how to prevent fever before the second hepatitis B vaccinations. Fever of any level in a neonate, as Dr. Wiznitzer testified and as reflected in the medical articles filed with his expert report, would be a matter of concern for a pediatrician, and a symptom warranting an office visit and possibly a sepsis workup. I find it highly unlikely that reports of a fever after vaccination in an infant less than one week old, persisting for the period described, would elicit the "wait and see" attitude attributed to Dr. Buttleman as well as the lack of documentation in the infant's records.

It is also significant that the first references to A.H.T. suffering a fever after her initial vaccination were not made until May 2010, when she had her first visit to Dr. Shoffner. References to fever also occurred in Ms. Holt's and Mr. Tipton's largely identical affidavits, filed in September 2011, shortly after A.H.T.'s diagnosis with a mitochondrial disorder. Fever appears to be significant, if not absolutely essential, to the causation theory advanced by Dr. Kendall in this case, and the facts of the Poling case and the Shoffner study (Pet. Exs. 68-69) were widely discussed.¹²² Apparently A.H.T.'s parents did not report a fever to Dr. Brady (who claimed to have seen A.H.T. in

¹²² See Pet. Ex. 83 for an example of the publicity regarding the Poling case.

June 2002) as the fever is not mentioned in Dr. Brady's statement, Pet. Ex. 66. Although Dr. DeMio claimed that A.H.T.'s parents mentioned a post-vaccination fever at their initial visit with him in 2005, such a fever is not mentioned in Pet. Tr. Ex. 1, the history and intake form from this visit, Dr. DeMio's other records, or his 2012 statement. There is no evidence that a post-vaccination fever was mentioned to anyone until A.H.T. saw Dr. Shoffner, the author of Pet. Ex. 68, an article about the incidence of fever in autistic regressions in children with mitochondrial disorders, in May 2011.

I find that A.H.T. did not experience a fever after her initial hepatitis B vaccination.

6. Development.

(a) A.H.T. had essentially normal growth and development between birth and one year of age. Although at nine months of age she was not responding well to her name and may not have been using meaningful sounds, at 12 months of age, her language skills were assessed as normal.

(b) A.H.T. acquired age-appropriate cognitive and motor skills at least through 15 months of age.

(c) None of the health care providers who treated her from five days of age to 15 months of age expressed any concern about her cognitive development.

(d) At 18 months of age, she was noted by her pediatrician to lag in language acquisition.

(e) A.H.T.'s parents did not have concerns about her development until she was about 18 months of age.¹²³ In making this finding I reject petitioner's contrary testimony, and instead adopt the histories that reflect Ms. Holt's first concerns arose when A.H.T. was about 18 months of age. The first of these histories was provided when A.H.T. was just a little over 24 months of age, very close in time to the events in question.

7. Symptoms after the Second Vaccination.

There is no reliable evidence that A.H.T. experienced any reaction to her second hepatitis B vaccination. I conclude that there were no specific symptoms that worsened soon after the second vaccination.¹²⁴

¹²³ Ms. Holt clearly had concerns earlier about A.H.T.'s crying, sleeping patterns, and gastrointestinal symptoms, but no concerns about her cognitive development were expressed until the 18 month appointment.

¹²⁴ This conclusion is based on the contemporaneous medical records and Ms. Holt's journal, which does not reflect any additional or worse problems around the time of the second vaccination, in spite of entries reflecting her concerns about vaccination generally. See Pet. Ex. 6, pp. 40-42, 44-45. Additional support for this conclusion is found in the early medical histories. See Pet Ex. 52, p. 2234 (history provided to Dr.

D. Mitochondrial Disorder Diagnosis.

The second factual controversy concerns the basis for A.H.T.'s diagnosis with a mitochondrial disorder in August 2011.

1. Evidence Used in Diagnosis.

A.H.T. first saw Dr. Shoffner on May 18, 2011, having been referred by Dr. Levinson, to determine if her "clinical manifestations [were] related to a defect in cellular energetics or another class of metabolic disease." Pet. Ex. 47, p. 2117. The thorough diagnostic workup she received at this visit consisted of a clinical history, tests performed on blood, urine, and cerebral spinal fluid, a muscle biopsy taken to assess mitochondrial function in living and fresh frozen tissue, and DNA analysis, among others. See *generally* Pet. Ex. 26. The clinical history is set forth in Pet. Ex. 47, pp. 2117-24 (reflecting the history reported at the initial visit in March 2011) and in Pet. Ex. 61, pp. 2342-48 (report from the August 10, 2011 visit). Summaries of test results and the diagnostic score sheets¹²⁵ appear in Pet. Exs. 26, 47, and 61, but the actual test reports only appear in Pet. Ex. 26. Two diagnostic reports from Dr. Shoffner were filed, one dated August 1, 2011, and the other dated August 10, 2011. Both of these reports used score sheets to determine a diagnosis. Pet. Exs. 26, pp. 522-82 (copy containing diagnosis and test results); 47, pp. 2109-16 (without test results); 61, pp. 2346, 2349.

a. Medical History Provided for Clinical Symptom Assessment.

The records from the May 18 visit contain a number of excerpts from A.H.T.'s medical records documenting some of her symptoms. Other symptoms, such as reports of frequent fevers and respiratory infections, are reflected only by parental history, and are either in conflict with the contemporaneous records or are not supported by the medical records or other evidence.

The "Neuromuscular" section of the medical history portion of Dr. Shoffner's records included the statements that "[p]arents and records report fatigue with activity" and that A.H.T. had "[g]eneralized hypotonia." Pet. Ex. 47, p. 2120. However, the filed medical records do not document fatigue with activity or generalized hypotonia, although some reports of low muscle tone appear in the PT and OT records. Fatigue is mentioned in her records, but primarily in the context of A.H.T. reporting fatigue when she was asked to perform activities that she did not like. A physical examination of

Hefner in September 2002); Pet. Ex. 34, p. 1287 (history provided to pediatric gastroenterologist Dr. Thomas Stephen in October 2003), which do not identify any worsening of the symptoms at a time after the second vaccination. Even Dr. DeMio concluded, after hearing petitioner's testimony, that there was no evidence that A.H.T. worsened after the second vaccination. Tr. at 245-46.

¹²⁵ The score sheets cover clinical criteria, biochemical testing, and genetic testing. In the absence of an identified genetic defect, such score sheets are the way mitochondrial disorders are diagnosed.

A.H.T. found normal strength and gait, no neuromuscular eye movement problems,¹²⁶ and normal reflexes. *Id.*, pp. 2123-24. There is no indication that the examiner found evidence of hypotonia, generalized or otherwise.

This record also contains the first-ever report of a fever within one to two days of the initial hepatitis B vaccination, as well as a report of frequent fevers. Pet. Ex. 47, p. 2121. The medical records pertaining to fevers, respiratory infections, fatigue, and hypotonia are discussed in more detail below, along with the expert testimony regarding them.

The history also reflects the parental report that A.H.T. did not speak her first words until 30 months of age. *Id.* This history conflicts with the contemporaneous records reflecting language acquisition and use when A.H.T. was 12 -18 months old and Ms. Holt's earlier histories reporting no concerns about A.H.T.'s language until she was about 18 months old. At that point, the issue was that she was not using two-word phrases, not that she had failed to acquire any words at all.¹²⁷ In the histories provided at the initial early intervention examinations, A.H.T.'s parents reported that she used words, but they would come and go from her vocabulary.

Several pages of the initial consultation report include general information about genetics, ASD, and mitochondrial disorders. Pet. Ex. 47, pp. 2124-28. The section also references Dr. Shoffner's "manuscript . . . discussing the association of autistic regression in conjunction with fever" and his opinion that "fever is a significant variable associated with autistic regression in a subset of patients with autism spectrum disorders."¹²⁸ *Id.* The report concluded with a general section on followup (*id.*, p. 2127) and diagnostic recommendations which may or may not have been specific to A.H.T. (*id.*, p. 2128).

b. Testing.

In general, the test results themselves are not in controversy (see, e.g., Res. Ex. G at 1-2 (Dr. McCandless commenting that the muscle biopsy results clearly show some diminution of function in the ETC); Tr. at 532, 564 (testimony that the laboratory where testing was performed had "a good reputation," and that Dr. McCandless sent

¹²⁶ A.H.T.'s records contain multiple notes from ophthalmologists, neurologists, and other medical specialists, all of whom note normal eye movements and examinations. There is no evidence of a problem with her eye muscles. Tr. at 469-70, 644. An optometrist did use the term, but none of the physicians A.H.T. saw found the type of oculomotor dysfunction seen in mitochondrial disorders. Tr. at 470-71.

¹²⁷ According to Dr. Wiznitzer, notations about speech and precursors to speech in A.H.T.'s medical records prior to 18 months of age reflect no issues. Tr. at 642.

¹²⁸ This reference is likely the Shoffner study, Pet. Ex. 68, which was discussed in the context of Dr. Kendall's causation opinions.

cerebrospinal fluid [“CSF”] samples to it for his own patients).¹²⁹ However, the relationship between the test results and A.H.T.’s clinical presentation is contested and is discussed in Part D(4) below.

The only positive result from the muscle biopsy was in the enzymology test, which measured enzyme activity in skeletal muscle. A.H.T. had evidence of moderately impaired function in Complex I and Complex III¹³⁰ of the ETC (Pet. Ex. 26, p. 564 (skeletal muscle enzymology showing decreased activity); (Res. Ex. G at 2 (Dr. McCandless’ characterization of the defect as “moderate”)), with corroborating results from the clear native gel test for enzyme assembly (Pet. Ex. 26, pp. 530-31).¹³¹ The enzymology and clear native gel results were reflected as abnormal on the evaluation summary (*id.*, p. 523) and were also scored as part of the biochemical criteria diagnostic score sheet (*id.*, p. 526).

Other tests of mitochondrial function were “unremarkable,” the term this laboratory used for negative results. See *id.*, pp. 532 (insufficient samples for testing Complexes I-IV, and Complex V measured as unremarkable); 533-34 (finding overall assembly of supercomplexes tested to be unremarkable on blue native gel analysis);¹³² 563 (Western blot protein analysis with Complexes I-V all reported as unremarkable, reflecting appropriate levels in skeletal muscle).¹³³

Doctor McCandless expressed some concern about whether the test really showed a defect in Complex III, or merely one in Complex I. When the activity of Complexes I and III was measured jointly to assess “supercomplex” activity, there was a

¹²⁹ He identified Dr. Hyland (whose name was misspelled in the transcript at “Highland”) as the person at the laboratory to whom he sent the samples. Tr. at 532; see also Pet. Ex. 26, pp. 535-36 (examples of test interpretations performed by Keith Hyland, Ph.D.).

¹³⁰ The transcript uses Arabic numbers for the five complexes of the ETC, but the references in the records use Roman numerals. I use Roman numerals as well.

¹³¹ The activity of the ETC, which takes place largely on the inner of the two membranes comprising the outer part of the mitochondria, consists of five protein complexes (Complexes I-V). Tr. at 463-64. A different biochemical step in the conversion of nicotinamide adenine dehydrogenase to ATP takes place in each complex. Tr. at 464. This conversion process is referred to as “oxidative phosphorylation” or “OXPHOS” in the laboratory reports and occasionally in the testimony. See, e.g., Pet. Ex. 26, p. 530; Tr. at 318-19 (Dr. Kendall explaining that OXPHOS enzymology is a measure of the activity of the ETC). Complexes in the ETC also interact with other metabolic processes occurring in the mitochondria in creating ATP. Tr. at 464-65.

¹³² The report on the blue native gel testing indicated that the test would “not detect mild decreases in the quantity of monomeric OXPHOS enzymes or supercomplexes.” Pet. Ex. 26, p. 534. Doctor McCandless testified that the blue native gel test would be more accurate in detecting mitochondrial dysfunction than the clear gel. Tr. at 497-98.

¹³³ The report on the Western blot testing indicated that the test “can detect OXPHOS defects that are not evident by OXPHOS enzymology.” Pet. Ex. 26, p. 563. Other laboratory documents indicated that this is one of the better tests for detecting mitochondrial disorders (*id.*, p. 570), but noted that the results can be normal even in patients with identified genetic mutations (*id.*, pp. 572-23).

diminution in activity. Tr. at 474; see also Tr. at 321 (Dr. Kendall's explanation of supercomplexes); Pet. Ex. 26, p. 564 (laboratory explanation of supercomplexes). But, when Complex III activity was measured independently, the value recorded (see Pet. Ex. 26, p. 564) was just over 50% of the mean. Tr. at 493-94. Doctor McCandless explained that because the result was 50% of normal, most practitioners would think that the level of Complex III activity was unlikely to be associated with any clinically significant dysfunction. Tr. at 495. However, Dr. Shoffner's laboratory reported the test result as abnormal, because it was outside the reference range established by his laboratory. Tr. at 494.

