In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 10-0197V
Originally filed March 17, 2016
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(To be published)

H.L., on behalf of A.I., A.I., deceased, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	*	Vaccine Act Entitlement; Causation-in-fact; Significant Aggravation; FluMist Vaccine; Metabolic Decompensation/Leigh Disease

Robert J. Krakow, New York, New York, for Petitioner.
Justine Walters, U.S. Department of Justice, Washington, DC, for Respondent.

DECISION

HASTINGS, ***Special Master***.

This is an action in which the Petitioner, H.L., seeks an award under the National Vaccine Injury Compensation Program (hereinafter "the Program"[1]), on account of the death of her daughter, A.I. For the reasons set forth below, I conclude that Petitioner is *not* entitled to an award.

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1 The applicable statutory provisions defining the Program are found at 42 U.S.C. § 300aa-10 *et seq.* (2012 ed.). Hereinafter, for ease of citation, all "§" references will be to 42 U.S.C. (2012 ed.).

I

THE APPLICABLE STATUTORY SCHEME

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In other cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation, of course, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. HHS*, 940 F.2d 1518, 1525 (Fed. Cir. 1991). The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause or even the predominant cause of the injury or condition, but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. HHS*, 956 F.2d 1144, 1148 (Fed. Cir. 1992).

The *Althen* court also provided additional discussion of the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and

> effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

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

Where a petitioner in a cause-in-fact or "off Table" case is seeking to prove that their vaccination aggravated a pre-existing injury, the court must also apply three additional factors originating the standard for assessing aggravation claims in "Table" injury cases. *See Loving v. HHS*, 86 Fed. Cl. 135, 144 (Fed. Cl. 2009)(combining the first three *Whitecotton* factors for claims regarding aggravation of a Table injury with the three *Althen* factors for off table injury claims to create a six-part test for off Table aggravation claims); *see also W.C. v. HHS*, 704 F.3d 1352, 1357 (Fed. Cir. 2013)(applying the six-part *Loving* test.). The additional *Loving* factors require the Petitioners to demonstrate aggravation by showing: (1) the vacinee's condition prior to the administration of the vaccine, (2) the vacinee's current condition, and (3) whether the vacinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. *Id*.

Since *Althen*, the Federal Circuit has addressed the causation-in-fact standard in several additional rulings, which have affirmed the applicability of the *Althen* test, and afforded further instruction for resolving causation-in-fact issues. In *Capizzano v. HHS*, 440 F.3d 1317, 1326 (Fed. Cir. 2006), the court cautioned Program fact-finders against narrowly construing the second element of the *Althen* test, confirming that circumstantial evidence and medical opinion, sometimes in the form of notations of treating physicians in the vaccinee's medical records, may in a particular case be sufficient to satisfy that second element of the *Althen* test. Both *Pafford v. HHS*, 451 F.3d 1352, 1355 (Fed. Cir. 2006), and *Walther v. HHS*, 485 F.3d 1146, 1150 (Fed. Cir. 2007), discussed the issue of which party bears the burden of ruling out potential non-vaccine causes. *DeBazan v. HHS*, 539 F.3d 1347 (Fed. Cir. 2008), concerned an issue of what evidence the special master may consider in deciding the initial question of whether the petitioner has met her causation burden. The issue of the temporal relationship between vaccination and the onset of an alleged injury was further discussed in *Locane v. HHS*, 685 F.3d 1375 (Fed. Cir. 2012), and *W.C. v. HHS*, 704 F.3d 1352 (Fed. Cir. 2013). *Moberly v. HHS*, 592 F.3d 1315 (Fed. Cir. 2010), concluded that the "preponderance of the evidence" standard that applies to Vaccine Act cases is the same as the standard used in traditional tort cases, so that *conclusive* proof involving medical literature or epidemiology is *not* needed, but demonstration of causation must be more than "plausible" or "possible." Both *Andreu v. HHS*, 569 F.3d 1367 (Fed. Cir. 2009), and *Porter v. HHS*, 663 F.3d 1242 (Fed. Cir. 2011), considered when a determination concerning an expert's credibility may reasonably affect the outcome of a causation inquiry. *Broekelschen v. HHS*, 618 F.3d 1339 (Fed. Cir. 2010), found that it was appropriate for a special master to determine the

reliability of a diagnosis before analyzing the likelihood of vaccine causation. *Lombardi v. HHS*, 656 F.3d 1343 (Fed. Cir. 2011), and *Hibbard v. HHS*, 698 F.3d 1355 (Fed. Cir. 2012), both again explored the importance of assessing the accuracy of the diagnosis that supports a claimant's theory of causation. *Doe 11* v. HHS, 601 F.3d 1349 (Fed.Cir. 2010) and *Deribeaux v. HHS*, 717 F.3d 1363 (Fed. Cir. 2013), both discuss the burden of proof necessary to establish that a "factor unrelated" to a vaccine may have caused the alleged injury.

Another important aspect of the causation-in-fact case law under the Program concerns the factors that a special master should consider in evaluating the reliability of expert testimony and other scientific evidence relating to causation issues. In *Daubert v. Merrell Dow Pharmaceuticals, Inc*., 509 U.S. 579 (1993), the Supreme Court listed certain factors that federal trial courts should utilize in evaluating proposed expert testimony concerning scientific issues. In *Terran v. HHS*, 195 F.3d 1302, 1316 (Fed. Cir. 1999), the Federal Circuit ruled that it is appropriate for special masters to utilize *Daubert*'s factors as a framework for evaluating the reliability of causation-in-fact theories presented in Program cases.

The Petitioner in this case alleges that the influenza vaccination that A.I. received on January 11, 2008, *did not initially cause* Leigh Disease, but rather, that the vaccination *significantly aggravated* her pre-existing Leigh Disease, causing it to worsen. According to *W.C. v. HHS*, 704 F.3d 1352 (Fed. Cir. 2013), "the National Vaccine Injury Compensation Program *** allows certain petitioners to be compensated upon showing, among other things, that a person 'sustained, or had *significantly aggravated*' a vaccine-related 'illness, disability, injury, or condition.'" *Id*. at 1355-56, *quoting* 42 U.S.C. § 300aa-11(c)(1)(C)) (emphasis added.) In *Whitecotton v. HHS*, 81 F.3d 1099, 1103 (Fed. Cir. 1996), the U.S. Court of Appeals for the Federal Circuit stated that "the statutory requirements to make out a *prima facie* significant aggravation claim are analogous to those required to make out a *prima facie* initial onset claim." The Vaccine Act states that "[t]he term 'significant aggravation' means any change for the worse in a preexisting condition which results in markedly greater disability, pain or illness accompanied by substantial deterioration of health." § 300aa-33(4).

The elements of an off-Table *significant aggravation* case are set forth in *Loving v. HHS*, 86 Fed. Cl. 135, 144 (2009). There, the court combined the test from *Althen*, above, which defines off-Table causation cases, with the test from *Whitecotton v. HHS*, 81 F.3d 1099, 1107 (Fed. Cir. 1996), which concerns on-Table significant aggravation cases. The resulting test has six components, which are:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving, 86 Fed. Cl. at 144; *see also W.C. v. HHS*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (holding that "the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims").

II

PROCEDURAL HISTORY

On April 1, 2010, Petitioner H.L. filed a petition through her attorney, Robert Krakow, under the National Vaccine Injury Compensation Program, on behalf of her deceased daughter, A.I. (ECF No. 1.) The petition alleged that A.I. was administered an influenza vaccine under the brand name "FluMist" on January 11, 2008, and that that vaccine "significantly aggravated [A.I.'s] metabolic and mitochondrial disorder leading to serious complicating medical problems and causing her death on April 5, 2008." (*Id*., ¶¶ 10, 11.) According to the Petition, A.I.'s diagnosis at death was "Leigh's encephalopathy syndrome," respiratory failure, and sepsis. (*Id*., ¶ 53.)

At that time, Petitioner filed medical and other records marked as Exhibits 1 to 22. Also on April 1, 2010, a notice was filed assigning the case to Special Master Golkiewicz. (ECF No. 2.)

Respondent filed a "Rule 4 report" on June 30, 2010, contending that the Petitioner had not met her burden of proving causation or significant aggravation. (ECF No. 8.) Although Respondent did not dispute that A.I. suffered from the terrible condition known as "Leigh Disease," or that her death was ultimately attributable to it (*id*., p. 8), the government contended that the facts of this case were not sufficient to justify a finding that the Leigh Disease was caused or aggravated by A.I.'s vaccination, particularly in the absence of any causal connection having been made by any of A.I.'s treating physicians (*id*., pp. 10-11).

After a number of extensions of time, Petitioner filed an expert report by Dr. Frances D. Kendall on January 1, 2012. (Ex. 24.) Shortly thereafter, the case was reassigned to Chief Special Master Patricia Campbell-Smith. (ECF No. 29.) On July 17, 2012, Respondent filed an expert report by Dr. Shawn E. McCandless. (Ex. A.)

Subsequently, the case was reassigned to me on May 28, 2013, and I scheduled an evidentiary hearing for July 26, 2013. Pre-hearing submissions were submitted by both parties on July 3, 2013, as was a supplemental declaration by H.L. on July 19, 2013 (Ex. 93). At the hearing, held on July 26, 2013, I heard testimony from H.L. as well as Drs. Kendall and McCandless. (*See* Transcript of Proceedings ("Tr."), ECF No. 70.)

From that point forward, Petitioner requested a large number of extensions before finally submitting a post-hearing brief on December 14, 2014. (ECF No. 114.) Respondent's response was filed on April 22, 2015 (ECF No. 123), followed by Petitioner's reply brief on June 9, 2015 (ECF No. 127).