High resolution respirometry testing of A.H.T.'s muscle did not identify any specific abnormalities. Pet. Ex. 26, p. 565. Notes in the methodology section of this report indicated that discrepancies between enzymology (the only clearly positive test result in A.H.T.'s case) and this test are common, because they measure different aspects of mitochondrial function.¹³⁴ However, the respirometry test "may more closely reflect the *in vivo* state of the respiratory chain and oxidative phosphorylation function. Large functional excesses of respiratory chain complexes are present, thus allowing better function *in vivo* than is demonstrated by enzymological techniques." Pet. Ex. 26, p. 565 (citation omitted). The muscle histology and immunochemistry test was likewise unremarkable, and the report noted that the negative result on immunofluorescence testing "significantly decreases the possibility of defects that impair mitochondrial protein synthesis as well as disorder[s] that impair OXPHOS enzyme assembly." Pet. Ex. 26, p. 571.

Tests on blood, urine and cerebral spinal fluid were also performed. The parties disagreed about the significance of the level of methyltetrahydrofolate found in A.H.T.'s cerebral spinal fluid.¹³⁵ It was not one of the tests that resulted in points on the diagnostic score sheet, and the result was within the laboratory's reference range (reported at 44, with the laboratory reference range from 40-128 nmol/L) (Pet. Ex. 26, p. 560). Doctor Kendall's testimony that this result was below normal (Tr. at 323) was incorrect, but this may have been because Dr. Shoffner recommended treatment. Pet. Ex. 61, pp. 2347-48.

Doctor Kendall testified that a cerebral folate deficiency "can be" a potential indicator of mitochondrial dysfunction and is seen in "some subsets of mitochondrial disease," particularly in patients with genetic defects in mtDNA. Tr. at 322-23. She added that a cerebral folate deficiency could produce such clinical symptoms as irritability, poor sleeping, seizures, and brain atrophy. *Id.* Doctor McCandless testified

¹³⁴ A caveat also appears on the enzymology test report: "Enzymology should not be the sole criteria used to assess patients for the presence or absence of mitochondrial disease and mitochondrial dysfunction." Pet. Ex. 26, p. 564.

¹³⁵ Doctor Kendall agreed that this test result was "not traditionally considered" in the diagnosis of mitochondrial disease. Tr. at 374. Doctor McCandless testified that it showed "there may be a mild cerebral folate deficiency. Tr. at 491-92. He also indicated that the level found "seems kind of borderline." Tr. at 492.

that a cerebral folate deficiency was not diagnostic of mitochondrial dysfunction because such results were seen in many neurological diseases. Tr. at 491-92. However, in his August 1 report on testing and diagnosis, Dr. Shoffner appeared to relate the cerebral folate deficiency to A.H.T.'s autism diagnosis by referencing four medical journal articles "for cerebral folate deficiency and autism." Pet. Ex. 47, p. 2111 (citations omitted). Nevertheless, his report also noted, "[c]erebral folate deficiencies have a variety of causes. The symptoms are complex and include developmental delays, autistic features, seizures, irritability, ataxia, spastic paraplegia, dykinesias, and epilepsy." Pet. Ex. 47, p. 2125 (citations omitted).

Tests other than those on muscle tissue and body fluids were performed as well during the assessment. A.H.T.'s resting metabolic rate was measured, with results at 76% of the predicted value.¹³⁶ Pet. Ex. 26, p. 537. When Dr. Kendall was asked whether she considered this a symptom that she would use in making a diagnosis of a mitochondrial disorder, she was somewhat equivocal, testifying that "[i]t would certainly be considered in the context of other findings." Tr. at 314. Notwithstanding her equivocation, a low resting metabolic rate was a part of the diagnostic criteria used by Dr. Shoffner and was one of the test results for which points were assigned on Dr. Shoffner's score sheets. Pet. Ex. 47, p. 2112.

There does not appear to be any dispute concerning the test result itself, but Dr. McCandless pointed out that A.H.T.'s lack of muscle mass was a factor that should be considered in the weight to give the test results. Tr. at 479. The test report reflected A.H.T.'s body mass index as 15.7, indicating that she was underweight. Pet. Ex. 26, p. 537. Being underweight or out of condition might tend toward decreased muscle mass and a finding of a decreased resting metabolic rate.¹³⁷ *Id.*, p. 538.

¹³⁶ Resting metabolic rate is sometimes referred to as "basal metabolism," which is the energy expended to keep body systems functioning while at rest. *Medical Dictionary for the Health Professions and Nursing*. (2012). Retrieved April 7, 2015 from <http://medical-dictionary.thefreedictionary.com/resting+metabolic+rate>; DORLAND's at 1142. Doctor Kendall testified that the resting metabolic rate is determined by measuring heart rate, blood pressure, and oxygen consumption and analyzing them through a series of complicated formulas. Tr. at 364-65. Doctor McCandless added that the rate is sometimes determined by putting the person being tested in a pod, and measuring oxygen consumption and carbon dioxide production and comparing the results to norms for a person of the same size. Tr. at 477-78. The laboratory report did not explain how A.H.T.'s resting metabolic rate was measured. Pet. Ex. 26, p. 537; see also Tr. at 476-77.

¹³⁷ Prior to this testing, A.H.T. had a very sedentary lifestyle, with activities such as drawing, reading, and playing with stuffed animals described as her preferred activities. She had "unlimited access" to video games. Pet. Ex. 38, p. 1709 (functional behavioral assessment). She was home-schooled and rarely taken out into the community, typically remaining in her pajamas throughout the day. *Id.* Her exercise seemed largely to consist of OT one or two times per week and swimming occasionally. See generally Pet. Exs. 27 (OT); 38 and 57 (behavioral support services records reflecting occasional outings and swimming).

Doctor McCandless also pointed out the equivocal nature of such testing, as both low and high resting metabolic rates can be indicators of some mitochondrial diseases. Tr. at 478-79. Doctor Shoffner's report supported this testimony.¹³⁸

With some minor exceptions, all other tests were "unremarkable," according to Dr. Shoffner's evaluation summary.¹³⁹ Pet. Ex. 26, pp. 522-23. Doctor McCandless testified that to make a reliable diagnosis, "you have to put together the whole package, all the metabolites, the clinical history, these findings," (Tr. at 499) which he summarized and interpreted as follows:

[A.H.T.] has some abnormal tests pointing to [Complex I and Complex III] in the muscle biopsy. She has almost no evidence of metabolites accumulating that would be the result of dysfunction of mitochondria, and the only thing that was in any way abnormal in my opinion is that mildly elevated lactate and pyruvate, which I did not find at all compelling for mitochondrial dysfunction. I think it's much more likely to be an artifact. So except for the two pieces of data that suggest a I [and] III defect in the biopsy, which I don't quibble with, I think this sort of all together, just the laboratory part of it, I would say this is possibly mitochondrial disease. Mitochondrial dysfunction, possibly.

Tr. at 500.

2. Diagnostic Scoring Systems and Criteria.

The experts agreed that in the absence of an identified genetic defect affecting mitochondrial function, there are no "gold standard" tests for diagnosing mitochondrial disorders. Tr. at 323, 439; *see also* Pet. Ex. 26, p. 563 (report from Dr. Shoffner's laboratory stating that a single test is rarely sufficient to diagnose or exclude mitochondrial disease).

¹³⁸ The materials accompanying the test results from Dr. Shoffner's laboratory indicated that patients with ETC defects "may show increased resting metabolic rates possibly reflecting an increased oxygen consumption to compensate for reduced ATP synthesis or decreased resting metabolic rates reflecting decreased oxygen utilization by tissue mitochondria." Pet. Ex. 26, p. 577.

¹³⁹ Evaluations of A.H.T.'s plasma amino acids, urine organic acids, electrolytes, and ammonia levels did not reveal any clinically significant abnormalities. Res. Ex. G at 1; *see also* Tr. at 487-88 (Dr. McCandless testifying about his own laboratory, which performs such tests). Her cerebral spinal fluid test results were treated as normal on the score sheets. Although the lactate/pyruvate ratio was slightly elevated (Res. Ex. G. at 2; Pet. Ex. 26, p. 562), points are not assigned unless the CSF pyruvate rate is elevated. Although the plasma lactate and pyruvate were both minimally elevated, the level was within the range seen in children who were uncooperative with the blood draw. Res. Ex. G. at 2; Pet. Ex. 26, pp. 543, 545; Tr. at 362 (testimony of Dr. Kendall that the most common explanation for mildly elevated serum lactate is "a collection artifact" and that this is the reason the serum lactate testing is performed on multiple occasions); Tr. at 480 (testimony of Dr. McCandless that this was a borderline elevation much more likely to be consistent with artifact than a mitochondrial disorder).

Several different scoring systems involving various diagnostic criteria are used in evaluating patients for the presence of mitochondrial disorders. Two of these, the Bernier and Nijmegen criteria, were discussed at various points during the expert testimony. See, e.g., Tr. at 324, 377-78 (Dr. Kendall discussing Bernier on cross-examination), 439 (Dr. McCandless identifying the various criteria discussed). However, regardless of the scoring system used, clinical judgment regarding the patient's presentation plays a significant role in making a diagnosis. See Tr. at 302, 409-10, 533-34. Even when genetic evidence for a mitochondrial defect is present, a patient may not display clinical symptoms, particularly if the defect is present in mtDNA.¹⁴⁰

Doctor Shoffner used the Nijmegen criteria as the basis for his diagnoses.¹⁴¹ See Pet. Ex. 61, p. 2349-50. He also used genetic criteria in diagnosing patients, but as

¹⁴⁰ Not all cells—even cells in the same tissue—have the same number of mitochondria, and within a cell, any defect may be present only a few of that cell's mitochondria. Tr. at 430-31. This is referred to as heteroplasmy, a mixture of normal and abnormal mitochondrial genomes. See NELSON'S at 391. If there are enough mitochondria without the defect, there may be no clinical effect. Doctor McCandless also indicated there was debate about whether individuals who had genetic mutations associated with well-recognized mitochondrial disorders but who did not have clinical symptoms could be said to have a mitochondrial disorder diagnosis. Tr. at 441-42; see also Pet. Ex. 26, p. 572 (statement in Dr. Shoffner's report that defects are highly variable even among individuals who harbor identical mutations). Heteroplasmy may increase or decrease over time, depending on how many of which type of cells divide and how the percentage of defective mitochondria are shared among the daughter cells.

¹⁴¹ Doctor Shoffner's two reports (see, e.g., Pet. Ex. 61, p. 2349) reference the Nijmegen criteria and cite to the study filed as Court Ex. I, Wolf & Smeitink. This study was performed in association with the Nijmegen Center for Mitochondrial Disorders, hence the reference to it as the Nijmegen criteria. The article notes that additional material from the study (which explains the parameters for awarding points) is located on the website of the journal NEUROLOGY. Wolf & Smeitink, Court Ex. I at 1402 [text box at bottom of first column, which refers to the explanations of the general criteria, found at: <http://www.neurology.org/content/suppl/2002/11/11/59.9.1402.DC1/MDCgeneralcriteria.html>]. Doctor Shoffner's citation to this journal article references the November 12, 2002 date of publication used to access the link to the additional materials, indicating that he incorporated the supplemental materials into his "Clinical Criteria" score sheet. See *id.*; Pet. Ex. 61, p. 2349. This supplemental material will be referred to as "Wolf & Smeitink, Court Ex. I, Supplemental Material."

Wolf & Smeitink proposed and tested new mitochondrial disease diagnostic criteria (abbreviated in the study as "MDC") for diagnosing ETC disorders in infants and children. They found that the MDC/Nijmegen criteria, which use "more precise definition of clinical and metabolic items and the independent scoring of muscle biochemical investigations" to be accurate in identifying infants and children with ETC disorders. The authors noted that the previously proposed modified adult criteria for diagnosing children had no clear definitions for the various clinical and laboratory findings. Wolf & Smeitink, Court Ex. I, at 1402. The authors concluded that splitting the diagnostic criteria into two subsets, general (which included the clinical, metabolic, imaging, and pathologic criteria) and biochemical (which included the results of muscle biopsies testing ETC function), enhanced diagnostic confidence. *Id.* at 1402 (Abstract). The authors recommended a "careful clinical and metabolic workup" before scheduling a muscle biopsy, indicating that the clinical criteria should be evaluated for evidence of mitochondrial disease before performing a muscle biopsy. *Id.* at 1404.

A.H.T. had no identified genetic defect related to mitochondrial function,¹⁴² these will not be otherwise discussed. For the Nijmegen scoring system, two scores are generated, one for the biochemical criteria (muscle biopsy test results) and one for the clinical criteria. The scores on the clinical criteria and biochemical criteria score sheets are evaluated independently; the scores are not combined. Wolf & Smeitink, Court Ex. I, at 1402.

The clinical criteria are divided into four categories of symptoms, two of which are largely based on test results, and two of which are symptoms-based.¹⁴³ Up to 4 points can be awarded in each of the two categories based on test results and up to 2 points can be awarded in each of the two symptoms-based categories.

Scoring can be very subjective and the clinical scoring systems can be manipulated. Doctor McCandless explained that “[t]here are proposed ways of scoring the combination of clinical and biochemical findings to determine whether somebody is more or less likely to have a primary mitochondrial disease. There’s [sic] lots of problems with those scoring systems.” Tr. at 439. He added that “what becomes clear is that the clinical criteria are very subjective and that if you believe somebody has mitochondrial disease, you can very easily make their score give you a result that they have mitochondrial disease.” Tr. at 440. Referring to a chart she supplied with her expert report (Pet. Ex. 79 at 2500), Dr. Kendall discussed the many types of symptoms that could be indicative of mitochondrial disease. Tr. at 306-08. She also testified that the various diagnostic criteria did not work with all patients. Tr. at 323-25. Nevertheless, as the Nijmegen study pointed out, diagnosis standardization is necessary in order for proper investigation and treatment protocols to be established. Wolf & Smeitink, Court Ex. I, at 1401.

According to Dr. McCandless, the biochemical criteria also present difficulties for interpretation. While less subjective than the clinical scoring, the biochemical criteria for

¹⁴² With the advent of new tests and better identification of causal genes, about half of patients with a mitochondrial disorder diagnosis have genetic defects or evidence of a depletion syndrome. However, Dr. Kendall indicated that fewer than half the patients in her practice have an identified genetic problem. Tr. at 326-28. No genetic defect pertinent to a mitochondrial disorder diagnosis was identified in A.H.T. Tr. at 326-27. A chromosome microarray detected no significant copy number changes. Pet. Ex. 26, pp. 553-54. A test of tissue harvested during the muscle biopsy to determine if there were any problems with the quantity of mtDNA within the tissue was reported as negative, indicating that A.H.T. did not have an mtDNA depletion syndrome. A genetic test for one of the known mtDNA disorders was also performed and was also negative. Pet. Ex. 26, pp. 569-70. Other genetic tests were recommended but if they were performed, no results were filed. Pet. Ex. 26, p. 524.

¹⁴³ The two categories based on test results are (1) metabolic and imaging studies and (2) tissue morphology. See Pet. Ex. 61, p. 2349. The two more subjective categories are (1) neuromuscular manifestations and (2) central nervous system and any other organ involvement. *Id.* There are specific findings listed for each subcategory, which are further explained in Wolf & Smeitink, Court Ex. 1, Supplemental Materials at <http://www.neurology.org/content/suppl/2002/11/11/59.9.1402.DC1/MDCgeneralcriteria.html>. The relationship between this website and the Nijmegen criteria used by Dr. Shoffner is described in n.141, above.

diagnosing mitochondrial disorders are controversial and researchers have encountered problems in producing consistent and reliable diagnoses using them. Tr. at 440. Doctor McCandless testified that it was not uncommon to see “subtle abnormalities” on biochemical testing in patients who did not have a primary mitochondrial disorder. Tr. at 568.

3. Diagnoses.

Doctor Shoffner made two assessments of the likelihood that A.H.T. has a mitochondrial disorder. His August 1, 2011 diagnosis of a *possible* mitochondrial disorder is reflected in two exhibits. Pet. Exs. 26, pp. 522-82 (copy containing diagnosis and test results); 47, pp. 2109-16 (copy from Dr. Levinson’s records without test results). On these score sheets, A.H.T. received 2 points for having a low resting metabolic rate and 1 point for “exercise intolerance.”

In the August 10, 2011 report, which coincided with the date Dr. Shoffner met with A.H.T. and her parents for the second time, he changed his diagnosis from a *possible* to a *probable* mitochondrial disorder. See Pet. Ex. 61, pp. 2346, 2349. No explanation was offered for the change in diagnostic category in the report, and the earlier, less definitive diagnosis was not mentioned.

In the August 1 version of the report and diagnosis, Dr. Shoffner set forth his methodology for reaching the diagnosis:

We performed a careful assessment of this patient. The data from the evaluation is correlated with diagnostic criteria for mitochondrial disease. At this juncture we have data supporting an impairment of mitochondrial function that appears to be due to a mitochondrial disease. This patient is characterized by a decreased resting metabolic rate, increases in blood lactate and pyruvate, increased lactate/pyruvate ratio in CSF, abnormal OXPHOS enzymology, a cerebral folate defect, and a possible decrease in supercomplex formation.

Pet. Ex. 47, p. 2111. However, when he scored A.H.T.’s clinical picture and tests, he did not assign points for the blood and CSF levels of lactate and pyruvate, probably because they did not meet the criteria specified on the score sheets, which require elevated blood lactate on three occasions and an elevation in CSF lactate. See Pet. Ex. 47, p. 2112 (score sheet reflecting the requirements). A.H.T.’s CSF lactate and pyruvate were both in the normal range, although the ratio between lactate and pyruvate was elevated. Doctor Shoffner apparently thought this was significant enough to mention in his summary (quoted above), but Dr. McCandless testified that the ratio was not important so long as neither lactate nor pyruvate was elevated. Tr. at 480. On the August 1 score sheet, A.H.T. was assessed as having a possible, not a probable, mitochondrial disorder. *Id.*

The diagnostic change in the August 10 report was based on 1 additional point in the clinical criteria portion of the scoring system.¹⁴⁴ Doctor Shoffner increased the score in “Central nervous system and other organ involvement” category from 1 point (accounting for A.H.T.’s developmental delay/ASD diagnosis) on the August 1 report to 2 points on the August 10 report. The increased score was based on the involvement of two or more organ systems. *Compare* Pet. Ex. 26, p. 525 *with* Pet. Ex. 61, p. 2349; see *also* Tr. at 616-17. This resulted in a total score of 5, the lowest score in the “probable” diagnosis category. The scoring sheet does not require the identification of the other organ system (or systems) and Dr. Shoffner did not indicate which second organ system showed symptoms of mitochondrial disease.¹⁴⁵ According to Dr. Kendall, A.H.T. had evidence of mitochondrial disease affecting her neuromuscular, neurological, and nutritional/gastrointestinal systems. Tr. at 371.

Scoring was otherwise the same in both reports. No additional testing or examinations between the August 1 and August 10 reports were reflected in the records.

It is difficult to determine what precipitated the increased score in the organ system involvement category. A comparison of Pet. Ex. 61 to Pet. Ex. 26 reveals several additions to the “History of Present Illness” section of the clinical history, but the additions were not identified as the reason the scoring changed and do not appear to reflect the involvement of a second organ system. Under “Neurobehavioral features,” the additions were: (1) “Significant emotional lability is observed” (found in 1(e), Pet. Ex. 61, p. 2342) and (2) “Social Communication Questionnaire completed during today’s clinic visit,” with a note that the score “is not inconsistent with ASD” (found at 1(f), *id.*). “Abnormal social and emotional behavior” was added as 2(d), under the “Neuropsychological evaluation” heading. Under “Neuromuscular, Frequent Illnesses,” episodic headaches and chronic pain were added as (3(d) and (e)).¹⁴⁶ The report of

¹⁴⁴ The biochemical criteria score sheet (reflecting the muscle biopsy test results) remained at 1.5, reflecting a possible mitochondrial disorder diagnosis, in both reports. Pet. Exs. 26, p. 525; 61, pp. 2349-50.

¹⁴⁵ In general information provided as a part of one of his reports, Dr. Shoffner indicated that the “most common manifestations” in organs other than the central nervous system are cardiac, muscle (fatigue, exercise intolerance and weakness were mentioned as symptoms of muscle manifestations), endocrine, liver, and renal systems. Pet. Ex. 26, p. 577. Unlike Dr. Kendall, he did not list the gastrointestinal system separately. *Id.*; Pet. Ex. 79 at 2500 (extensive list of organ systems and symptoms that Dr. Kendall associated with mitochondrial disorders). Based on the testimony of Drs. Kendall and McCandless, both of whom discussed gastrointestinal manifestations of mitochondrial disease, this was likely an oversight on Dr. Shoffner’s part.

¹⁴⁶ A.H.T.’s medical records do not support this report of either headaches or chronic pain. Although there were reports of abdominal pain with constipation (e.g., Pet. Ex. 23, p. 243), occasional ear pain (*id.*, p. 261), pain with urinary tract infections (*id.*, p. 264), pain with cough and viral syndrome (Pet. Ex. 52, pp. 2212-13), and reports of chest pain made to her cardiologist (Pet. Ex. 13, p. 103), the first report of generalized or chronic pain was in the intake form completed for Dr. Levinson in May 2010. Paradoxically, the intake information also indicated that A.H.T. habitually underreacted to pain. Pet. Ex. 47, p. 2055. There were no reports of chronic pain to her therapist (Pet. Ex. 16, pp. 132-43) or her clinical psychologist (Pet. Ex. 51, pp. 2188-2210) in 2009. Doctor Puri and his associates, who saw A.H.T. from

frequent respiratory infections and fevers was moved to this section as well. *Id.* These additions and changes do not account for the change in diagnosis from a possible to a probable mitochondrial disorder.

4. Mitochondrial Diagnostic Issues in Controversy.

Doctor McCandless did not contest the laboratory evidence of some diminution in function in Complex I and possibly some problem in supercomplex formation in A.H.T. However, he opined that A.H.T. did not have a mitochondrial disorder based on her entire clinical picture and that the dysfunction in Complex I (and possibly Complex III) was not responsible for the symptoms A.H.T. displayed. Tr. at 423.

The factual basis for concluding that A.H.T. has exercise intolerance was one of the issues raised during the hearing. See Tr. at 347-48 (cross-examination of Dr. Kendall regarding the exercise intolerance finding by Dr. Shoffner). Subtraction of the 1 point assigned for exercise intolerance would change the most recent diagnosis from “probable” to “possible.” Also disputed is the involvement of the second organ system—one other than the central nervous system—with dysfunction sufficient to qualify her as having a possible or probable mitochondrial disorder diagnosis under the Nijmegen diagnostic criteria. Two possible candidate systems were discussed by the experts: gastrointestinal and autonomic. A.H.T.’s early gastrointestinal problems were discussed *supra*; the more recent history is set forth below. Dysfunction in the autonomic system rests on the evidence concerning whether A.H.T. truly had recurrent fevers without a concurrent illness. It is also possible that Dr. Shoffner used neuromuscular manifestations (based on the reports of “generalized hypotonia” mentioned in his reports) in concluding that A.H.T. had symptoms of a second organ system involvement, although this is less likely, as he did not assign any points for “muscle weakness” on either of the score sheets. See Pet. Exs. 47, p. 2120; 61, p. 2349.

Because Dr. Shoffner’s score sheets begin with the neuromuscular manifestations, I begin there as well.

a. Exercise Intolerance.

The experts often discussed resting metabolic rate, hypotonia (low muscle tone), and exercise intolerance together in their answers. Tr. at 347 (Dr. Kendall defining

2004-11, did not record a history of chronic pain, and reflected a history of headaches only after her motor vehicle accident in February 2011. See *generally* Pet. Ex. 31 and p. 1240 (“concern for headaches following head trauma”). There is some evidence that claims A.H.T. or her mother made of pain were manipulative or exaggerated. See Pet. Exs. 38, p. 1762 (behavioral support analyst noting that A.H.T. complained of pain to avoid work) and 43, p. 1869 (physical therapist noting inconsistent reports of pain in post-vehicle accident therapy). A.H.T.’s parents first reported chronic pain to Dr. Shoffner at the August 10, 2011 visit (“Child is felt to have chronic pain” (Pet. Ex. 61, p. 2342), but on August 22, 2011, they reported to the behavioral support analyst that the “Georgia doctors” thought she was in a lot of pain routinely. Pet. Ex. 57, p. 2295. Without being aware of this circular attribution, the analyst expressed her concern that pain would be used as an excuse for not implementing behavioral interventions. *Id.*

fatigue as an inability to do normal daily activities without feeling overwhelmingly tired, and equating fatigue with exercise intolerance); 364-65 (Dr. Kendall testifying that exercise intolerance could be determined by history, observation, or the resting metabolic rate); 541-42 (Dr. McCandless testifying that the muscle findings that are most compelling for a mitochondrial diagnosis are large group muscle weakness, excessive fatigability, muscle breakdown, or clearly reduced exercise tolerance, not the fine motor skills delay A.H.T. displayed). The explanatory materials from the Wolf & Smeitink article, Court Ex. I, define exercise intolerance as “a symptom characterized by abnormal premature fatigue/weakness/muscle aches or cramps after normal play or activities of daily living.” *Id.*, Supplementary Materials, Section A (Muscular Presentation).

This conflation by the witnesses is understandable, because the score sheets used by Dr. Shoffner (and the Nijmegen criteria upon which the score sheets are based) have some overlap. Exercise intolerance is a subcategory under “Neuromuscular manifestations.” Decreased resting metabolic rate is a subcategory under the category “Metabolic and imaging studies.” However, “resting metabolic rate” is “pled in the disjunctive,” as the term is followed by “or abnormal exercise studies (cycle ergometry protocol).” Thus one could argue that “exercise intolerance” counts twice, both as a neuromuscular manifestation and as an abnormal test result.

It is doubtful that this result is intended, however, as the Nijmegen criteria were established to avoid overemphasizing any one symptom, test result or manifestation. Wolf & Smeitink, Court Ex. I, at 1402-03. It is impossible, based on the scoring limitations by category, to obtain a diagnosis of a “probable” mitochondrial disorder by results in one category alone.¹⁴⁷ In any event, A.H.T.’s resting metabolic rate was not measured via cycle ergometry (see Pet. Ex. 26, p. 537), and is thus not likely the basis for the point scored for exercise intolerance.