The parties were subsequently permitted to file additional supplemental briefs, which they did on August 3, 2015 (Respondent), and September 3, 2015 (Petitioner). (ECF Nos. 130,

133.) These briefs principally addressed the significance of the Federal Circuit's decision in *Paluck v. HHS*, 786 F.3d 1373 (Fed. Cir. 2015), which was raised for the first time in Petitioner's reply brief.[2]

III

FACTS

A.I. was born prematurely on December 7, 2001, at 29 weeks of gestation, and was not discharged from the hospital until approximately two months later. (Ex. 1, p. 140.) During this time she had feeding and breathing difficulties, pneumonia, and gastro-esophageal reflux disorder ("GERD"). (Ex. 19, pp. 443-44.) Following her discharge, A.I. was seen regularly by Brighton Pediatrics. She was generally described as doing "well" and as being "alert," but her premature birth was noted several times in the medical records. (*See, e.g.*, Ex. 1, pp. 110-29.)

In the course of her pediatric care, A.I. was treated for common infections on a number of occasions. (Ex. 1, pp. 4-7.) At various points, she had conjunctivitis, upper respiratory infections, bronchitis, otitis media, sinusitis, viral gastroenteritis, and other illnesses. (*Id.*) A.I. developed fevers on multiple occasions, but was able to recover from those illnesses. (*Id.*, pp. 65, 91, 107.) In January of 2003, A.I. was hospitalized with fever, diarrhea, and dehydration. (Ex. 3, pp. 53-56; Ex. 14, p. 26.) Her records indicate a 103-degree fever on December 1, 2003, at which point it was noted that she was falling and clumsy. (Ex. 1, p. 91.)

In A.I.'s first year, her development was viewed as appropriate for her adjusted age, and she was growing well. (Ex. 1, p. 110.) At about age 14 months, however, A.I. was observed to have motor delay and possible speech delay. (Ex. 1, p. 102.) These delays were noted again at 16 months (Ex. 1, p. 98) and 18 months (Ex. 1, p. 94). At about 30 months, it was noted that A.I. was a late walker and that she still fell down frequently. (Ex. 1, p. 83.) At about 35 months of age, A.I. visited the pediatrician after falling and hitting her head. (Ex. 1, pp. 79-80.) At this time her developmental delay was again noted, as was the fact that she appeared "wobbly" when she walked. (*Id.*)

In addition to mild illnesses and developmental concerns, A.I. had some surgeries. She was also diagnosed with esotropia, an eye condition, and had corrective surgery for that condition at 31 months. (Ex. 2, pp. 20-22.) At age 49 months, she had an adenoidectomy and tube placement in her ears. (Ex. 8, p. 9.)

On January 11, 2008, A.I., now six years old, saw her pediatrician following two days of coughing, and a fever registering 102 degrees that morning. (Ex. 1, pp. 39-40.) By the time of her exam, her fever had reduced to 100.3. (*Id.*) She was diagnosed as having an upper respiratory infection, which had improved by her next visit on January 16, 2008. (Ex. 1, pp. 38, 40.) During the visit on January 11, 2008, A.I.'s pediatrician administered a FluMist vaccine, recommended Tylenol for her fever, and prescribed donatussin. (Ex. 1, p. 40.)

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[2] *Paluck* was decided on May 20, 2015, after Respondent had filed her brief, but before Petitioner filed her reply.

H.L. testified that after that point, A.I. began demonstrating unusual symptoms. In particular, later in the evening on January 11, A.I. began experiencing "staring spells." (Tr. 23-26.) [3] Continuing to feel unwell, A.I. stayed home from school through January 18, 2008. (Ex. 5, p. 95; Tr. 25, 28.)

On January 22, 2008, A.I. collapsed three times during the school day, and was taken to the emergency room at the Children's Hospital. (Ex. 4, pp. 3-4.) Her parents reported that over the previous week, A.I. had light sensitivity in her eyes, painful urination, and periods of disorientation, which resolved with stimulation. (Ex. 6, p. 5.) A.I. was discharged the same day with instructions to follow up with her pediatrician. (Ex 4, p. 4.)

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[3] There is no documentation in the medical records directly supporting H.L.'s testimony that A.I. experienced staring spells on the day of her FluMist vaccination. Ordinarily medical records "warrant consideration as trustworthy evidence." *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). Accordingly, where subsequent testimony conflicts with contemporaneous medical records, special masters frequently accord more weight to the medical records. *See, e.g., Reusser v. Sec'y of Health & Human Servs.*, 28 Fed. Cl. 516, 523 (1993) ("[W]ritten documentation recorded by a disinterested person at or soon after the event at issue is generally more reliable than the recollection of a party to a lawsuit many years later."). However, "it must be recognized that the 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. Since medical records typically record only a fraction of all that occurs, the fact that reference to an event is omitted from the medical records may not be very significant." *Murphy v. HHS*, 23 Cl. Ct. 726, 733 (Fed. Cl. 1991)(*aff'd* 968 F.2d 1226 (Fed. Cir. 1992)). Here, there is nothing in the records to either support or directly contradict H.L.'s account of the staring spells that allegedly occurred immediately after A.I.'s vaccination. The record for A.I.'s next medical exam on January 16 indicates that A.I.'s activity level was "down," but does *not mention staring spells*. (Ex. 1, p. 37.) I note, however, that H.L. testified that at the time she witnessed A.I.'s staring spells, she did not have the vocabulary to describe it. (Tr. 23.) But in any event, the record for A.I.'s next visit on January 28 *does* explicitly reference the staring spells, and does so without any reference to when they began. (Ex. 1, p. 35.) Despite the lack of any notation in the January 16 records, this later entry provides some corroboration of H.L.'s account, although it does not specify *when* the staring spells occurred. (Also note that at Ex. 1, p. 4, there seems to be a handwritten notation on *1/23/08* mentioning "staring spells".) I also find it noteworthy that H.L. was able to anchor her recollection of the staring spells to two specific instances, one in which A.I. seemed to ignore H.L. when they returned home and it was time to get out of the car, and one in which H.L. observed A.I. apparently ignoring her brother. (Tr. 23-25.)

Assessing these factors, I do find it strange that if A.I. actually experienced staring spells on January 11, these would not have been reported at the January 16 visit. However, for purposes of deciding this case at this time, I will *assume* that A.I. did experience her first staring spells on January 11, as Petitioner asserts.

However, while walking to the car in the emergency room parking lot, A.I. collapsed again. (Ex. 3, pp. 31, 34; Ex. 4, p. 4.) A.I.'s father carried her back to the emergency room, and A.I. was diagnosed with staring spells and "weakness." (Ex. 3, p. 40; Ex. 6, p. 8.) The plan remained for her to follow up with her pediatrician in two days. (*Id.*) The next day, A.I.'s pediatrician noted that she was experiencing "drop attacks" and "staring spells," and referred her for an EEG. (Ex. 1, p. 4.) On January 24, 2008, an EEG was performed, which came back normal.

On January 28, 2008, A.I. was seen at her pediatrician's office for a follow-up visit. (Ex. 1, p. 35.) The doctor's impression was ataxia, weakness in legs, and probably mild Guillain-Barré syndrome, and A.I. was referred to a pediatric neurologist. (*Id.*, p. 36.) Two days later, A.I. was seen by pediatric neurologist, Benjamin Ross. (Ex. 6, pp. 27-30.) Upon examination, Dr. Ross concluded that Guillain-Barré was unlikely. (Ex. 6, p. 29.)

On February 11, 2008, A.I. had an MRI of her brain, which was abnormal, and suggestive of a possible mitochondrial disorder. (Ex. 19, p. 244; Ex. 6, pp. 31-32.) At Dr. Ross' request, the family returned to his office on February 19, 2008, to discuss the results. (Ex. 6, pp. 31-32.) At this time, A.I. was no longer having sudden falls, but continued to have intermittent staring spells and increased difficulty eating and drinking. (*Id.*, p. 31.) Dr. Ross recorded additional family history, and ultimately concluded that given A.I.'s abnormal MRI, recent symptoms, and family history, the likely diagnosis was a mitochondrial disorder. (*Id.*, p. 33.) Specifically, Dr. Ross was concerned A.I. had "Leigh syndrome," and recommended further investigation. (*Id.*)

On February 21, 2008, A.I. was evaluated by clinical geneticist Dr. Margarita Sifuentes Saenz, and metabolic attending Dr. Janet Thomas, at the Children's Hospital. Dr. Saenz noted that in mid-January, shortly after A.I. received the FluMist vaccine, she began manifesting some atypical behaviors, including staring spells, increased fatigue, increased loss of balance, and drop-like attacks. (Ex. 3, pp.16-20.) Dr. Saenz and Dr. Thomas concluded that A.I.'s clinical and other features were strongly indicative of Leigh syndrome, but apparently did not fulfill the stringent diagnostic criteria. (*Id.*, pp. 18-19.)

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On March 15, 2008, A.I. was taken by ambulance to the Children's Hospital because she had an episode of unconsciousness and difficulty breathing. (Ex. 14, p. 46.) At the emergency room, her physician diagnosed A.I. with possible hypoxic seizures and respiratory distress, and she was transported to Presbyterian/St. Luke's Medical Center (PSL) on that the same day, for overnight observation. (*Id.*, pp. 42-43, 46.) At PSL, a sleep study was conducted, and came back grossly abnormal. (Ex. 3, p. 48.) The study showed an apparent seizure, severe sleep-disordered breathing manifested by prolonged obstructive hypoventilation, snoring, and labored breathing with associated hypoxemia. (Ex. 6, p. 1.)