Instead, it appears that the score was assigned based on A.H.T.’s parents’ report to Dr. Shoffner that she had exercise intolerance. See Pet. Ex. 47, p. 2120 (“Parents and records report fatigue with activity”). No medical or other records reporting exercise intolerance were excerpted and included as support for this assertion, although excerpts for many other records were interspersed throughout the medical history. See *generally, id.*, pp. 2117-22. The most recent record from the pediatric cardiologist who diagnosed A.H.T.’s heart murmur is excerpted immediately below the “parents and records” comment. This cardiologist saw A.H.T. twice, in June 2009 (Pet. Ex. 13, pp.

¹⁴⁷ The maximum score for a category varies from 2 to 4 points. The two categories where 4 points could be scored are those involving laboratory tests. One, “tissue morphology,” includes fairly definitive evidence of abnormalities in tissue that are strongly associated with mitochondrial dysfunction, none of which applied to A.H.T. The other category where up to 4 points could be scored is “metabolic and imaging studies,” which involve tests run on blood, cerebral spinal fluid, and urine, as well as imaging tests, in addition to the exercise ergometry or resting metabolic rate testing discussed above. The two other categories, which are much more subjective, each have a limit of 2 points. A total score is computed by adding scores from the four categories. A total score of 4 results in a “possible” mitochondrial disorder diagnosis; a score of 5 results in a “probable” diagnosis.

105-06) and in July 2010 (*id.*, pp. 103-04). This excerpt quotes from A.H.T.'s second visit, which does not mention exercise tolerance.

However, at the initial visit, the cardiologist wrote that A.H.T. "had a normal energy level and exercise tolerance and can easily keep up with other children." Pet. Ex. 13, p. 105. Doctor McCandless commented on this record in his testimony to support his opinion that A.H.T. did not have evidence of exercise intolerance, explaining that cardiologists "know how to elicit a history of exercise intolerance or fatigue" and that this cardiologist elicited a history that A.H.T.'s exercise tolerance was normal. Tr. at 535. Either the record from this initial visit was not provided to Dr. Shoffner or he failed to read and include it in his summary of relevant medical records.

Doctor Kendall testified that she had no idea how Dr. Shoffner came to the conclusion that A.H.T. had exercise intolerance. Tr. at 364-65. She also testified that "[a]t some point in the records there were indicators as such. Otherwise I wouldn't have stated it," but she could not recall where in the records exercise intolerance was mentioned. Tr. at 348.

My review of the records failed to disclose any physician who even mentioned exercise intolerance before Dr. Shoffner did so.¹⁴⁸ Ms. Holt reported fatigue to Dr. Kartzinel in the initial intake form (Pet. Ex. 24, p. 465) in June 2007, but also reported that A.H.T. was "overactive" (*id.*). In the intake information provided to Dr. Levinson in May 2010, Ms. Holt reported that A.H.T. had "high energy, yet complains of fatigue when asked to do simple tasks." Pet. Ex. 47, p. 2055. This comment is similar to those of the behavioral analysts in 2010-11 who noted that A.H.T. displayed "a lack of motivation" or complained of fatigue or being sick when asked to do tasks that she did not like. Pet. Ex. 38, pp. 1773, 1794-95. A.H.T.'s PT and OT records in general demonstrated her ability to do aerobic exercise, but also reflected her lack of cooperation when asked to do exercises or activities that she did not favor. See Pet. Exs. 37, p. 1363 (record reflecting A.H.T.'s discharge from PT, and noting that she

¹⁴⁸ Doctor Kendall also testified that A.H.T. had fatigue (Tr. at 312-13), but most if not all of the instances where fatigue is mentioned, the context does not suggest general fatigue that interfered with activities of daily living. For example, in July 2004, A.H.T.'s occupational therapist commented that she appeared tired and irritable, but the comment was preceded by the report that A.H.T. continued to have difficulty sleeping. Pet. Ex. 55, p. 2280. This comment occurred during the period when Dr. Grimes noted that the family was struggling with A.H.T.'s significant sleep disturbance. Pet. Ex. 17, p. 144. Records from this time frame describe A.H.T. as active and playful (primary care provider in August 2004 (Pet. Ex. 52, p. 2225)), "a little hyperactive" (neurologist in September 2004 (Pet. Ex. 31, p. 1264)); and active at OT in October 2004 (Pet. Ex. 55, pp. 2265-66)). Later evaluations contained similar comments. See, e.g., Pet. Ex. 28, p. 1081 (described as active on clinical observation during PT evaluation). When fatigue was mentioned, it was usually in the context of an excuse for something A.H.T. did not want to do, or attributed by her parents to a drug or therapy. See, e.g., Pet. Ex. 38, pp. 1690 (Rozerem (a drug A.H.T. was taking for sleep disturbances) was reported to cause fatigue and drowsiness); 1794-95 (using tiredness as an excuse to avoid home school). Much of A.H.T.'s physical activity when older was in the context of OT services, and while she occasionally refused to use the treadmill or exercise bike, she would do preferred activities such as Wii games or riding a bicycle with training wheels. See, e.g., Pet. Ex. 27, p. 585.

could perform 30 minutes of aerobic activity); 27, p. 589 (OT therapy review indicating that A.H.T. was “controlling and avoidant of most non-preferred activities”).

When questioned about A.H.T.’s exercise intolerance at the hearing, Ms. Holt testified that she was a very hyperactive child who never took naps. Tr. at 72. She reported that A.H.T. participated in gymnastics and horseback riding. *Id.* She also enjoyed swimming. See Pet. Exs. 47, p. 2058 (report to Dr. Levinson that A.H.T. was swimming and hiking); 56, p. 2287 (report to neuropsychologist that she enjoyed swimming). Ms. Holt characterized her as “awake and raring to go.” Tr. at 72. She was able to keep up with other children her age, but would get pale and out of sorts at points. One of the reasons her parents thought she might be bipolar is that she would sometimes have too much energy and at other times, not enough. Tr. at 72.

Doctor McCandless specifically referenced Ms. Holt’s testimony about A.H.T.’s activity level as well as the dearth of evidence in the medical records about exercise intolerance when he testified that he did not see evidence of exercise intolerance. Tr. at 534-35.

b. Other Organ Systems.

The supplemental materials to Wolf & Smeitink, Court Ex. I, contain a list of candidate organ systems with qualifying symptoms under each system. The only organ system involvement even possibly applicable to A.H.T. would be the gastrointestinal system (listed in Part C, Multisystemic involvement), the autonomic nervous system (referred to in Part B, CNS [Central Nervous System] involvement,¹⁴⁹ and the muscular system (referred to in Part A, Muscular presentation). Doctor Kendall testified that central nervous system effects can include “developmental delays, autistic features and autism, [and] seizures.” Tr. at 301. Muscle function can be affected, producing hypotonia and weakness. Cardiomyopathies, endocrine disorders, and systemic problems, such as failure to thrive, short stature, and fatigue, are also features of mitochondrial disorders, as well as “GI problems, such as everything from reflux to severe dysmotility where patients are TPN or liquid food-dependent.” *Id.*

(1) Gastrointestinal System.

The gastrointestinal system category in the Nijmegen supplemental materials lists five types of symptoms, chronic hepatic dysfunction, failure to thrive, pancreatic dysfunction, intestinal pseudo obstruction, and unexplained chronic diarrhea lasting longer than three weeks. Although Dr. Kendall testified that virtually any gastrointestinal problem from reflux to severe dysmotility (pseudo obstruction) would be symptomatic of a mitochondrial disorder (Tr. at 301), Dr. McCandless disagreed. He explained that the

¹⁴⁹ A.H.T. had already received the maximum score (1 point) for CNS involvement, based on her ASD and developmental delay diagnoses. Thus, even if she had an autonomic disorder related to temperature regulation, it is doubtful that it would result in an increased score. Nevertheless, because the experts testified about the importance of the overall presentation of a child in making a mitochondrial disorder diagnosis, I discuss the evidence of dysautonomia.

types of gastrointestinal problems seen in mitochondrial disorders are more serious than simple constipation, particularly constipation successfully treated with diet and which resolved over time. Tr. at 553-54. Based on A.H.T.'s records, none of her gastrointestinal problems appear to meet the Nijmegen criteria, supporting Dr. McCandless' testimony that A.H.T.'s gastrointestinal symptoms were not of the nature generally observed in children with mitochondrial disease or dysfunction with gastrointestinal involvement.

Gastrointestinal dysfunction is often a symptom of mitochondrial disease. However, the type and intensity of the dysfunction seen in patients with mitochondrial disease is different from the mild constipation or alternating constipation and diarrhea that A.H.T. experienced. Tr. at 569. The term "gut motility issues" can refer to "any problem with the sort of coordinated movement of the muscles in any part of the gut from the esophagus through to the anus." Tr. at 570. In contrast, "constipation" refers to problems at the end of the gut, with many possible causal factors ranging from an absence of nerve endings through dietary problems. Children with mitochondrial problems can have constipation, but by itself, constipation would not be a sign that points to a mitochondrial diagnosis. Tr. at 570-71. What is much more suggestive is a defect of motility in the small intestine or difficulty with stomach emptying. Tr. at 571.

Although there are numerous references in A.H.T.'s medical records to a history of constipation (or alternating constipation and diarrhea), her early problems were reported as "better" at her one year checkup, and there is little evidence that A.H.T. experienced continuing problems with constipation or diarrhea after about 2009. Between these periods, Ms. Holt provided historical information that A.H.T. had experienced both constipation and diarrhea on a regular basis, but there is no evidence of medical treatment for persistent diarrhea. Rather, diarrhea seemed to be either a symptom of a concurrent illness or was attributed by Ms. Holt to diet or one of the many medical interventions to which A.H.T. was subjected. There were some interventions for constipation and A.H.T. had an endoscopy and colonoscopy, but these procedures did not identify any significant problems. Other than a telephonic consultation with Dr. Buie about six months after the procedures, she did not continue to see a gastroenterologist.

By way of examples, at the January 2005 evaluation at the Weisskopf Center when A.H.T. was not quite three years of age, a history of "chronic" problems with alternating constipation and diarrhea was reported, but her bowel issues were said to have improved with institution of the GF/CF diet and use of a probiotic. Pet. Ex. 46, p. 2037. There were reports of constipation and diarrhea again when she began treatment with Dr. DeMio in the fall of 2005. See, e.g., Pet Ex. 23, pp. 236-37, 256-57, 267. An abdominal x-ray showed "moderate constipation," but no evidence of any bowel obstruction or loop distention. Pet. Ex. 42, p. 1834. Testing for parasites, occult blood, gliadin antibodies, and other possible causal agents for gastrointestinal problems were all negative. See, e.g., Pet. Exs. 24, pp. 377-79; 42, p. 1840. Doctor DeMio thought treatment with secretin and Gastrocrom helped. See, e.g., Pet. Ex. 23, p. 256.

At her initial visit with Dr. Kartzinel in June 2007, A.H.T. was reported to have chronic constipation as well as bloating, excessive gas, and crying and straining before bowel movements, and occasional incontinence. Pet. Ex. 24, pp. 464, 467. An abdominal x-ray showed evidence of mild to moderate constipation. *Id.*, p. 401. She was prescribed Creon for constipation at some point (*see id.*, pp. 454, 456), but it is unclear how long she took it, as at a February 2008 visit to Dr. Hefner, it was not listed as one of her medications (Pet. Ex. 52, p. 2216).

By 2009, however, there were few, if any, contemporaneous reports of constipation and diarrhea, chronic or otherwise. Doctor Puri noted she had “normal bowel and bladder function” at an annual visit in August 2009. Pet. Ex. 31, p. 1243. The initial correspondence from Ms. Holt to Dr. Levinson did not list any current medications for constipation or diarrhea, but problems with constipation and hard stools were mentioned. Pet. Ex. 47, p. 2055. Doctor Levinson’s other records do not include any significant complaints regarding bowel function.

At a June 2011 visit to Dr. Puri’s practice, A.H.T.’s gastrointestinal function was reported as normal, although her history of frequent urinary tract infections was noted. Pet. Ex. 31, p. 1240. A similar report was given in September 2011. *Id.*, p. 1233.

At the time of her August 11 visit to Dr. Shoffner, A.H.T. was taking Colace, a stool softener, indicating that some mild constipation might still be a problem. Pet. Ex. 61, p. 2343. However, her diet may have contributed to the need for a stool softener, as she was reported to refuse vegetables and was resistant to drinking water or other fluids. *Id.* As Dr. Wiznitzer noted, both diet and temperament issues can affect constipation. Tr. at 659.

The most recent record filed (Dr. DeMio’s letter and consultation notes from August 2012) reflected that A.H.T. suffered from gastrointestinal infections, but the records did not list constipation or diarrhea as symptoms. Pet. Ex. 87.

(2) Fever and Illnesses.

Doctor Kendall testified that A.H.T. had a history of temperature instability, which could be reflective of dysautonomia. Tr. at 308. Dysautonomia is considered a malfunction of the autonomic nervous system. DORLAND’S at 575. She described dysautonomia as “having one’s thermostat broken.” Tr. at 309-10. She testified that there was evidence in the records that A.H.T. had fevers of unknown origin, which she defined as fevers not associated with intercurrent illnesses, but she could not point to any particular record in which such fevers were reported. Tr. at 309.