After admission to PSL, A.I. exhibited progressive respiratory and swallowing difficulties. A gastronomy tube was placed on March 21, 2008. (Ex. 20, p. 1.) Following the surgery, A.I.'s neurologic status deteriorated, and she became unresponsive over time. (*Id.*)

MRI examinations showed a worsening of the lesions in the brain consistent with Leigh syndrome. (*Id.*) Tragically, on April 5, 2008, A.I. passed away, with "Leigh Syndrome" being the listed cause of death. (*Id.*, pp. 1-3.) No autopsy was performed. (*Id.*, p. 3.)

IV

ISSUES TO BE DECIDED

In this case, Petitioner seeks a Program award, contending that A.I.'s death was "caused-in-fact" by the "FluMist" vaccination administered to her on January 11, 2008. The issues to be resolved in this decision can be narrowed considerably, in that both experts agree that A.I. suffered from Leigh Disease (also known as "Leigh Syndrome"), an inborn metabolic disorder, and that she ultimately died as a result of a metabolic decompensation, a common occurrence among Leigh Disease patients. (Tr. 54, 121.) Moreover, both experts also agree that metabolic decompensation can be caused by a fever or infectious illness, and that A.I. had such an illness in January 2008 that likely contributed to the metabolic decompensation which ultimately led to her death. (Tr. 56-59, 77, 99-100, 174-75.) The only significant disagreement is on the particular question of whether the FluMist vaccine administered on January 11, 2008, *additionally* played any causal role in triggering that metabolic decompensation. After careful consideration, I conclude that Petitioner has *failed* to meet her burden.[4]

Petitioner argues that the FluMist vaccine acted in concert with A.I.'s intercurrent illness, creating a combined stress event that resulted in the cascade of symptoms leading to her death. Petitioner's argument is based on five main contentions raised by her expert, Dr. Kendall, which are addressed in detail below. Briefly, these points are: A.I.'s decline was temporally related to her vaccination; there is no evidence that A.I. experienced metabolic decompensation following prior, more severe, illnesses, in the absence of the FluMist vaccination; post-marketing evidence for the FluMist vaccine has specifically reported instances of this vaccine exacerbating symptoms of mitochondrial encephalomyopathy (Leigh Disease); studies showing a link between vaccines and autistic regression in patients with metabolic disorders demonstrate that vaccines are metabolic stressors; and, studies showing that the *wild flu virus* is capable of causing cell death (the process at work in a fatal metabolic decompensation such as A.I. experienced). Dr. Kendall acknowledged that there is no direct scientific evidence that immunizations can cause the type of metabolic decompensation at issue in this case (tr. 83, 86), but argued, in effect, that the above points circumstantially demonstrate that the vaccine played a causal role in A.I.'s death, by aggravating her pre-existing Leigh Disease.

Respondent's expert, Dr. McCandless, disagreed with each of these contentions. He argued that Dr. Kendall presented studies that are mismatched to the facts of this case, and that she sought to draw inferences from the articles that are not supported by the actual findings of the studies. Dr. McCandless also took issue with the purported significance of postmarketing experience, and stressed that the medical community overwhelmingly recommends flu vaccinations to patients with inborn metabolic disorders. Dr. McCandless stressed that metabolic

[4] Petitioner has the burden of demonstrating the facts necessary for entitlement to an award by a "preponderance of the evidence." § 300aa-13(a)(1)(A). Under that standard, the existence of a fact must be shown to be "more probable than its nonexistence." *In re Winship*, 397 U.S. 358, 371 (1970) (Harlan, J., concurring).

decompensation can occur without any apparent trigger, and opined that in A.I.'s case the most likely trigger, if any, was an upper respiratory infection that A.I. suffered *prior* to her FluMist vaccination.

V

SUMMARY OF EXPERT WITNESSES' QUALIFICATIONS AND OPINIONS

In this case, each side presented the expert reports and hearing testimony of one medical expert. At this point, I will briefly summarize both the qualifications and the opinions of these expert witnesses.

A. Petitioner's expert

1. Dr. Frances D. Kendall

Petitioner has relied primarily on the expert report and testimony of Dr. Frances D. Kendal. Dr. Kendall has been practicing with a special attention to mitochondrial diseases for 20 years. (Ex. 24, p. 1; Tr. 43-44.) She was trained at Harvard Medical School and Boston Children's Hospital before she started Horizon Molecular Medicine, a laboratory dedicated to the molecular and enzymatic diagnosis of mitochondrial patients. (Tr. 43-44.) Her current practice, Virtual Medical Practice, is devoted to the care of patients with mitochondrial and other rare genetic disorders. (Ex. 24, p. 1; Tr. 44.)

Dr. Kendall received her B.A. in 1982 from Temple University, and her M.D. in 1987 from UMDNJ-New Jersey Medical School. (Ex. 25, p. 1.) From 1987 to 1988, she interned at the pediatrics department of Thomas Jefferson University Hospital. (*Id*.) She completed her residency in pediatrics from 1988 to 1990 at that hospital, serving as Chief Resident from 1989 to 1990. (*Id*.) She completed a fellowship in genetics and metabolism at the Children's Hospital and Harvard Medical School from 1990 to 1993, while also completing a research fellowship in genetics and metabolism at Tufts University from 1991 to 1993. (*Id*.) She has been an active member of the Society of Inherited Metabolic Diseases since 1998. (Ex. 25, p. 2.)

Dr. Kendall was an instructor in pediatrics at Harvard Medical School from 1993 to 1998. (*Id.*, p. 3.) She has been board-certified in pediatrics since 1990, and board-certified in medical genetics since 1996. (*Id.*, p. 1.) In 2008, Dr. Kendall was appointed an Assistant Professor at the Emory University School of Medicine. (*Id*.) Dr. Kendall was the attending physician for the IEM-PKU[5] Program at the Children's Hospital in Boston from 1993 to 1995, and was later the assistant director of that program from 1996 to 1998. (Ex. 25, p. 2.) She was the director of the mitochondrial disorders program at the Children's Hospital from 1994 to 1998. (*Id*.) Dr. Kendall also served from 1998 to 2001 as the director of the Medical Genetics and Metabolic Screening Laboratory at Children's Healthcare of Atlanta, where she currently serves as an attending physician. (*Id*.) She lists seven articles on her curriculum vitae, as well as numerous lectures and several reviews and abstracts. (Ex. 25, pp. 3-7.)

[5] IEM refers to "inborn errors of metabolism," and PKU to phenylketonuria, a particular form of IEM.

2. Summary of Dr. Kendall's opinion

Dr. Kendall devoted much of her expert report to establishing that A.I. in fact had Leigh Disease, a form of mitochondrial disorder, which involves a "homoplasmic 8993 mtDNA mutation." (Ex. 24, pp. 4-7.) Ultimately, Dr. Kendall argued that this left A.I. at risk for metabolic decompensation, and that her infectious illness of January 10th and 11th, combined with the added stress of her flu vaccination, "caused increased stress to her body and resulted in a cascade of events that ultimately resulted in her demise." (Tr. 53-55.) At the hearing in this case, however, Dr. Kendall acknowledged that there is no direct scientific evidence that immunizations can cause the type of metabolic decompensation at issue in this case. (Tr. 83, 86.)

Rather, in her expert report Dr. Kendall argued that "recent studies have documented the association of developmental regression and autism in patients with mitochondrial disease following exposure to immunizations." (Ex. 24, p. 7.) She posited that "[c]learly, the onset of regressive clinical symptoms following immunizations in one subset of mitochondrial patients provides precedent for the development of similar regression following vaccination in another subtype of affected individuals, namely Leigh disease patients with the mtDNA 8993 mutation, who have already been shown to regress with other stressors." (*Id*.)

On that basis, Dr. Kendall opined, coupling A.I.'s Leigh Disease diagnosis with the temporal relationship between her vaccination and the onset of A.I.'s decompensation, that A.I.'s decline, and ultimately her death, were the result of the flu vaccination's significant aggravation of her pre-existing Leigh Disease. (Ex. 24, p. 8.) In that regard, Dr. Kendall stressed that A.I.'s medical history showed that she was able to tolerate previous illnesses and vaccinations without difficulty. (*Id*.)

B. Respondent's expert

1. Dr. Shawn McCandless

Respondent has relied primarily on the expert report and testimony of Dr. Shawn McCandless. Dr. McCandless received a B.S. in Chemistry in 1984 from Westminster College, and his M.D. from Temple University School of Medicine in 1988. (Ex. L, p. 1.) Dr. McCandless completed his residency in pediatrics at the University of Wisconsin Hospital and Clinics from 1988 through 1991. (*Id*.) He then completed a registrar in pediatrics from 1991 to 1992 at Gloucestershire Royal Hospital. (*Id*.) From 1996 to 1999, Dr. McCandless completed a residency in medical genetics at the University Hospitals of Cleveland/Case Western Reserve University. (*Id*.) He completed a fellowship in biochemical genetics from the same hospital. (*Id*.)

Dr. McCandless is currently an associate professor of genetics, pediatrics, and pathology at Case Western Reserve University. (Ex. L, p. 1.) He is board-certified in both clinical biochemical genetics and pediatrics. (*Id*., p. 2.) He is also a member of the Genetics and Birth Defects Section of the American Academy of Pediatrics, and is currently on the board of directors of the Society for Inherited Disorders of Metabolism. (*Id*., p. 3.) He lists 35 peer-reviewed articles on his *curriculum vitae*, as well as numerous book chapters, reviews, and presentations. (*Id*., pp. 5-8.)

2. Summary of Dr. McCandless' opinion

Dr. McCandless agreed with Dr. Kendall's assessment to the extent of her conclusion that A.I. suffered from a homoplasmic 8993 mutation consistent with Leigh Disease (Ex. A, p. 2), but rejected Dr. Kendall's further suggestion that A.I.'s immunization contributed to her significant deterioration (*id.,* p. 3; Tr. 174.) Rather, Dr. McCandless contended that "[t]he clinical course described here is characteristic of the underlying condition [*i.e.*, Leigh Disease]," and further argued that "[t]he metabolic community has not been able to identify any clear association with immunization and metabolic decompensation (acute metabolic illness) or neurological deterioration." (Ex A, p. 3.)