Doctor Wiznitzer testified that his review of the medical records did not support the assertion that A.H.T. had recurrent fevers, absent those fevers connected to an intercurrent illness. Tr. at 632. My review of the medical record is in accord with Dr. Wiznitzer’s.

The first reference to a fever in A.H.T.'s records is a temperature of 101.9° during a bout with otitis media when she was 15 months old. Pet. Ex. 52, p. 2231. In her initial developmental examination at Carriage House in January 2004, Ms. Holt reported that A.H.T. "was hardly ever sick," except with bowel problems. Pet. Ex. 39, p. 1825. At her evaluation by the Weisskopf Center in January 2005, her parents reported "occasional" upper respiratory infections. Pet. Ex. 46, p. 2037. Records from ST reported occasional respiratory infections in January 2005 (Pet. Ex. 18, pp. 200-01), followed by a bilateral ear infection in February 2005 (Pet. Ex. 52, pp. 2224), and MRI evidence of "sinus disease" in March 2005 (Pet. Ex. 31, p. 1273). No fevers were reported in conjunction with these illnesses.

The next report of fever is in a telephonic consultation with Dr. DeMio in November 2005, after A.H.T. began chelation therapy. Pet. Ex. 23, p. 237. In February 2006, Dr. Puri noted a history of "no fever, chills, weight fluctuation." Pet. Ex. 31, p. 1254. Doctor DeMio noted two episodes of vomiting in February 2006, one of which was accompanied by fever. Pet. Ex. 23, p. 241. He also recorded a report of a "low grade fever" in late May 2006 in conjunction with diarrhea, irritability, and a change in medication. *Id.*, pp. 245-46. In July 2006, A.H.T. had a cough and there was a report of fever, but the temperature recorded (36° Celsius) is not febrile. *Id.*, p. 249.

There are several reports of illnesses in 2007 without any fever. See, e.g., Pet. Ex. 23, p. 266; Pet. Ex. 52, pp. 2213 (sinus infection with no fever); 2217 (respiratory infection without fever).

In the initial history provided for Dr. Kartzinel in June 2007, the first reports of "recurrent fever" and "periodic recurrent infection" appear, but no details were provided. Pet. Ex. 24, p. 465. These reports do not appear substantiated by the foregoing medical records. Although Ms. Holt was supposed to track fevers for Dr. Kartzinel (see *id.*, p. 467), there is no evidence she did so. Most of the entries concerning fever in the rest of Dr. Kartzinel's records document the lack of fever, rather than the presence of one (see, e.g., *id.*, pp. 372, 454-56); see also Pet. Ex. 52, p. 2216 (no fever in presence of urinary tract infection in 2008).

A.H.T.'s parents reported to Dr. Jones, a clinical psychologist, in February 2009 a history of frequent high fevers as a baby and toddler, another report not borne out by the primary care or other records. From 2002 through 2005, there are only two medical references to the presence of a fever, and none reflecting a high fever.

In March 2010, at eight years of age, A.H.T. experienced a febrile illness with a high fever, reportedly peaking at 105.2°. The highest temperature recorded by medical personnel at the emergency room was 103.6°. A.H.T.'s temperature declined to normal several hours after her arrival and the administration of Motrin and Tylenol. Pet. Exs. 37, pp. 1333-36 (emergency room records reflecting temperatures, a urinary tract infection, cough and congestion, and "stomach flu") and 52, p. 2212 (Dr. Hefner's records from four days later diagnosing a viral syndrome).

Although there are later reports of “recurrent fevers since infancy” (see Pet. Ex. 31, p. 1240 (in June 2011)) and recurrent fevers of 105+ (see Pet. Ex. 47, p. 2055 (in May 2010)), these histories appear to suffer from the same lack of support as the initial report to Dr. Katzinel in 2007.

(3) Muscle Weakness (Hypotonia).

The Supplemental Materials, Part A, reflect that mitochondrial disease can manifest with muscular signs and symptoms. Exercise intolerance, one of the muscular symptoms listed, was discussed above. Most of the other listed signs and symptoms are clearly inapplicable to A.H.T. Although 1 point may be assigned for reduced muscle power, the specified manifestations do not apply to A.H.T. Reduced muscle power is defined as “Gowers sign or absent or bad head control or delayed motor milestones...or muscular hypotonia.”¹⁵⁰

Doctor Shoffner did not assign any points on the diagnostic score sheet for hypotonia, but he commented on A.H.T.’s “generalized hypotonia” in his diagnostic reports.¹⁵¹ Pet. Ex. 47, p. 2120. Thus, it is possible that he considered muscle weakness as the second organ system involved when he changed A.H.T.’s possible mitochondrial disorder diagnosis to a probable one.

The medical and treatment records are in conflict regarding whether A.H.T. had hypotonia. Additionally, there is a dispute concerning the nature of any hypotonia or muscle weakness she may have displayed, with Dr. Kendall testifying that hypotonia in general would constitute a symptom of a mitochondrial disorder and Dr. Wiznitzer and Dr. McCandless opining that the descriptions of A.H.T.’s therapists suggested that she had centralized or brain-based hypotonia, not the muscle weakness seen in mitochondrial disorders. Tr. at 303, 310, 344 (Dr. Kendall), 455, 538-41 (Dr. McCandless), and 582, 585-87 (Dr. Wiznitzer); see *also* Supplemental Materials, Part A (reference to “muscular” hypotonia).

Children with mitochondrial encephalopathies presenting in the neonatal period are profoundly hypotonic; Dr. McCandless described them as “very, very floppy.” Tr. at 455. None of A.H.T.’s early pediatric records reflect any concern about her tone. According to Dr. Wiznitzer, her gross motor development was normal and there were no references to problems with truncal or extremity tone in her pediatric records. Tr. at 645. She reached motor milestones at appropriate times, according to her pediatric records. See *generally* Pet. Exs. 52, 58; see *also* Tr. at 645 (testimony that the medical records documented good head control and normal achievement of motor milestones).

¹⁵⁰ Gower’s sign refers to a method for standing up from a lying position by pushing with the hands on the lower limbs to substitute for the lack of muscle strength to stand normally. See DORLAND’S at 1711-12.

¹⁵¹ No points may have been assigned because Wolf & Smeitink, Court Ex. I, Supplemental Materials, indicate that hypotonia in the first six months of life is necessary to meet the criteria. None of A.H.T.’s early pediatric records support such a finding, and A.H.T. met early motor milestones regarding head control, rolling, sitting, and crawling.

Doctor Shoffner recorded milestone achievements (other than language acquisition) at times consistent with the early pediatric records. Pet. Ex. 61, pp. 2342-43. As Dr. McCandless testified, primary care physicians are often the first to note generalized hypotonia, and even inexperienced parents or grandparents may report that the infant does not feel “right” when an infant is hypotonic. Tr. at 586. No such reports were made by A.H.T.’s caregivers or parents. Doctors McCandless and Wiznitzer noted that both her medical records during the first year of her life and her parents’ descriptions of how A.H.T. appeared in infancy were not consistent with hypotonia. Tr. at 611-12, 644-49. Doctor McCandless commented that in A.H.T.’s first year, her back arching would be evidence of increased tone, not low tone. Tr. at 540.

Slightly diminished muscle tone was first noted by an occupational therapist in May 2004. Pet. Ex. 55, p. 2256. However, neither of the first two neurologists she saw that year commented on any reduced tone. Although he did not comment specifically on A.H.T.’s tone, Dr. McKiernan found normal, symmetric reflexes (Pet. Ex. 40, p. 1830) and Dr. Puri found normal muscle strength (Pet. Ex. 31, p. 1264.). However, in between these two neurology visits, decreased truncal and upper extremity tone were noted at another occupational therapy assessment. Pet. Ex. 28, p. 1090. The developmental pediatrician at the Weisskopf Center recorded low muscle tone, but it was not clear whether this represented her own observation or was simply part of a summary of the evaluation team’s findings. Pet. Ex. 46, pp. 2037-38.

Therapists targeted fine and gross motor skills and motor planning over the next several years. See, e.g., records from the Weisskopf Center, Pet. Ex. 46, pp. 2047 (noting the OT therapy planned), 2038 (noting fine motor and adaptive skill deficits and decreased muscle tone). However, Dr. Puri and his associates continued to find normal muscle tone, strength and bulk (Pet. Ex. 31, p. 1261); no focal motor weakness but some mildly decreased coordination (*id.*, p. 1258); normal muscle strength, bulk and tone and normal reflexes (*id.*, pp. 1252, 1255); normal bulk, strength and tone, with reflexes slightly brisk (*id.*, p. 1249). Based on the varying order in which these neuromuscular findings are listed in Dr. Puri’s records, it does not appear that they were part of a pre-configured form or document, and are thus more likely to represent actual observations by pediatric neurologists observing A.H.T. over time.

A physical therapy evaluation in March 2007 showed that A.H.T., who was then about five years old, was functioning about six months to a year below the typical five year old. Pet. Ex. 37, p. 1495. A PT assessment a few months later listed diagnoses of hypotonia, lack of coordination, motor coordination disorder, muscle weakness, and pronated feet. The evaluator noted that her muscle tone was “slightly low,” affecting her posture. She had functional strength in her arms, but slightly decreased strength in her abdominal muscles. She also had decreased motor planning skills and bilateral coordination difficulties. Pet. Ex. 33, p. 1282. Five months later (in February 2008), she was discharged from physical therapy because she scored in the 25th to 50th percentiles on the Peabody motor scales. Her muscle tone remained slightly low, but she had increased her strength in shoulders, arms, and core. *Id.*, p. 1286. In October 2008, Dr.

Murray noted that A.H.T. had made great strides in improving her fine and gross motor abilities. Pet. Ex. 16, p. 142.

In September 2009, A.H.T. was re-evaluated for PT services. Her mother reported that she had been discharged from PT in the spring of 2008 “because she could not focus enough to make progress” (Pet. Ex. 37, p. 1356), a report different from the reason reported by the therapist at the time of discharge (Pet. Ex. 33, p. 1286). At the re-evaluation, she was found to have good motor planning, but “mildly low” muscle tone throughout her trunk and lower extremities. Pet. Ex. 37, p. 1357. She continued to receive PT services until February 2010, when she was discharged as having reached her maximal level, although there was still some weakness in core muscles. The therapist noted that Ms. Holt remained concerned about A.H.T.’s endurance and coordination. However, she could perform 30 minutes of aerobic activity, and the therapist suggested she should participate in extracurricular activities involving physical movement. *Id.*, pp. 1362-63.

Thereafter, records from various therapists continued to reflect low muscle tone or mild hypotonia. See, e.g., Pet. Ex. 28, p. 1080. However, through August and November 2011, her neurologist continued to find her tone and strength normal. Pet. Ex. 31, pp. 1234, 1238.

The conflict between therapists and neurologists with regard to hypotonia can be resolved best by Dr. Wiznitzer’s explanation of the difference between brain-based hypotonia and muscle-based hypotonia. He testified that A.H.T. has a developmental coordination disorder, a condition often associated with mild hypotonia that is brain-based, not muscle-based. Children with brain-based hypotonia have normal strength and intact reflexes (which A.H.T. demonstrated on physical examination by Dr. Puri and his associates). A child with a primary muscle disorder will have a correlation between strength and tone—the weaker the strength level, the lower the tone. Central, or brain-based, hypotonia is not correlated with mitochondrial disorders, as it has nothing to do with energy load or energy reserves. Tr. at 645-49.

This “brain based” hypotonia appears consistent with the first description of hypotonia by a physician. In early 2005, Dr. Williams, the developmental pediatrician at the Weiskopff Center, diagnosed A.H.T. with “central nervous system dysfunction” as manifested by her toe-walking and decreased tone. Pet. Ex. 46, p. 2038.

5. Summary.

In summary, Dr. Shoffner relied upon parental reports for many of the clinical criteria in diagnosing A.H.T. with a probable mitochondrial disorder. That reliance was misplaced, as the medical records do not support many of the conditions Dr. Shoffner recorded as existing. Doctor McCandless pointed out why he came to different conclusions regarding A.H.T.’s clinical symptoms: an expert reviewing records in preparation for an expert report and testimony has the luxury of devoting considerable time to a comprehensive review that a busy clinician would not have. Tr. at 545-46. My

own review of the records comports with the testimony of Drs. Wiznitzer and McCandless in most respects.

6. Expert Opinions and Discussion Regarding Diagnosis.

Doctor Kendall opined that A.H.T. had symptoms consistent with a mitochondrial disorder and agreed with Dr. Shoffner's diagnosis. Doctor DeMio also agreed with the mitochondrial disorder diagnosis. Tr. at 217.

Referring to the chart in her report (Pet. Ex. 79 at 2500), Dr. Kendall testified that A.H.T. had evidence of central nervous system involvement in her developmental delays and autistic features (Tr. at 307), evidence of peripheral nerve involvement in her dysautonomia as manifested by temperature instability (Tr. at 308-09); evidence of muscle system involvement in her history of hypotonia, constipation, and possibly in oculomotor dysfunction (Tr. at 310-12); and systemic involvement based on her fatigue (Tr. at 312-13). She testified that these symptoms could be seen in mitochondrial dysfunction. Tr. at 330. However, A.H.T.'s medical records did not provide supportive evidence that she actually had many of the symptoms relied upon, or that she experienced symptoms of the requisite degree.

Separate from the problems in the scoring system discussed above and from Dr. Kendall's list of mitochondrial disorder symptoms A.H.T. purportedly displayed, respondent's experts had a more basic and fundamental disagreement with Dr. Shoffner's diagnostic conclusions and the opinions of Drs. Kendall and DeMio. They opined that A.H.T. simply did not fit the picture of a child with a mitochondrial disorder, based on her presentation in the neonatal period, her pattern of meeting motor and other milestones in infancy, and the specific developmental delays and behavior problems she displayed in the remainder of her childhood.

Doctor McCandless provided numerous reasons to conclude that A.H.T. did not have a primary mitochondrial disorder and that A.H.T.'s clinical presentation was unrelated to any mitochondrial dysfunction. Tr. at 423. Doctor Wiznitzer supported Dr. McCandless' observations and opinions. In addition, he cogently explained why Dr. DeMio's brain inflammation theory did not fit the facts.

a. Clinical Presentation at "Onset."

Although Dr. Kendall opined that A.H.T. had a mitochondrial disorder which was aggravated by her hepatitis B vaccination to produce an "encephalopathic picture" (Tr. at 335), she never precisely stated in testimony or her report that A.H.T. had a "mitochondrial encephalopathy." Nevertheless, that was the clear import of her testimony that A.H.T.'s underlying mitochondrial disorder was aggravated by the hepatitis B vaccination, producing encephalopathic symptoms beginning shortly after the vaccination was administered. Both of respondent's experts opined that A.H.T. did not have a mitochondrial encephalopathy.

In describing his own experiences with patients who presented in early infancy with significant mitochondrial dysfunction and disease, Dr. McCandless testified that every baby he had treated “was critically ill,” hospitalized in intensive care, and often on life support. Tr. at 443-44. He stated that a “baby who’s encephalopathic from mitochondrial dysfunction at day five of life” would be unlikely to survive at home. Tr. at 453-54, 455-56. Doctor Wiznitzer presented very similar testimony. Tr. at 682-84.

In Dr. McCandless’ experience, a neonatal or early presentation of mitochondrial disease leads to a progressive deterioration, with a “universally bad” outcome. Tr. at 445. In a case of neonatal onset, a child would be unlikely to have a period of normalcy for five days and then “crash and burn.” If A.H.T. had experienced a mitochondrial encephalopathy, he would expect her to have “profound hypotonia,” with extremely floppy muscles. Tr. at 455.

Even based on the symptoms described by her parents, A.H.T.’s condition did not approach the severity described by Dr. McCandless. Doctor Kendall never described what she would expect to find in a neonate presenting with the first symptoms of an underlying mitochondrial disorder; it was one of the many questions about typical presentations that she dodged. Tr. at 348-49.

A child who experienced an encephalopathy within a week of birth would not present as normal to a pediatrician a week or two later and at subsequent visits. A.H.T. would have demonstrated a change in mental status, diminished oral intake, and significant hypotonia, and her irritability would have been noted by the physician during well-child visits. Instead, A.H.T.’s records, both from Dr. Buttleman and Dr. Hefner, indicate that she was alert and behaving normally for her age. Tr. at 636-37. Had there been an insult to the brain in the neonatal period sufficient to produce developmental delays a few years later, the records would have reflected some impairment in her development within a few months of the vaccination, with delays in motor development, adaptive skills, and early communication. Instead, the records reflected basically normal development during this period. Tr. at 637.

Brain damage, inflammatory or otherwise, sufficient to cause encephalopathic symptoms would be observable on neuroimaging. A.H.T.’s March 2005 MRI did not demonstrate an acute insult. At a minimum, atrophy would have been present, and evidence of scarring or abnormal signaling in the white matter and basal ganglia would likely be present. None of these problems were seen on this MRI. Tr. at 642-43. According to Dr. Wiznitzer, petitioner’s theory of a systemic inflammatory response to the initial vaccination causing brain inflammation, followed by normal development, and then subsequent developmental delay, was biologically implausible. Tr. at 680-82. Doctor Kendall testified that a neonate with a primary mitochondrial disease could have a normal MRI (Tr. at 349). However, she did not say that this would be likely; did not specifically address whether a neonate with a mitochondrial encephalopathy could have a normal MRI; or whether it was likely that brain inflammation would be seen on an MRI.

Although one decompensation or regression in the presence of a febrile illness does not necessarily imply that a child with a mitochondrial disorder will have a similar experience with other illnesses, Dr. McCandless pointed out that A.H.T. apparently never again reacted to a fever or a febrile illness the way she purportedly did with the hepatitis B vaccination. He pointed to the lengthy gastrointestinal illness A.H.T. experienced in January 2003 (see Pet. Ex. 52, p 2233). A.H.T., who had been at approximately the 25th percentile on the weight chart at about nine months of age (Pet. Ex. 58, p. 2314), dropped to the 5th percentile at one year of age (Pet. Ex. 52, p. 2232). This type of illness was, according to Dr. McCandless, the type most likely to cause a child with a mitochondrial disorder to decompensate. Tr. at 597. Yet, A.H.T. weathered this gastrointestinal illness and an ear infection with fever at 15 months of age (Pet. Ex. 52, p. 2231) with no apparent health or neurological impact.

b. Later Clinical Presentation.

Based on petitioner's claim that A.H.T. was encephalopathic shortly after the vaccination, both Drs. Wiznitzer and McCandless testified there would have been altered brain function and severe neurological changes to cause the encephalopathy. Tr. at 454, 683-84. It would be extremely unlikely for a neonate to thereafter have essentially normal development, meeting milestones in many areas and, in particular, in gross and fine motor skills. Doctor McCandless was aware of "no credible reports" of a period of normal development after a severe encephalopathy. Tr. at 454. As he explained, "the pattern and the arc of the clinical findings is, in my opinion, not consistent with a significant mitochondrial encephalopathy." *Id.*

The MRI performed when A.H.T. was three years old (Pet. Ex. 31, p. 1273) was normal, and thus belied the existence of the type of brain injury caused by either a mitochondrial encephalopathy or the brain inflammation Dr. DeMio insisted was present. In a "hit from mitochondrial disease to the brain," Dr. McCandless would expect to see atrophy on the brain on MRI later in life. Tr. at 455. Neither Drs. Kendall nor DeMio offered any testimony countering Dr. McCandless's expectation that an MRI would reveal such encephalopathic symptoms.

Moreover, A.H.T.'s clinical course from the days after the vaccination through the time of the hearing was not what would be expected in a child with a mitochondrial disorder. As Dr. McCandless noted, there was no indication in the medical records of any deterioration in neurological status, plateaus in development, or the loss of developmental milestones. Res. Ex. G at 2.

Developmental delay, which A.H.T. has, can certainly be a part of the mitochondrial disease picture, but many children have delayed development without having a mitochondrial disease. There are certain types of developmental delay that are more characteristic of children with mitochondrial disease, such as global developmental delay and hypotonia involving both gross and fine motor delay. Tr. at 582-83. A.H.T. did not have global developmental delay; she had very specific delays in speech and language, which might be seen in mitochondrial disease, but not

typically. Tr. at 583. Doctor McCandless also opined that A.H.T.'s central nervous system abnormalities were not "the typical ones we see in patients with confirmed mitochondrial disease." Tr. at 536. Isolated speech delay is not "specific or even highly suggestive of mitochondrial disease." Tr. at 538. He also noted that isolated speech delay was not particularly indicative of mitochondrial disorders, although dysarthria, a defect in the way that muscles control speech, is much more common than a simple delay. *Id.*

c. Evidence of Dysfunction and Clinical Symptoms.

The major problem respondent's experts expressed with finding that A.H.T. has a primary mitochondrial disorder is the presence or absence of the symptoms used in diagnosing such a disorder. Tr. at 569-71. Doctor McCandless found inadequate evidence of a mitochondrial disorder. He acknowledged that A.H.T. had evidence of mitochondrial dysfunction on the laboratory tests, but thought that the laboratory findings alone were not sufficient to conclude that they were responsible for her clinical symptoms. He indicated that they could be reflective of whatever neurological process caused her clinical symptoms rather than the cause of the symptoms. Tr. at 566-67; Res. Ex. G at 2. That is, the mitochondrial dysfunction found is not the cause of A.H.T.'s speech and behavioral problems, and may even result from them or the drugs used to treat them. Tr. at 565, 567-69.

d. Brain Inflammation.

Late in the hearing, petitioner's counsel appeared to disavow Dr. Kendall's testimony about A.H.T. experiencing an encephalopathic event after vaccination. He explained that petitioner was not relying on the theory that the vaccination caused an encephalopathy, but rather that A.H.T. "had an inflammatory antigenic response and now has identified mitochondrial dysfunction." Tr. at 679. In response to a colloquy with Dr. Wiznitzer, Mr. Downing clarified that this inflammatory response was a systemic inflammation, causing brain inflammation as well. Tr. at 680-82.

Doctor McCandless noted that inflammation was not a component of mitochondrial dysfunction (Tr. at 557-58), but Dr. Wiznitzer primarily addressed this theory, which appeared to be based on Dr. DeMio's testimony. Succinctly, brain inflammation sufficient to overload the mitochondria and cause dysfunction leading to the clinical symptoms of developmental delay and behavioral problems would require the same type of brain damage seen in an encephalopathy, and would thus be detected on MRI. None were. Tr. at 680-84.

e. Improvement on Treatment.

(1) Opinions.

Doctor Kendall testified that the efficacy of treatment for a mitochondrial disorder would support the diagnosis as being correct. Tr. at 328. Her testimony also suggested

that lack of improvement might cause doubts about the validity of the diagnosis: “If they don’t [improve] or worsen, then you’re probably looking at something different or potentially at least.” *Id.* She stopped short, however, of opining that A.H.T. experienced improvement with her mitochondrial treatment.

Doctors DeMio and Levinson attempted to fill that gap, opining that A.H.T.’s condition improved after institution of treatment. Tr. at 213-14 (Dr. DeMio); Pet. Ex. 59 at 2337 (noting that since he began treating A.H.T., he recorded “improvement in language, sensory issues, behavior and motor skills.”). Neither pointed to any objective evidence of improvement. Moreover, A.H.T.’s parents also testified that she had improved since mitochondrial treatment had begun. Tr. at 47 (Ms. Holt) (remarking that as a result of treatment, “we have seen an incredible difference....she is more engaged socially”); 117 (Mr. Tipton) (stating that after treatment for a mitochondrial disorder “[s]he’s a new child. It helped.”).

Doctor McCandless opined that a therapeutic response to mitochondrial disease therapy would not be evidence that the person treated had a mitochondrial disease.¹⁵² Tr. at 468. The treatments A.H.T. was given (coenzyme Q10, carnitine, a B vitamin cocktail, and possibly the methylfolate therapy) would be highly unlikely to lead to any improvement in A.H.T. Although he recommended or offered such therapies in his own clinical practice, he thought that the evidence supporting their efficacy was anecdotal. In his own experience, patients felt better temporarily on coenzyme Q10, but the effect was temporary in all but the rare patient with a coenzyme Q10 deficiency. Tr. at 460-462, 466. As a measure of the lack of clinical improvement, he observed that most patients quit taking the treatment in a year or two. Tr. at 461. Nevertheless, the possibility that coenzyme Q10 might prevent further deterioration led him to continue to prescribe it. Tr. at 467-68.

He illustrated his testimony by showing where coenzyme Q10 is involved in the ETC function, thus explaining why it would be unlikely to help in a Complex I or III defect. Tr. at 466. He also noted that A.H.T. had no evidence of a coenzyme Q10 deficiency. Tr. at 490.

Some people with mitochondrial disease have low carnitine, and treatment with carnitine supplements is prescribed. Tr. at 469. However, A.H.T. had no objective evidence of a carnitine deficiency. Tr. at 490 (Dr. McCandless reviewing laboratory reports and testifying that A.H.T.’s carnitine level was “completely normal”).

(2) Observations of Treeters.

The therapy records provide evidence of A.H.T.’s condition before and after the mitochondrial disease treatment prescribed by Dr. Shoffner was initiated in mid-August,

¹⁵² He mentioned that he was currently involved with a clinical trial of coenzyme Q10 (Tr. at 419), but did not proffer any testimony explicitly based on this ongoing research, instead prefacing his remarks about its efficacy based on his own experience. Tr. at 440.

2011.¹⁵³ These records show that her speech and behavior improved over time, but a systematic comparison of the frequency of problem behaviors in the months before and after beginning therapy does not support the testimony regarding positive change after beginning the prescribed mitochondrial treatment.