Specifically, Dr. McCandless rejected Dr. Kendall's suggestion that medical literature supports the claim that immunization can lead to autistic regression, and further disputed Dr. Kendall's comparison of A.I.'s condition to cases of autistic regression. (Ex. A, pp. 3-4; Tr. 135-37.) He noted that Dr. Kendall's opinion proposes that in A.I.'s case "an immunization contributed to the neurological deterioration in the underlying mitochondrial condition, rather than the much better known, and more likely, association with the concurrent febrile illness that was present before the immunization was given." (Ex. A, p. 3.) In other words, Dr. McCandless argued that while it is possible that A.I.'s *infectious febrile illness*, which already existed prior to her FluMist vaccination, contributed to A.I.'s neurological deterioration, there is no reasonable basis for the assertion that the *FluMist immunization* additionally contributed. (Ex. A, pp. 3-4; Tr. 173-74.)

VI

SUMMARY OF MY OPINION

After reviewing the record of this case, I have found that Dr. Kendall's view of the case was quite unpersuasive, while Dr. McCandless's opinion was far more persuasive. On the whole, in contrast to Dr. McCandless's coherent and sound testimony, Dr. Kendall *failed* to persuade me that key pieces of evidence, upon which she relied, supported her contentions. I find that Dr. Kendall overstated the significance of other pieces of information, such as the FluMist postmarketing experience, and effectively admitted that certain aspects of her causation opinion were speculative. As indicated above, there is much that these two experts agree upon. Where they part, however, is where Dr. Kendall sought to make inferential leaps not supported by the record in this case. Simply put, Dr. Kendall failed to convince me that *any* of the main points she used to support her theory establish the specific propositions that she advanced. Her testimony is therefore unpersuasive, and fails to meet Petitioner's burden of demonstrating that it is "more likely than not" that A.I.'s FluMist vaccination contributed to triggering the metabolic decompensation that led to her death, or in any other way significantly aggravated the metabolic condition (Leigh Disease) which was present in A.I. from her birth.

VII

DR. McCANDLESS WAS FAR MORE PERSUASIVE THAN DR. KENDALL

A. Dr. Kendall's opinion was flawed in several respects.

There were several severe deficiencies in Dr. Kendall's presentation in this case. First, the timing of A.I.'s metabolic decompensation, as alleged by Petitioner, makes it *less likely* that the FluMist vaccine contributed to her injury, and *more likely* that the injury was a result of her upper respiratory infection. Dr. Kendall also ineffectually argued that A.I.'s ability to tolerate prior illnesses provides evidence of a causal role for her vaccination. Indeed, she effectively acknowledged that her argument on that point is speculative. Moreover, Dr. Kendall greatly overstated the significance of postmarketing information contained in the FluMist packaging. Contrary to her assertion, FluMist is not contraindicated for those with Leigh Disease.

1. The timing of the onset of A.I.'s neurodegenerative symptoms makes A.I.'s pre-existing infectious illness the more likely explanation of her decline.

Dr. Kendall argued that the timing of the onset of A.I.'s metabolic decompensation is consistent with her theory that it was caused by the FluMist vaccine. But as to A.I.'s metabolic decompensation, Dr. Kendall's written report was *not* specific in noting any specific particular "first symptom." Dr. Kendall simply asserted that "the onset of her regressive clinical symptomology was temporally related to exposure to the influenza vaccine following which she developed a neurodegenerative course followed by death." (Ex. 24, p. 8.) At the hearing, however, Dr. Kendall indicated that the first indication of A.I.'s decline was the staring spells that she allegedly experienced the day of her vaccination. (Tr. 62-63.) According to Dr. Kendall, the timing of those *staring spells* is a key component of her opinion that A.I.'s metabolic decompensation was caused, at least in part, by the vaccination. (Tr. 63-64.) Dr. Kendall, however, has offered no citation to any medical literature supporting her contention that a mitochondrial decompensation could occur within hours of a vaccination, as a result of such vaccination. Indeed, Dr. Kendall has not cited to any medical literature specifically addressing the timing of mitochondrial decompensation *at all*.[6]

Dr. McCandless, on the other hand, indicated that if, in fact, A.I. experienced staring spells on the same day that she received her vaccination, that would indicate that the decompensation was more likely a result of A.I.'s pre-existing *infectious illness* than the FluMist. (Note that A.I.'s records show that she was diagnosed as having an *upper respiratory infection* on January 11, 2008, the day that she received the vaccination to which Petitioner points). (Ex.

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[6] As discussed below, Dr. Kendall relies chiefly on the Shoffner and Poling articles to link vaccination to mitochondrial regression -- a reliance which I reject in Section VII(B)(1) of this Decision below. With regard to timing, however, the Shoffner study is not more specific than to say that the authors considered cases where regression occurred "within two weeks" of a febrile episode. (*See* Ex. 24, Ref. 28, p. 2.) The study does not report that any subject experienced regression *immediately after* immunization. And although the Poling subject was reported to have regressed within 48 hours of immunization (*see* Ex. 24, ref. 27, p. 1), as described below, that timing in the Poling case was consistent with the causal *presumption* for encephalopathy under the *Vaccine Injury Table*, an injury not alleged in this case.

1, pp. 39-40.) Citing to "The Otolaryngological Manfiestations of Mitochondrial Disease and the Risk of Neurodegeneration With Infection" by Edmonds *et al.*, published in *The Journal of the American Medical Association (Otolaryngology – Head & Neck Surgery)* (Ex. 37), Dr. McCandless persuasively argued that there should typically be a period of several days between the time of an infectious insult and the onset of neurological consequences. (Tr. 172-73.) The Edmonds article states that "The timing of the infection and the neurodegenerative event varied. In a few patients (3/13), the neurologic setback occurred early in the course of infection. In most patients (10/13), the neurologic event occurred 3 to 7 days after the onset of infection and frequently appeared at a time when the infection was resolving." (*Id.*, p. 360.)

Although the Edmonds paper noted that a minority of patients experienced neurologic setbacks "early in the course of infection," it also shows that if A.I.'s staring spells were a consequence of her *upper respiratory infection*, she would fall among the *majority* of patients in the Edmonds study who experienced neurodegenerative events *several days after* the onset of infection, and as the infection was resolving.[7] As noted, A.I.'s medical records show that she was diagnosed with an upper respiratory infection on January 11, 2008, the same day she received her vaccination. (Ex. 1, pp. 39-40.) The records indicate that A.I. had been coughing for two days prior, and had had a fever of 102 degrees. (*Id*.) Although Dr. Kendall argued that this was a mild illness, she appeared to accept the diagnosis of upper respiratory infection. (Tr. 73-74, 99-100.) By the time A.I. saw the doctor, however, it appeared that she was getting better and her fever had gone down to 100.3 degrees. (Ex. 1, p. 40.) Both experts agree that the fever had reduced enough that the vaccination was no longer contraindicated. (Tr. 58-59, 73, 204-07.) Thus, consistent with the majority of the Edmonds subjects, it appears that the onset of A.I.'s neurodegeneration occurred approximately two to three days following the onset of her *infection*, as the infection was resolving. But the onset occurred only *hours* after *vaccination*, which would likely be *too soon* to be related to the vaccination. Therefore, contrary to Dr. Kendall's opinion, it appears that the upper respiratory infection is a more likely explanation for A.I.'s decompensation, based on the testimony of A.I.'s mother that A.I. experienced staring spells on the day that she received the vaccination.[8]

Significantly, the Federal Circuit has cautioned against relying on isolated small-scale studies as creating clear-cut periods of onset. *Paluck v. HHS*, 786 F.3d 1373, 1383-84 (Fed. Cir. 2015). Here, however, the Edmonds study remains the *only* evidence in this record regarding the expected timing of a neurologic deterioration such as A.I. experienced. It is therefore a

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[7] Moreover, I note that there is nothing in the Edmonds paper to suggest that "early in the course of infection" would be as little as the *several hours* that occurred, according to Petitioner, between A.I.'s vaccination and her staring spells, and Petitioner has not otherwise pointed to any support for such a contention.

[8] If, alternatively, I were to find that the January 22 collapse, occurring 11 days post-vaccination, was the first symptom, that would place A.I.'s neurodegenerative event on the far side of the bell curve suggested by the Edmonds study, regardless of whether it was caused by the vaccination or the upper respiratory infection. (Ex. 37, p. 361.) But I would still have to reject the Petitioner's causation claim in this case, for all of the *other* reasons stated in this Decision.

significant, albeit not dispositive, piece of evidence supporting my conclusion that among these two competing expert opinions, Dr. McCandless is more persuasive on this particular point. In any event, Dr. Kendall cited no medical literature to substantiate her claim of a temporal relationship between *vaccination* and decompensation. Thus, her claim of a temporal relationship in A.I.'s case is unsupported and speculative, with or without reference to the Edmonds study. In that regard it is important to note that even if a broad reading of the Edmonds study indicated that an immediate neurologic deterioration following *infection* is possible, that still would not mean that its findings could be extended to *vaccinations* or combinations of metabolic factors other than infection. Such scenarios were simply not addressed in the study. [9]

2. A.I.'s ability to tolerate prior illnesses is not evidence of vaccine causation.

Dr. Kendall found it unlikely that A.I.'s upper respiratory illness *alone* could have caused her metabolic decompensation, without the vaccination. Looking at the specifics of A.I.'s clinical history, Dr. Kendall argued that her theory is supported by the fact that A.I. did not experience a metabolic decompensation after prior illnesses or vaccinations, contending that A.I.'s ability to tolerate prior illnesses and vaccinations makes it more likely that the January 11 illness required the *additional* stress of the FluMist vaccination to overwhelm A.I.'s system. (Tr. 67, 73-74.) That is, Dr. Kendall argued that A.I. "was in a weakened state. Her body was already stressed from the intercurrent illness [the URI] and then she was added another stressor [the vaccination] on top of that." (Tr. 67.) Dr. Kendall opined that a mild illness such as A.I. experienced on January 11, which was short in duration and did not include excessive fever or eating difficulty, would not ordinarily lead to metabolic decompensation on its own. (Tr. 73-74.)

Dr. McCandless indicated, however, that the causes of metabolic decompensation are not well understood, and stated his opinion that there is not always *any* identifiable precipitating factor. (Tr. 138-39.) Significantly, Dr. McCandless further indicated that most Leigh Disease patients do not decompensate with every illness, and that nobody is able to predict when an illness will be a precipitating factor. (Tr. 139-40.) On cross-examination, Dr. Kendall effectively conceded these points. (*E.g.*, Tr. 99-100.) Specifically, Dr. Kendall testified that metabolic decompensation is common after an infectious illness, and that absent the ability to measure oxidative stress, she cannot say for sure whether A.I.'s January 11 illness alone was sufficient to cause metabolic decompensation. (*Id*.) Moreover, she acknowledged not only that Leigh Disease *typically* results in premature death (Tr. 95-96), but also conceded that metabolic decompensation can occur *without* any known stressor (Tr. 100).

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[9] One could argue that the Edmonds article provides some support for Dr. Kendall's position, in that a minority of subjects experienced deterioration "early in the course of infection," language which could conceivably be interpreted to be analogous to a decompensation only hours after a *vaccination* in this case. (Ex. 37, p. 360.) Nonetheless, even if I accept the presence of a temporal relationship in satisfaction of *Althen* Prong 3 based on Petitioner's filing of the Edmonds article, I would still find that the article is relevant to, and supportive of, *Respondent's* arguments going to *Althen* Prong 2. That is, the Edmonds article as a whole suggests that the *infection*, rather than the vaccination, is a *substantially more likely* explanation for A.I.'s deterioration.

Thus, Dr. Kendall's assertion, that A.I.'s clinical history of tolerating prior illnesses and vaccines likely indicates vaccine involvement in her ultimate decompensation, is essentially speculation. The two experts agree that the significance of A.I.'s January 11 illness, or any of her prior illnesses, is effectively unknowable. Most significantly, Dr. Kendall admitted not only that she is unable to measure whether the January 11 illness would have been an insufficient trigger, she also admitted that no identifiable trigger is even required.[10]

3. FluMist postmarketing evidence regarding Leigh Disease is not evidence of vaccine causation.

Dr. Kendall additionally cited the postmarketing information provided as part of the FluMist packaging as further evidence that the FluMist vaccine in particular would have been capable of causing A.I.'s metabolic decompensation. (Tr. 56-57.) Specifically, Dr. Kendall noted that the packaging states that among the reported events occurring post-approval, there occurred instances of "exacerbation of symptoms of mitochondrial encephalomyopathy (Leigh Syndrome)." (Tr. 56-57; Ex. 30, p. 7.) Initially, Dr. Kendall contended that this notation was a contraindication for the vaccination. (Tr. 84-85.) Ultimately, however, she acknowledged that the package information regarding Leigh Disease was not a contraindication. (Tr. 106.)

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[10] This also raises a broader question going to proximate causation. That is, even if the FluMist vaccine could be considered a potential stressor as Dr. Kendall argues, given the nature of Leigh Disease as a condition that *almost invariably* leads to metabolic decompensation and ultimately premature death even in the absence of a stressor, it could be argued that FluMist vaccination still would not necessarily constitute a "proximate cause" of A.I.'s death. (*See, e.g., Shyface v. HHS*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999) (noting that "but for" causation is insufficient without a logical sequence of cause and effect showing that the vaccine substantially contributed to the injury).) This would be a particularly challenging burden for the Petitioner in this case, because there has been evidence in this case that A.I. demonstrated some pre-vaccine neurodegenerative symptoms which may have been attributable to her Leigh Disease. (Tr. 143-44.) However, because I have found that Petitioner has not met her burden of establishing that the FluMist vaccine was even a *plausible* triggering event of A.I.'s metabolic decompensation, it is not necessary to reach that question. In this regard, I stress that even if Dr. Kendall were able to establish that A.I.'s January 11 upper respiratory infection lacked sufficient metabolic demand to cause a decompensation on its own, this still would not lead to the conclusion that A.I.'s FluMist vaccination was necessarily an additional contributing stressor. As described in Section VII(B)(1) below, Dr. Kendall has not established that the vaccine itself had a material impact on metabolic demand, and, in any event, as noted in this section, both experts agree that metabolic decompensation in Leigh Disease patients can occur *without any* known stressor.

Petitioner's brief also makes much of one statement by Dr. McCandless that A.I.'s overall clinical course was "atypical." (ECF 137, p. 8.) However, Dr. McCandless further addressed that same issue elsewhere in his testimony. For example, he explained that that A.I.'s course in fact was "typical" *except* for the fact her major decompensation occurred later in her life than is usually the case with Leigh Disease patients. (Tr. 123-24.) He added, moreover, that while 75% of Leigh Disease patients experienced their major decompensation by age three, still the other 25% experience their decompensation, like A.I., *after* age three. (Tr. 177.) Therefore, he explained, to that extent A.I.'s case is not really "atypical" after all. (*Id*.)

Nonetheless, Dr. Kendall characterized it as "specifically warn[ing] physicians to avoid its use in mitochondrial patients" (tr. 56), and further testified that it would make her "very cautious" (tr. 106).

Dr. McCandless, likewise, indicated that the package insert would cause him to consider the risk of administering the FluMist vaccine to a child with Leigh Disease. (Tr. 191.) He also testified, however, that he would still perceive the risk to be low. (*Id*.) Dr. McCandless explained that postmarketing experience is the result of a reporting requirement mandated by the FDA to ensure that *potential issues* may be investigated where there are reports of a particular occurrence after vaccination. (Tr. 166-69.) He argued that postmarketing information itself is therefore not evidence of a causal connection.[11] (*Id*.) Moreover, Dr. McCandless stressed that postmarketing experience is distinct, and of lesser significance than, either contraindications or warnings, and that, according to the package information, the FluMist vaccine is not contraindicated for individuals with Leigh Disease. (*Id*.)

In that regard, Dr. McCandless also stressed that, as a general matter, the medical community as a whole largely agrees that vaccines should be routinely administered to individuals with metabolic disorders. Specifically, Dr. McCandless agreed with the statement made in "Attitudes Regarding Vaccination Among Practitioners of Clinical Biochemical Genetics" by Barshop *et al.*, published in *Molecular Genetics and Metabolism*, that "it is clear that the general opinion held by practitioners in the field of clinical biochemical genetics favors the full schedule of vaccination for their patients. The overwhelming majority feel that the benefits of the current schedule outweigh the risks to individuals with undiagnosed metabolic disease. Most have never observed any significant adverse event which was attributed to a vaccine reaction." (Tr. 154-55; Ex. 36, p. 2.[12]) He also cited "Immunization for Patients With Metabolic Disorders" by Kingsley *et al.*, published in *Pediatrics*. (Tr. 155-57.) The Kingsley article indicates that a review of English language medical literature found that "contraindications against immunizations were not found in the available infectious disease and metabolic disease databases for inborn errors of metabolism." (Ex. D, p. 11.) These articles further support Dr. McCandless's opinion that the postmarketing experience reported in the

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[11] *Accord, Werderitsh v. HHS*, No. 99-319V, 2005 WL 3320041, at *8 (Fed. Cl. Spec. Mstr. Nov. 10, 2005) (Special Master Sweeney stating that "Vaccine manufacturers must report adverse events to the FDA, whether or not the adverse event is considered to be product-related. [Citations omitted]. Further, '[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.' [Citations omitted]. Thus, federal regulations specifically preclude the contents of drug product labels, as reproduced in the PDR, from serving as admissions regarding causation.").

[12] This article was mistakenly identified in the hearing transcript as Exhibit 26.

FluMist package insert falls well short of constituting either a warning or a contraindication, and is not good evidence of causation.[13]

Most significantly, however, Dr. McCandless also pointed out that there is no monograph or other information reporting on the details of the FluMist postmarketing information regarding Leigh Disease. (Tr. 169.) Therefore, he argued, the packaging report of exacerbation of Leigh Disease could be based on a very few, or even a single instance, of such an occurrence. (Tr. 168-69.) In fact, Dr. McCandless suggested that based on the first appearance of this postmarketing information in the FluMist packaging--that first appearance *post-dated* A.I.'s metabolic decompensation--that it could theoretically refer solely to A.I.'s case. (*Id*.) While such a suggestion is clearly speculative, the fact remains that absent more detailed information

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[13] I note that to the extent that Dr. McCandless (and the articles he cites) are addressing *risk*, this is therefore not evidence going *directly* to the issue of causation. For example, while the Barshop article indicates that the great majority of clinicians believed the benefit of vaccinating metabolic disorder patients to outweigh the risk, a small minority did report having seen *at least one* instance of an adverse outcome attributable to a vaccine. (Ex. 36, pp. 1-2.) Thus, I do not find that the articles in themselves *disprove* a causal connection, in that they do not dispute that adverse events, whether vaccine-related or not, *can* happen, albeit rarely, soon after vaccination. Rather, I find these articles to bear specifically on the significance of the postmarketing information presented by Dr. Kendall. For example, in *Christiansen v. HHS*, 08-244V, 2012 WL 6766650 at *12 (Fed. Cl. Spec. Mstr. Dec. 20, 2012), faced with evidence that most pediatricians would have disregarded a specific package contraindication, the special master discounted the significance of that contraindication because it likely represented defensive medicine on the part of the manufacturer, and "does not guide practice in the field." In this case, these articles convince me that Dr. McCandless' opinion regarding the administration of the flu vaccine to an individual with Leigh Disease is an accurate reflection of the medical community as a whole. In fact, even Dr. Kendall indicated that a case like A.I.'s would be rare, and that she will continue to immunize her patients who have mitochondrial disease even in light of the postmarketing information. (Tr. 105-06.) It is highly unlikely that these attitudes would prevail if the postmarketing information provided the type of stark warning that Dr. Kendall implies, as opposed to being preliminary fact-gathering that does not necessarily indicate a causal connection, as Dr. McCandless argues.