A.H.T.'s behavior (including her sleeping patterns) were out of control at the time she began receiving behavior support therapy in December 2010, after nearly two months of observation and analysis of her behavior and interactions with parents and others. Pet. Ex. 38, pp. 1709-13 (summary, background information, and intervention plan). A.H.T., who was then eight years old, was presenting what were termed "challenging behaviors," including tantrums, escaping from caregivers when outside the home (termed "elopement" by the behavioral analysts), and both physical and verbal aggression. *Id.*, p. 1750

These terms, however, do not adequately capture the nature of A.H.T.'s behavior. She ordered adults to be quiet and to leave, called them names, and talked about urination, defecation, and vomiting multiple times daily. See, e.g., Pet. Ex. 38, pp. 1691, 1751, 1764, 1799. She interrupted adult conversations frequently. See, e.g., Pet. Exs. 7, p. 57; 38, p. 1691. She threw coins, toys, towels, glassware, bicycles, and furniture during tantrums. See, e.g., Pet. Exs. 27, p. 585; 38, pp. 1765, 1792. She hit adults and other children. See, e.g., Pet. Exs. 38, pp. 1754-55; 57, p. 2293. She hit and kicked the family dogs, as well as hitting them with towels, pillows, and stuffed animals, and grabbed the dogs' genitals. See, e.g., Pet. Ex. 38, pp. 1751, 1778, 1793.

A.H.T. presented behavior problems in other therapy sessions as well as at home, prior to initiating mitochondrial disease treatment.¹⁵⁴ She put her hand down her throat to induce vomiting and had been vomiting in the classroom prior to switching to home school (Pet. Exs. 7, p. 57; 38, p. 1779), gagged herself when she did not want to do an activity in OT (Pet. Ex. 27, p. 684) and turned over chairs and had tantrums in ST (*id.*, pp. 608-09). During attempts to conduct home school activities, she fell on the

¹⁵³ In May 2011, when A.H.T. was first evaluated for a mitochondrial disorder, she was receiving speech, occupational, and behavioral therapy. Other than an emergency room visit as the result of an automobile accident in March 2011, resulting in an evaluation by Dr. Hefner (her primary care provider) (Pet. Ex. 52, p. 2211), some physical therapy for injuries received in the accident (Pet. Ex. 43), and a visit to her pediatric neurologist's office for headaches related to the accident in June 2011 (Pet. Ex. 31, p. 1240), she was not seeing any other treaters. Her last primary care visit had been in March 2009, and the last documented contact with Dr. Levinson had been in June 2010, when he ordered some laboratory tests. Pet. Ex. 47, pp. 2140-43. Thus, it does not appear that A.H.T. was receiving treatment for anything other than her developmental delays and behavioral problems.

¹⁵⁴ In an occupational therapy review in February 2011, the therapist reported a "major outburst" in the last two treatment sessions and that A.H.T. became "very controlling and aggressive" when asked to perform non-preferred activities. Pet. Ex. 27, p. 671. The therapist also expressed concern that her verbal aggression would progress into physical aggression. *Id.* Her progress in OT was impeded by her "explosive and avoidant behaviors." *Id.*, p. 589. She also had tantrums in physical therapy sessions. Pet. Ex. 43, p. 1869. Her speech therapist reported "outbursts," hitting windows, and throwing toys. See, e.g., Pet. Ex. 27, pp. 612-13.

floor, laughed hysterically, threw pencils, wrinkled worksheets, and cried and screamed. Pet. Ex. 38, p. 1709.

A.H.T.'s behavior improved while receiving behavioral support services, particularly after her parents began more consistent compliance with the program's methodology,¹⁵⁵ but a comparison of her behavior in the four months prior to institution of treatment with the four months after treatment began does not demonstrate any significant improvement after treatment began. See Pet. Ex. 57, pp. 2299-2310. The summary chart for the behavioral support plan from December 2011 reflected a comparison of behaviors before and after A.H.T. began taking supplements as treatment for her mitochondrial disorder in early August 2011. Notations reflect that "many target behaviors have been on the rise for the last month." Pet. Ex. 57, pp. 2304-06.

A.H.T. also received ST services before and after beginning mitochondrial therapy, but there are only a few filed ST records from periods after the mitochondrial therapy began. Pet. Ex. 27, pp. 607, 614 (ST records from late August and early September 2011). Nevertheless, earlier ST records show progress in speech and both good and bad days in terms of behavior during therapy. See, e.g., *id.*, pp. 588-89, 607-11, 614, 616. More than a year after beginning mitochondrial therapy, Dr. DeMio's records reflect speech and behavior issues that were very similar to those she displayed before the mitochondrial therapy was initiated.¹⁵⁶ Perhaps the most significant improvement was A.H.T.'s return to school outside the home, although this change from home-schooling was being planned as early as the spring of 2010. See Pet. Ex. 38, pp. 1758, 1783, 1800 (planning changes in sleeping patterns, discussing school placement, and focusing on specific behaviors to change prior to returning to school); 47, p. 2057 (attending school).

On August 17, 2011, a week after A.H.T.'s diagnosis, Dr. Levinson recorded that A.H.T. was sleeping better, her speech was easier and more age-appropriate, and she had improved "processing speed and fluency" according to Ms. Holt, but she was

¹⁵⁵ Over the course of behavioral therapy, her parents began more systematic implementation of the behavioral modification strategies, resulting in improved behavior. See, e.g., Pet. Ex. 57, p. 2293 (assessment from August 16, 2011 noting that A.H.T. had not engaged in physical aggression for three consecutive weeks, elopement for five consecutive weeks, and showed some improvement in the number of interruptions of adult conversations, but continued tantrums, as well as noting that her parents were much more responsive to the behavioral therapists). However, target behaviors re-emerged in the fall of 2011. See *id.*, pp. 2299-2310.

¹⁵⁶ Petitioner's Ex. 87 includes notes from Dr. DeMio's August 30, 2012 office visit. His notes from the office visit described A.H.T. as "in her own world, talking to herself, and hyper-focused on her video game." She was described as "paranoid," thinking people looking at her have bad intentions. She had experienced regression in spelling, was searching for words she had easily used in the past, was sometimes untruthful, was verbally aggressive with her mother, and still licked her hands. *Id.*, p. 2565. Nevertheless, she was doing well academically in school. *Id.*, p. 2566.

cranky and dystonic. Pet. Ex. 47, pp. 2056-57. At this telephone consultation,¹⁵⁷ he increased the amount of riboflavin, carnitine and coenzyme Q10 she was receiving. *Id.*, p. 2057. A.H.T. had started school that week. *Id.* The same day as this consultation, A.H.T.'s speech therapist noted that A.H.T. was unwilling to discuss her anger with the therapist, but that there were "increased positive behaviors." Pet. Ex. 27, p. 607.

The record from the next consultation with Dr. Levinson, held on October 26, 2011, began with a report by her parents that A.H.T.'s language was "phenomenal" with an improvement in expressive language with more age-appropriate speech, but only limited improvement in receptive language. Pet. Ex. 47, p. 2058. Her behavior was "[m]ore compliant and appropriate," she was "dealing with structure better," was limited in aggression toward animals and only rarely was aggressive toward Ms. Holt. Her tactile defensiveness regarding clothing was notably decreased. She continued to have problems with lying and impulsivity, but both were reduced. *Id.* By report, her handwriting, a fine motor skill, continued to improve, and a notation reflected that A.H.T. was swimming and hiking. *Id.* Additionally, the speech therapy records also reflected an improvement, but not one described as "phenomenal." Pet. Ex. 27, p. 614.

A.H.T. was seen by psychotherapist Heather Bass for three sessions in November and December 2011 for complaints of anxiety related to a motor vehicle accident. Her parents reported that the anxiety was overwhelming and disruptive to her functioning. They were seeking help for her "aggressive and out of control behaviors" at home and with the behaviorist. Doctor (Psy.D.) Bass described her as friendly, cooperative and playful in their first two sessions, but A.H.T. presented as socially and emotionally delayed. She had difficulty maintaining a mutual conversation. A.H.T.'s anxiety appeared to focus on medical procedures after the accident, but she refused to discuss any details. During the third session, she was slightly agitated, and became distressed, more agitated, and uncooperative after the session ended. She refused to leave the office with her babysitter and demanded that her mother come and pick her up. Pet. Ex. 44, p. 1878.

(3) Assessment of Evidence on Improvement after Treatment.

The behavioral support records are the most compelling evidence of the lack of therapeutic effects of the mitochondrial therapy as they involved a systematic comparison of the frequency of problem behaviors before and after the treatment began. Without complete speech therapy records (only two were filed after beginning mitochondrial therapy), it is difficult to find objective evidence of improvement in her language ability. Moreover, even if the records demonstrated improvement, I note that A.H.T. continued to make progress in language while in speech therapy prior to

¹⁵⁷ There is no indication in Dr. Levinson's records that he personally observed A.H.T. or conducted any type of physical examination of her. In view of the location of his practice (Florida) and the fact that A.H.T. had a speech therapy session the same day in the Louisville, KY, area, it is likely that this was a telephonic consultation. See Pet. Ex. 27, p. 607 (speech therapy record dated "8-17-11").

beginning mitochondrial therapy. The records available show she was meeting goals set during therapy before August 2011.¹⁵⁸

E. Factual Findings Regarding Mitochondrial Diagnosis.

1. Dysautonomia.

There is no reliable evidence that A.H.T. had problems with temperature regulation or that she experienced high fevers not associated with an illness. She was seen by a health care provider for only one fever of 105° and that fever was associated with an illness. The records from this emergency room visit in 2010 do not reflect that such fevers were common, had occurred in the past, or had occurred without an accompanying illness. The histories in records of recurrent high fevers were not supported by any records of treatment for such fevers or attempts to ascertain a cause for recurrent high fevers, and contradicted histories provided earlier.

2. Frequent Respiratory Infections.

It is unlikely that A.H.T. experienced frequent respiratory infections as an infant, toddler, or older child. Her parents reported that she was generally healthy as an infant when she was first evaluated for developmental delays, and her medical records support that she was not often ill as an infant. The extensive therapy and medical records do not reflect missed therapy sessions due to illnesses and show only occasional upper respiratory illness visits. The behavioral analysts visited A.H.T. regularly at home for more than a year, and their records do not reflect any recurrent or frequent illnesses of any type.

3. Hypotonia.

A.H.T. did not have generalized hypotonia. Reports of low tone or hypotonia appear in some therapy records, but no neurologist ever diagnosed generalized hypotonia or low muscle tone. She did have some mild brain-based hypotonia, but not the muscle-based form seen in mitochondrial disease. She was not a floppy baby. She had normal strength and reflexes on nearly every examination performed. No concerns about her motor development were expressed by anyone until A.H.T. was evaluated by therapists in May-June 2004.

4. Exercise Intolerance.

There is no reliable evidence that A.H.T. had exercise intolerance or fatigue that interfered with activities of daily living. Prior to her diagnosis by Dr. Shoffner, A.H.T. was assessed by a pediatric cardiologist who found no history of exercise intolerance.

¹⁵⁸ For example, A.H.T. met both of her current short term goals in July 2011, with a notation that Ms. Holt was excited about her progress (Pet. Ex. 27, p. 608); met both short term goals in June 2011 (*id.*, p. 610), with comments that she was “[g]reat on task” and had excellent behavior with progress toward her language goals (*id.*, p. 611). These were the two months before she began mitochondrial therapy.

According to her therapists, she could perform 30 minutes of aerobic exercise. Her failures to perform tasks in therapy or chores or schoolwork at home were behavioral in nature, not grounded in muscle weakness or excessive fatigue.

5. Autistic Regression.

There is no evidence that A.H.T. ever experienced an autistic regression and no reliable evidence that she lost skills of any type that she had once displayed.

6. Therapeutic Effects from Mitochondrial Disorder Therapy.

A.H.T.'s trajectory in the areas of developmental delay (motor skills and speech) does not appear to have been altered by her mitochondrial disease treatment. Her behavioral problems were not affected by that treatment.

7. Gastrointestinal Problems.

The gastrointestinal problems A.H.T. displayed were not those typically seen in children with mitochondrial disorders. There is no evidence that she had diarrhea persisting longer than three weeks at a time. She was never diagnosed with or even evaluated for pseudo obstruction. There were frequent reports of constipation and some of diarrhea during the time frame when A.H.T. was being treated by Dr. DeMio, but it is difficult to determine whether either or both gastrointestinal conditions were adversely affected by the many treatments prescribed. By about nine years of age, A.H.T. appeared to have normal gastrointestinal function, as she was no longer taking medications targeting either constipation or diarrhea and reports to her neurologist reflected normal bowel function.

8. Developmental Delays.

A.H.T. had developmental delay in specific areas of development, primarily in speech, fine motor skills, and visual motor coordination. She was not globally delayed. She has normal or near normal intelligence.

9. Resting Metabolic Rate.

A.H.T.'s resting metabolic rate of 76% was below the reference range of 85-115% of the expected norm. Doctor Shoffner properly assigned points on the Nijmegen scale for this result. However, two alternate explanations for A.H.T.'s lower rate were present: A.H.T. was underweight and she had a relatively sedentary lifestyle.