Further, I note that Petitioner is correct in arguing that the mere fact that mitochondrial specialists would have their mitochondrial disease patients vaccinated, as posing a lesser risk than the absence of vaccination, does not necessarily *prove* that there is *no risk* in vaccination. As Petitioner has argued, there still could be a *small* risk in vaccination, and a particular vaccinee, such as A.I., might possibly be the rare victim of such a small risk. However, the recommendation of specialists, including Dr. Kendall herself, that mitochondrial disease patients be vaccinated, is at least *some* evidence contrary to Petitioner's assertion that vaccination is a *likely* cause of decompensation in mitochondrial disease patients. Further, in this case the burden is not on *Respondent* to show that vaccines can *never* cause decompensation in a Leigh Disease patient, but *on the Petitioner* to demonstrate that the vaccination in question "more likely than not" *did* aggravate A.I.'s Leigh Disease. This burden *has not* been carried by Petitioner, for all the reasons detailed in this Decision.

regarding the number of instances reported, the postmarketing information is simply not informative of any causal connection. Indeed, without even knowing how many reported instances there were, it is impossible to even credit it as suggesting any correlation or temporal association at all.[14]

B. Dr. Kendall's opinion is not supported by the medical literature that she submitted.

Dr. Kendall's failure to establish a factual basis for the application of her causal theory is reason enough to dismiss her opinion in this case. Nonetheless, I note also that her opinion is unpersuasive for the additional reason that it is not well supported by the medical literature that she submitted. That is, her opinion goes well beyond the findings of the studies she cited, essentially engaging in speculation on multiple points underlying her theory.

1. Dr. Kendall has not demonstrated how articles purporting to show a link between immunization and "autistic regression" are relevant to A.I.'s case.

At base, Dr. Kendall's theory is predicated on the idea that the FluMist vaccine created "oxidative stress" (excess energy demand) that contributed materially to the event that triggered A.I.'s metabolic decompensation. Although Dr. Kendall does not claim that the vaccine *alone* was responsible for A.I.'s metabolic decompensation, absent evidence that a vaccine could have a *material* impact on cellular energy demand, Dr. Kendall has no explanation for how the *vaccine* could have played any role in A.I.'s death.

In that regard, Dr. Kendall relied on a case study by Poling *et al.* titled "Developmental Regression and Mitochondrial Dysfunction in a Child With Autism" (Ex. 24, Ref. 27 (ECF No. 26-8)) as evidence that "if mitochondrial dysfunction, from either a primary genetic abnormality or secondary inhibition of oxidative phosphorylation by other factors, is present at the times of infections and immunizations in young children that the added oxidative stresses from immune activation on cellular metabolism are likely to be very critical for the highly energy dependent central nervous system." (Ex. 24, p. 7.) Dr. Kendall also cited "Fever Plus Mitochondrial Disease Could be Risk Factors for Autistic Regression" by Shoffner *et al.*, an article appearing in the *Journal of Child Neurology*. (Ex. 24, Ref. 28 (ECF No. 26-9)(also filed as Respondent's Ex. K.) According to Dr. Kendall, this article shows, as a general proposition, how a stressor can precipitate a decline in a mitochondrial disease patient. (Tr. 76.) Specifically, in her expert report, Dr. Kendall cited the Shoffner article as further support for the proposition--introduced by her with the Poling case study--that there is a link between immunization and "autistic regression" among mitochondrial disease patients. (Ex. 24, p. 7.)

Dr. McCandless criticized Dr. Kendall's reliance on these articles, and in particular the Poling case study, because, he argues, they are not comparable to A.I.'s case. (Tr. 160-62.) Whereas the Poling subject experienced an autistic regression, it is undisputed that A.I. did *not*

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[14] For example, as I will explain below with regard to the Poling case report, a single case report is not strong evidence, because it could easily be the result of chance. I also note that in the *Christiansen* case cited in footnote 13 above, the special master found a study cited by a package insert to be unpersuasive, because it did not provide the necessary information on background incidence necessary to interpret its results.

experience an autistic regression.[15] (Tr. 88.) Moreover, it is also undisputed that A.I. had Leigh Disease, a type of mitochondrial disorder which the Poling child did *not* have. (*Id*.) Indeed, despite acknowledging this distinction (tr. 92-95), Dr. Kendall has come forward with no evidence supporting the notion that autistic regression can be equated to metabolic decompensation, making it difficult to draw any inferences from these articles regarding the cause of A.I.'s condition. Rather, in her expert report, Dr. Kendall argued in a wholly conclusory manner, and without apparent support, that "[c]learly, the onset of regressive clinical symptoms following immunizations in one subset of mitochondrial patients provides precedent for the development of similar regression following vaccination in another subtype of affected individuals, namely Leigh Disease patients with mtDNA 8993 mutation, who have already been shown to regress with other stressors." (Ex. 24, p. 7.) Dr. Kendall simply has not substantiated her assertion, either in her expert report or in her hearing testimony, that the regression in the Poling case is at all similar to the metabolic decompensation experienced by A.I. [16]

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[15] For example, Dr. McCandless noted that while the mechanism of autistic regression is not known, regression caused by mitochondrial decompensation in a case of Leigh Disease results in nerve loss visible on MRI. (Tr. 137-38.) In that regard, it is noteworthy that A.I. was in fact found to have abnormal MRI findings (Ex. 19, p. 244; Ex. 6, pp. 31-32), whereas MRI studies of the Poling subject following regression were interpreted as normal (Ex. 24, Ref. 27, p. 1).

[16] Indeed, in her post-hearing brief, Petitioner surprisingly included a motion to "compel" me to accept Respondent's concession in the *Poling* Vaccine Act case, as decisive in *this* case, on the basis of "judicial estoppel," despite explicitly conceding that "the nature of the regression in the instant case is different on a factual basis." (ECF No. 114, pp. 91-92.) This issue has already been extensively and persuasively addressed by two other special masters in *Vernacchio v. HHS*, No. 08-504V, 2015 WL 1396357 (Fed. Cl. Spec. Mstr. Mar. 6, 2015), and in *R.K. v. HHS* (Fed. Cl. Spec. Mstr. Sep. 28, 2015) ("Ruling on Motions") (not yet published or on Court website), *aff'd*, 2016 WL 552481 (Feb. 12, 2016). As indicated in *Vernacchio* and *R.K.*, Respondent cannot be compelled to concede Vaccine Act cases based on the Table Injury concession in the *Poling* case for a number of reasons. But in any event, Petitioner's acknowledgment of the factual difference between the cases renders the request moot. Although Petitioner is seeking only to have the *general theory* of injury (*i.e.*, *Althen* Prong 1), supposedly conceded in *Poling*, to be conceded in this case, such a concession in *Poling* would not be relevant to this case. Establishing a theory that a vaccine can cause injury "X" is not the same as proving that it can cause injury "Y," absent some evidence showing that injuries X and Y share sufficient commonality. And, as indicated herein, Dr. Kendall has not substantiated her claim that the regression in *Poling* is similar to the decompensation in this case. Indeed, Petitioner has admitted that the nature of the Poling regression is *different* than the decompensation that A.I. suffered. Thus, it cannot be said that Respondent is taking inconsistent positions in the two cases, a requirement for invoking judicial estoppel. *See, e.g., Vernacchio*, 2015 WL 1396357 at *5. This issue garnered further attention in this case, in post-hearing sur-reply briefs filed by the parties, in relation to the Federal Circuit's apparent indication in *Paluck v. HHS*, 786 F.3d 1373 (Fed. Cir. 2015) that Respondent had conceded "on appeal" the theory that vaccines can aggravate mitochondrial disorders. (ECF No. 127, pp. 2-3.) Respondent disputes that characterization. (ECF No. 130, p. 1.) In fact, the *Paluck* court indicated that Respondent "does

Moreover, any reliance by Dr. Kendall on these Poling and Shoffner articles, as evidence that *immunizations* in and of themselves can lead to such results, would be misplaced. As Dr. McCandless pointed out, the Shoffner article *concludes* that "[i]n our patients with mitochondrial disease and autistic spectrum disorders, the vaccines did not appear related to the neurologic regression." (Ex. K, p. 4; Tr. 162-64.) Moreover, as a single case report, the Poling article's suggestion of a temporal relationship is not in itself strong evidence of a causal connection, since it could easily be the result of pure chance.[17]

I am, of course, mindful of the recent Federal Circuit decision in *Paluck v. HHS*, 786 F.3d 1373, 1383-84 (Fed. Cir. 2015), in which the panel relied in part on the Poling case report. In that case, however, the Federal Circuit's actual consideration of the Poling report was limited to noting that, despite describing a young girl experiencing an apparent regression following vaccination, the report does not purport to establish any definitive *timeframe* for the onset of a causally-related neurological regression. (*Id*.) Any discussion of the significance of the Poling report with respect to the *validity* of the *Paluck* petitioner's theory of causation was unnecessary, because, as noted above, the court of appeals believed that the Respondent had effectively *conceded* the plausibility of the petitioner's "general causation" theory for purposes of the appeal in that case. Indeed, the Federal Circuit's decision in *Paluck* does not address the *validity* of the petitioner's causation theory in that case, but rather whether the special master had properly construed that theory for purposes of determining whether the Paluck child had a medical history consistent with the expected *timeframe* stated by the theory. In this case, unlike the appellate posture presented in *Paluck*, Respondent *clearly is* vigorously contesting Petitioner's "general causation" theory.

Nonetheless, it is noteworthy that the Court of Federal Claims cautioned in *Paluck* that although "case reports 'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value', *** 'the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" *See Paluck v. HHS*, 104 Fed. Cl. 457, 475 (2012) (quoting *Campbell v. HHS*, 97 Fed. Cl. 650, 668 (2011)).

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not meaningfully dispute" the petitioner's general causation theory "on appeal" in that case. *Paluck*, 786 F.3d at 1380. That statement would seem to indicate that the court recognized that Respondent had disputed the theory in the *courts below*, but was accepting the Court of Federal Claims judge's finding *for purposes of the Federal Circuit appeal* in that case. In any event, regardless of whether the Federal Circuit accurately characterized Respondent's position in that case or not, nothing in the Federal Circuit *Paluck* opinion indicates that Respondent can be compelled to concede any other case and, even if it did, this case remains *factually distinct*.

[17] Petitioner mentioned in her brief (ECF 114, p. 80, fn. 31) a certain statement made by a special master previously assigned to this case, Patricia Campbell-Smith (now Chief Judge of this Court), who seemed to indicate skepticism concerning Dr. Kendall's use of the Poling and Shoffner articles. (*See* Order issued on 9-21-12, ECF No. 37, p. 2.) Petitioner protested that Special Master Campbell-Smith had made that observation *before* the expert hearing in this case. (ECF 114, p. 80, fn. 31.) However, it is simply the case that *after* the evidentiary hearing in this case, in which I heard Dr. Kendall explain her interpretation of the Poling and Shoffner articles, I reached, on my own, an analysis of Dr. Kendall's reliance on those articles that was similar to that of Special Master Campbell-Smith.

In that regard, I note that I am not *entirely* discounting the evidentiary value of the Poling report. Importantly, however, as described in Section VII(A)(2) above, Dr. Kendall admitted that metabolic decompensation in Leigh Disease patients can occur *without* any known stressor. This testimony dramatically undercuts her reliance on a *single* case study to establish vaccine causation, even if that case were similar to this case (which it is not). It is also significant that another study filed into the record of this case attempted to screen for cases similar to the Poling case, and yet found that the only case similar to Poling, among its cohort population of 25 subjects, was the Poling case itself, suggesting a distinct possibility that the temporal association demonstrated in Poling was due to chance. (*See* Weissman *et al.*, "Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis," *PLoS One*: 3(11) (Nov. 2008) (Ex. 33).)[18]

Moreover, the Poling child at age 19 months reportedly experienced a severe neurologic episode within 48 hours of a DTaP vaccination, and another within five to 15 days of an MMR vaccine. (Ex. 24, Ref. 27, p. 1 (factual presentation).) Those neurological episodes occurred, therefore, within the periods for a DTaP *Table Injury* encephalopathy (72 hours) and a measles *Table Injury* 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 Poling child was eventually diagnosed with both autism and a mitochondrial disorder. (Ex. 24, Ref. 27, p. 2.) It is noteworthy, then, that the Poling child experienced encephalopathy within the *Table Injury* time

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[18] Petitioner filed the Weissman paper into the record of this case, though she did not present it as part of her case-in-chief. In post-hearing briefs, however, Petitioner stressed an isolated statement in the paper that "there might be no difference between the inflammatory or catabolic stress of vaccinations and that of common childhood diseases, which are known precipitants of mitochondrial regression." (*See, e.g.*, ECF No. 133, pp. 5-6 (quoting Ex. 33 at 4).) Petitioner argues that this constitutes evidence "supportive of causation, even if it does not 'prove' causation." (ECF No. 133, p. 6.) This argument is incorrect and misleading. The Weissman study is not a study of vaccines, and does not itself contain any data supportive of the quoted suggestion that *vaccinations* are "known" precipitants of mitochondrial regression. That statement was included in a discussion of the Poling case. (*See* Ex. 33, p. 4, Refs. 12, 36.) Moreover, the suggestion of the statement, that there may be no difference between vaccines and infections in terms of precipitating mitochondrial regression, cites to the above-discussed Edmonds study. (*See* Ex. 33, p. 4, Ref. 37.) And, significantly, the Edmonds study did not address *vaccinations*, suggesting that the Weissman citation to Edmonds was merely for the proposition that childhood *illnesses* can cause decompensation. (*See* Ex. 37.) Thus, the Weissman paper itself does not contribute any additional relevant data to this record. And in any event, to the extent that Petitioner would argue that the statement contained in the Weissman paper constitutes additional evidence of causation in itself, it is incredibly weak evidence. The statement upon which Petitioner relies says only that vaccines "might" have a metabolic impact. Such a statement expresses at best that the connection is merely possible, not probable. In that regard it is worth stressing that the study authors indicated in the same passage that the temporal relationship present in the Poling case does *not* prove causation, and that "large, population-based studies will be needed to identify a possible relationship of vaccination with autistic regression in persons with mitochondrial cytopathies." (Ex. 33, p. 4.)

for two different vaccinations (Ex. 24, Ref. 27, p. 1), thus carrying a *presumption* of causation under the Vaccine Injury Table. The same cannot be said of A.I. in this case.

During her testimony, Dr. Kendall additionally cited statements made in an article submitted by Respondent that, she argued, supported her contention. Specifically, Dr. Kendall cited statements from "Immunization Recommendations for Children With Metabolic Disorders: More Data Would Help" by Brady *et al*., appearing as a commentary in *Pediatrics*. (Ex. C.) Those statements are that "[v]accines may also cause metabolic changes that mimic, but typically less severely, the metabolic changes associated with inflammation and infection" (Tr. 71; Ex. C, p. 810), and that "[t]ransient metabolic changes associated with fever or anorexia may tip the balance in the child whose clinical status is fragile or not well controlled" (Tr. 71; Ex. C, p. 811).

Dr. McCandless argued, however, that the Brady article, as is the case with the Shoffner article, indicates only that immunizations "may" cause fever or anorexia, which in turn *may* have a metabolic impact. (Tr. 200.) Dr. McCandless noted that it is well-known that fever increases metabolic demand by approximately ten percent per degree Centigrade per 24 hour period. (Tr. 201.) Significantly, even Dr. Kendall indicated that she believed the ability of infectious illnesses to cause metabolic decompensation was related to qualifiers such as excessive fever, dehydration, or anorexia. (Tr. 73-74.) Moreover, I stress that the Brady article itself clearly states that the metabolic changes at issue are those "associated with fever or anorexia." (Ex. C, p. 811.) To the extent that the wording of the article suggests that the vaccine itself has been shown to mimic the metabolic changes that can be caused by inflammation and infection, Dr. McCandless argued, the vaccine might mimic the *immunological impact* of an infection, but there is no evidence establishing that it mimics *metabolic consequences*. (Tr. 197.) He also contended that that particular statement in the Brady article is not supported by its accompanying reference. (*Id*.)

Ultimately, I find that the Poling, Shoffner, and Brady articles do not provide persuasive evidence that a *vaccine*--as opposed to a fever or infection--can contribute to a regression or decompensation in a patient with mitochondrial disease. On cross-examination, Dr. Kendall made an important concession concerning this point, acknowledging that the Shoffner study in particular was concerned with fever, not immunizations, and that it did *not* conclude that there was any causal relationship between vaccines and autistic regression. (Tr. 90.) In this regard, I note that although A.I. was experiencing a fever around the time of her vaccination, it is undisputed that that fever *predated* the vaccination.[19]

[19] That is, A.I.'s records indicate that she had a fever of 102 degrees on the morning of the January 11 exam where she received her FluMist vaccination, but that it had reduced to 100.3 degrees by the time of her exam. (Ex. 1, pp. 39-40.) Both experts agree that the fever had subsided to the point that A.I.'s treating physician believed it was appropriate to administer the FluMist vaccination, which is contraindicated for severe illness, but not for mild illness. (Tr. 58-59, 73, 204-07.) I also note that A.I.'s medical record for the follow-up visit on January 16, 2008, indicates, based on parental reporting, that she had an additional fever of about 101 degrees two days earlier, *i.e.*, on or about January 14, or three days post-vaccination. (Ex. 1, p. 37.) No indication of the duration of that fever is given, and her temperature was 97.3 degrees at the time of that visit. (Ex. 1, p. 38.) H.L. specifically testified, however, that A.I. did *not* experience any

Significantly, Dr. Kendall admitted that she is not aware of any reliable study attributing acute metabolic decompensation to a flu vaccine among patients with Leigh Disease (tr. 86), and also more generally that there is no evidence that a vaccine alone can cause the type of metabolic decompensation at issue in this case (tr. 83). Moreover, Dr. Kendall acknowledged that the oxidative stress that she alleges to be created by the vaccine cannot even be measured. (Tr. 99.)[20] Petitioner has therefore failed to show that it is probable that A.I.'s vaccination could have acted as an additional stressor contributing to her decompensation.