10. Encephalopathy.

A.H.T. did not experience an encephalopathy after her hepatitis B vaccination. Although there is some conflicting evidence, specifically Dr. Kendall's opinion, her opinion was not strong and was based on some symptoms (fever, lethargy, and

extended somnolence) for which there is no reliable evidence. Even Dr. Kendall acknowledged that the irritability she relied upon could have been caused by the colic diagnosed by A.H.T.'s treating physicians. A.H.T. did not have the neurological and developmental sequelae that would be expected after an encephalopathic event capable of leading to developmental delays and behavioral problems months later.

11. Brain Inflammation.

Although A.H.T. likely experienced some immunological and possibly inflammatory response to her initial hepatitis B vaccination, it is highly unlikely that this response included brain inflammation. The evidence that she did so rests primarily on Dr. DeMio's opinion,¹⁵⁹ which, in turn, is based on many symptoms described by A.H.T.'s parents. There is no evidentiary support for a finding that A.H.T. had brain inflammation after the hepatitis B vaccination. The MRI performed when A.H.T. was about three years of age did not show evidence of an earlier or ongoing inflammatory process. Her period of normal or near normal development from birth through at least 15 months of age belies a finding that her brain was inflamed or otherwise damaged by an immunological or inflammatory response to the hepatitis B vaccine.

12. Mitochondrial Disorder Diagnosis.

Doctor McCandless' questioned Dr. Shoffner's conclusion that A.H.T. had exercise intolerance. Based on the assessment by A.H.T.'s therapist that she was capable of performing 30 minutes of aerobic exercise, and her pediatric cardiologist that she had no history of exercise intolerance, and the lack of any objective evidence that she could not perform activities of daily living due to fatigue, I conclude that the 1 point assigned on both the August 1 and August 10 score sheets should be subtracted.

Additionally, there was inadequate evidence of the involvement of a second organ system in A.H.T.'s clinical presentation meeting the requirements specified in the Supplemental Materials for the Nijmegen criteria. A.H.T.'s gastrointestinal symptoms and neuromuscular problems did not fit these requirements. Thus, I find that the August 1 assessment of a possible, rather than a probable, mitochondrial disorder best fits the facts of A.H.T.'s condition.

VI. Applying *Althen* and *Pafford*.

A. Legal Standards Applying to Off-Table Causation Claims.

When a petitioner alleges an off-Table injury, eligibility for compensation is established when, by a preponderance of the evidence, petitioner demonstrates that

¹⁵⁹ One could conclude from the use of antiviral therapies by Drs. Kartzinel and Levinson that they believed there was a viral cause for A.H.T.'s symptoms, which might implicate some form of brain inflammation. However, as noted in Pet. Tr. Ex. 2 at 1, the hepatitis B vaccine is not a live viral vaccine and is non-infectious. Thus it is unlikely that antiviral drugs could be effective in treating any sequelae it might have caused.

she received, in the United States, a vaccine set forth on the Vaccine Injury Table ["Table"] and sustained an illness, disability, injury, or condition caused by the vaccine or experienced a significant aggravation of a preexisting condition. She must also demonstrate that the condition has persisted for more than six months. Vaccine Act litigation rarely concerns whether the vaccine appears on the Table, the situs for administration, or whether the symptoms have persisted for the requisite time. In most Vaccine Act litigation, the issue to be resolved by the special master is whether the injury alleged was caused by the vaccine.

To establish legal cause in an off-Table case, Vaccine Act, a petitioner must establish each of the three *Althen* factors by preponderant evidence: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. *Althen v. Sec'y, HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); see *de Bazan v. Sec'y, HHS*, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); *Caves*, 100 Fed. Cl. at 132 (specifying that each *Althen* factor must be established by preponderant evidence), *aff. per curiam*, 463 Fed. Appx. 932, 2012 WL 858402 (Fed. Cir. 2012). The applicable level of proof is the "traditional tort standard of 'preponderant evidence.'" *Moberly v. Sec'y, HHS*, 592 F.3d 1315, 1322 (Fed. Cir. 2010) (citing *de Bazan*, 539 F.3d at 1351; *Pafford v. Sec'y, HHS*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Capizzano v. Sec'y, HHS*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *Althen*, 418 F.3d at 1278). The preponderance standard "requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence." *In re Winship*, 397 U.S. 358, 371 (1970) (Harlan, J., concurring) (internal quotation and citation omitted).

Another formulation of the causation requirement in off-Table cases is the "Can it cause?" and "Did it cause?" inquiries used in toxic tort litigation. These queries are also referred to as issues of general and specific causation. Prong 1 of *Althen* has been characterized as an alternative formulation of the "Can it cause?" or general causation query. Prong 2 of *Althen*, the requirement for a logical sequence of cause and effect between the vaccine and the injury, has been characterized as addressing the "Did it cause?" or specific causation query. See *Pafford v. Sec'y, HHS*, No. 01-165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352. The third *Althen* factor is subsumed into the other inquiries. Even if a particular vaccine has been causally associated with an injury, petitioner must still establish facts and circumstances that make it more likely than not that this vaccine caused his particular injury. Timing may be one of those circumstances.

Whether a case is analyzed under *Althen* or the "Can it cause?" formulation, petitioners are not required to establish identification and proof of specific biological mechanisms, as "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. The petitioner need not show that the vaccination was the sole cause, or even the predominant cause, of the injury or condition; showing that the vaccination was a "substantial factor" in causing the

condition and was a “but for” cause are sufficient for recovery. *Shyface*, 165 F.3d at 1352; see also *Pafford*, 451 F.3d at 1355 (petitioner must establish that a vaccination was a substantial factor and that harm would not have occurred in the absence of vaccination). Petitioners cannot be required to show “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. Causation is determined on a case by case basis, with “no hard and fast *per se* scientific or medical rules.” *Knudsen v. Sec’y, HHS*, 35 F.3d 543, 548 (Fed. Cir. 1994). Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280; but see *Knudsen*, 35 F.3d at 550 (when evidence is in equipoise, the party with the burden of proof fails to meet that burden).

By specifying petitioners’ burden of proof in off-Table cases as a preponderance of the evidence, directing special masters to consider the evidence as a whole, and stating that special masters are not bound by any “diagnosis, conclusion, judgment, test result, report, or summary” contained in the record (§13(b)(1)), Congress contemplated that special masters would weigh and evaluate opposing expert opinions in determining whether petitioners have met their burden of proof.¹⁶⁰ As discussed, *supra*, in Section III, it is now clearly established that special masters may use the framework established by *Daubert* to evaluate expert testimony on causation.

In summary, special masters decide questions of credibility, plausibility, probability, and reliability, and ultimately determine to which side the balance of the evidence is tipped. See *Pafford*, 451 F.3d at 1359. Bearing all these legal standards in mind, I analyze the evidence against the standards established.

B. Analysis.

In essence, petitioner has attempted to make this case into the Poling case. In her post-hearing brief at n.1, she commented on the similarities between A.H.T. and the Poling child, claiming that A.H.T.’s post-vaccination history is “surprisingly similar” to that of the Poling case. There are more differences than similarities.¹⁶¹

Petitioner’s causation claim was sometimes based on the theory supplied by the Shoffner paper and sometimes on a theory unsupported by anything other than Dr. DeMio’s opinion on brain inflammation and brain damage. Doctor McCandless thought the theory discussed in the Shoffner paper (and, to some extent, the Morgan paper,

¹⁶⁰ See § 13(a)(1)(A) (preponderance standard); § 13(a)(1) (“Compensation shall be awarded . . . if the special master or court finds on the record as a whole . . .”); § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation and special master is not bound by any particular piece of evidence).

¹⁶¹ In addition to the dissimilarities discussed below, the Poling child had marked reductions in enzymatic activities in Complexes I, III, and IV, persistent lactic acidosis, and abnormal muscle histology. Poling, Pet. Ex. 69, at 2-3, Table 1.

Res. Ex. I) merited additional study, but he was clear that the theory that a vaccine, with or without a fever, could cause onset or significant aggravation of a mitochondrial disorder was, at present, speculative. It may, at some future time, be sufficiently supported so as to constitute a reliable medical theory explaining either onset or significant aggravation of a mitochondrial disorder, but neither the Poling case study or the Shoffner paper carry sufficient indicia of reliability for me to credit Dr. Kendall's theory. Illness may aggravate or exacerbate an extant mitochondrial disorder, but there is little evidence that illnesses can trigger an underlying genetic disease. There is no evidence, other than Dr. Kendall's opinion, that a vaccination can do so. In the Shoffner paper, vaccination alone did not trigger a decompensation in any of the children. In the Morgan paper, the children with urea cycle disorders—those most likely to respond adversely to febrile events—did not experience more decompensations in the seven days after a variety of vaccinations than in the period more than 21 days after such vaccinations.

Even if I found the theory to be reliable rather than speculative, it would not help petitioner in this case. In spite of herculean efforts to make A.H.T.'s presentation look like that of the Poling child, the facts are such that, as Dr. Wiznitzer remarked, "[i]t doesn't fit." Tr. at 637. A.H.T. did not have a Table encephalopathy or even symptoms consistent with an encephalopathy after vaccination. She did not have a fever. She did not experience an autistic regression. She did not have a DTaP or MMR vaccination, both vaccines known to provoke fever, and with associated Table injuries of encephalopathy. She did not lose skills. She had normal development for many months after the vaccination, followed by some developmental delays and the emergence of ASD-type symptoms.

I also distinguish the mitochondrial disorder claimed in the Poling case from the laboratory evidence showing moderate mitochondrial dysfunction in A.H.T. Poling, Pet. Ex. 69, at 3; see Pet. Ex. 79 at 2497. Petitioner's conflation of the terms "mitochondrial disorder" and "mitochondrial dysfunction" raises problems with her attempts to equate A.H.T.'s case with the Poling case. Doctor McCandless' testimony that the mitochondrial dysfunction found is not the cause of A.H.T.'s speech and behavioral problems, and may even result from whatever is responsible for those symptoms or from the many drugs used to treat her further distinguishes this case from Poling. Tr. at 565-69; Res. Ex. G at 2.

Moreover, Dr. Kendall's theory appears to rely heavily, if not exclusively, on the presence of a fever, and Dr. DeMio's theory on fever as evidence of a systemic inflammatory event. I have carefully considered all of the evidence in reaching the conclusion that A.H.T. did not have a fever after her initial hepatitis B vaccination. Thus the predicate fact upon which the theories are based is not present. This lack of a logical connection between the theories and the facts is essentially insurmountable.

Timing is problematic as well. It defies logic to have an encephalopathic event (or brain inflammation sufficient to cause symptoms similar to such an event), followed by normal development, and then to attribute subsequent developmental delay to that

early encephalopathic event. Children with mitochondrial encephalopathies may well have delays and problems, but early onset is not followed by normal development. It is followed by progressive neurological deterioration in most cases.

The distinction between mitochondrial disorders and mitochondrial dysfunction may relieve petitioner from the need to explain how a vaccine can affect a disorder that is purely genetic, according to her own mitochondrial expert. But, to the extent petitioner has abandoned the claim of significant aggravation of a mitochondrial disorder set forth in the petition, substituting instead a claim that the vaccine caused or aggravated mitochondrial dysfunction, the problems noted earlier remain. A.H.T. was not febrile after her vaccination, had a diagnosis that fully explained any symptoms that might have been considered neurological, and, as Dr. McCandless so persuasively opined, her clinical presentation was not consistent with the mitochondrial dysfunction seen *in vitro*.

In discussing the scientific and medical issues in this case, I have occasionally referenced the OAP test cases. I have also done so in commenting on Dr. Levinson's "oxidative stress" theory. By joining the OAP, the evidentiary record in this case encompasses the OAP evidence. Even were I to disregard all the OAP evidence on oxidative stress, I would come to the same conclusions regarding his theory. He has failed to explain how the vaccines could cause oxidative stress or to point to any evidence of oxidative injury to her brain. Doctor Kendall's theory is speculative and supported by little more than her *ipse dixit*. To the extent there is any support for the proposition that vaccines and fever can trigger a mitochondrial disease or cause mitochondrial dysfunction, the facts of this case do not fit her theory. There was no fever, and many of the other symptoms she attributed to a mitochondrial disorder were not present. A.H.T.'s mitochondrial disorder diagnosis was much less definitive than she presented it to be. She did not persuasively connect the laboratory evidence of mitochondrial dysfunction discovered years after the vaccinations were administered to the symptoms A.H.T. displayed post-vaccination or the behavioral symptoms that manifested with speech delay many months later. Doctor DeMio's theory has even less support. There is no evidence that A.H.T. had brain inflammation, much less that it could produce the symptoms he attributed to such inflammation, and in the manner in which they actually presented.

A.H.T.'s problems are profound, and will no doubt continue to affect her life and the lives of her parents. I have nothing but sympathy for their experiences, but I cannot decide this or any other case based on sentiment. Unfortunately, this case does not present the "close call" in which the balance of the evidence might be tipped toward petitioner.

VII. Conclusion.

Petitioner has failed to produce preponderant evidence that the hepatitis B vaccinations A.H.T. received can or did cause or significantly aggravate the conditions from which she suffers. Accordingly, the petition for compensation is DENIED. The clerk is directed to enter judgment accordingly.

IT IS SO ORDERED.

s/Denise K. Vowell
Denise K. Vowell
Chief Special Master