Similarly, Petitioner pointed (ECF 114, p. 74; ECF 127, p. 10) to an article by Klein *et al*., "Evaluation of Immunization Rates and Safety Among Children With Inborn Errors of Metabolism," published in *Pediatrics* (Ex. M). Petitioner notes that the Klein article stated at one point that this study "did identify some evidence of increased frequencies of hospitalizations among 1- to 4-year-old children in the sickest IEM group during the 2 weeks after vaccination. This suggests that there may be a subset of more fragile children with IEMs who are at increased risk for adverse events during the immediate postvaccination period." (Ex. M, p. 1145.) The Klein authors, however, immediately added, after the language quoted above, that "this finding should be interpreted cautiously." (*Id*.) More importantly, the Klein authors went on to conclude that the "overall finding" of their study was that "children with IEMs [inborn errors of metabolism] received immunizations in a manner comparable with healthy children (*id*.), and that "[o]verall, vaccinating children with IEMs did not seem to place them at increased risk for postimmunization emergency-department visits or hospitalizations during the 30 days after vaccination" (*id*.).

Thus, when the Klein article is considered in its *entirety*, it supports Dr. McCandless' opinion in this case, not that of Dr. Kendall (as Dr. McCandless testified, *see* Tr. 151-54).

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fever during this time period (January 11 – 15). (Tr. 25-26.) But even assuming that A.I. in fact experienced a fever on January 14, it appears to be of little to no significance in that it *post-dates* the onset of A.I.'s metabolic decompensation (the January 11 staring spells) as alleged by Petitioner. (*See* Section VII (A)(1) above.) Moreover, neither expert specifically addressed the fact of this later fever about January 14. In fact, at no point has the Petitioner alleged that any of A.I.'s fevers were attributable to her FluMist vaccination.

[20] I note that Petitioner filed a medical article purporting to show that a live attenuated FluMist vaccine does produce measurable evidence of oxidative stress in subsequent breath tests. (*See* Philips, *et al*., "Effect of influenza vaccination on oxidative stress products in breath," J. Breath Res. 4 (2010) (Ex. 35).) Petitioner's counsel questioned Dr. McCandless about this article on cross-examination. (Tr. 213-15.) Dr. McCandless acknowledged that the study showed a physiological difference between vaccinated and unvaccinated individuals, but indicated that he could not opine on whether there were any metabolic differences. (*Id*.) In any event, Dr. Kendall never offered any testimony regarding this article, nor did she cite it in her expert report. Significantly, however, even if I accept that this study establishes that the FluMist vaccine is capable of producing measurable oxidative stress, that still does not mean that it produces *material* or *injurious* levels of oxidative stress. Dr. Kendall's testimony is that she is not aware of any study attributing metabolic decompensation to the flu vaccine. (Tr. 86.)

2. Dr. Kendall has not demonstrated that articles purporting to show that the wild flu virus can lead to cell death are relevant to A.I.'s case.

In addition to the above, Dr. Kendall also cited four articles that, she says, in combination show a potential mechanism whereby the *wild flu virus* acts to cause mitochondrial death, leading to cell death, leading to clinical symptoms. (Tr. 65.) That is, according to Dr. Kendall these articles "simply demonstrate pathophysiology in terms of what the influenza virus actually does in cells and in mitochondria." (Tr. 66.) Dr. Kendall stressed that she formed her opinion of this case prior to being aware of these studies, based on her clinical experience, but noted that these studies are consistent with her opinion, and that they provide a plausible basis for explaining how A.I.'s metabolic decompensation might have occurred.[21] (Tr. 65-66.) These articles are "Influenza Virus Induces Apoptosis via BAD-Mediated Mitochondrial Dysregulation" by Tran *et al.* (Ex. 67); "Human Influenza A Virus (IAV) Decreases Mitochondrial Respiration of Infected MDCK Cell" (Abstract) by Derakhshan *et al.* (Ex. 69)[22]; "Activated THP-1 Cells Depress Mitochondrial Respiration in HEP G2 Cells Infected With Influenza B Virus" by Schwarz *et al.* (Ex. 72); and "Influenza Virus PB1-F2 Protein Induces Cell Death Through Mitochondrial ANT3 and VDAC1" by Zamarin *et al.* (Ex. 75).

Dr. McCandless questioned Dr. Kendall's reliance on the Tran and Zamarin articles, both because they are not directly related to the specific mitochondrial function at issue in Leigh Disease (respiration), and because their focus is on viral reproduction rather than on the impact on the mitochondria. As a result, Dr. McCandless argued, one cannot extrapolate what energy demand the virus may be placing on the cell from these studies, as Dr. Kendall implicitly sought to do.[23] (Tr. 216-18; 220-21.)

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[21] In presenting these four articles Dr. Kendall seems to be suggesting that these articles further support her theory that the FluMist vaccine itself created a significant amount of metabolic stress, as discussed above. However, this suggestion simply was not persuasive, for the reasons discussed.

[22] What has been submitted as Exhibit 69 relative to the Derakhshan article is merely an abstract. It is a very brief one-page summary of a larger article that is not in evidence. In fact, Respondent's expert indicated that there was insufficient information provided for him to form any opinion on the article, which Petitioner's counsel characterized as "fair." (Tr. 218.) Thus Ex. 69 is of extremely limited, if any, evidentiary value.

[23] Moreover, I would go a step further and note also that the Tran article appears to be looking at the role that BAD-regulated mitochondria in *healthy* cells play in viral replication once infection has occurred. If, as the article seems to suggest, a BAD deficiency interferes with the "mitochondria-dependent apoptotic pathways" to the detriment of the infecting virus, then it seems reasonable to question whether the results of this study can even be carried over to already-dysfunctioning mitochondria, regardless of Dr. McCandless's other criticisms. In other words, the study's findings appear to be predicated on the presence of well-functioning mitochondria, something which is clearly not present for a patient with Leigh Disease.

Dr. McCandless also argued that the Schwarz study is not useful because the result is, in effect, artificial. That is, Dr. McCandless pointed out that the study was conducted with something called HepG2 cells, which are self-replicating cells used by laboratories that originate from human liver cells but are, in fact, distinct.[24] (Tr. 158-59.) Dr. McCandless argued that a cell culture study of this type is essentially of little value in determining what actually happens in live humans, because "what you can do in cell culture *** that you can't do in a person is that you can add a particular chemical, you can add a particular transcription factor [to see how the molecules in the cell react]," but "there are literally dozens of steps to go from that to what happens in a human being, what happens in an organism." (Tr. 159.)

Having read these three articles, I agree with Dr. McCandless' assessment. But regardless of those criticisms, I also find it dispositive that all three of these studies are looking at the *wild flu virus* as opposed to the type of *attenuated strain* contained in a FluMist vaccine. Dr. Kendall candidly acknowledged that this was a limitation on her reliance on these papers, and that she *did not know* if the outcome would be the same with an attenuated virus. (Tr. 101-02.) That is, although Dr. Kendall testified that she believed that an attenuated flu vaccine could lead to clinical symptoms, she conceded that the vaccine should produce an immune response *without* an infection. (Tr. 66-67.) Indeed, Dr. Kendall posited that vaccines mimic *less severely* the metabolic changes associated with inflammation and infection. (Tr. 103.) Nonetheless she testified that she "surmises" that the vaccine in question placed additional stress on A.I.'s system based on A.I.'s subsequent clinical presentation of metabolic decompensation. (Tr. 99.) Yet I must stress that there has been no suggestion in this case that A.I.'s FluMist vaccine generated any infection.

Thus, even if these articles did demonstrate a mechanism whereby the *wild* influenza virus could lead to acute metabolic decompensation as Dr. Kendall argues, by her own admission they still would not be informative as to whether the same can be said of an *attenuated* flu vaccine such as FluMist, where actual infection is not expected. This is critical, because, as described above, both experts agree not only that metabolic decompensation can be triggered by a number of different stressors, including a viral infection or other intercurrent illness (tr. 99-100, 139), but also that A.I. was recovering from such an illness at the time she received the FluMist vaccination. (tr. 56-58, 73, 174-75). And there is no evidence that A.I.'s FluMist vaccine created an actual infection, as opposed to merely an immune response, following her vaccination. Therefore, even accepting Dr. Kendall's reading of the articles,[25] they still would not support that part of Dr. Kendall's opinion that is actually controverted in this case--*i.e.*, that the FluMist vaccine *in particular* played any role in A.I.'s metabolic decompensation. [26]

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[24] The article itself describes HepG2 cells as "a well-differentiated continuous human liver cell line derived from a hepatoblastoma." (Ex. 72, p. 2.)

[25] I also found that the fourth article, by Derakhshan *et al*., also did not offer substantial support to Dr. Kendall's theory.

[26] I note that Dr. Kendall made a point of stressing that her opinion is based primarily on her clinical experience and is not entirely reliant on the four articles discussed in this section. (Tr. 65.) She also acknowledged, however, that absent what she argues is suggested by these

C. Summary regarding Dr. Kendall's causation opinion

In this case, Dr. Kendall candidly acknowledged that there is no direct evidence establishing that immunizations can trigger metabolic decompensation in patients with Leigh Disease. (Tr. 83, 101.) In and of itself, this is not fatal to Petitioner's claim. It is possible to establish a cause-in-fact claim circumstantially, and I give Dr. Kendall credit for forthrightly acknowledging the circumstantial nature of her opinion. Nonetheless, Dr. Kendall's testimony in favor of a circumstantial theory was flawed in several regards.

Overall, for all the reasons discussed above, Dr. Kendall failed to persuade me that key pieces of evidence she presented regarding her contentions actually supported her position. As explained above, though she set out to establish that A.I.'s vaccination contributed to A.I.'s decline by showing that FluMist is contraindicated for patients with Leigh Disease, that A.I.'s prior clinical history is significant in that she tolerated previous illnesses well, and that the timing of A.I.'s metabolic decompensation pointed to vaccine causation, she failed to show that any of these contentions are, "more likely than not," correct.

Furthermore, Dr. Kendall contended that the Poling and Shoffner studies supported her opinion that vaccines are in themselves metabolic stressors capable of causing a metabolic decompensation, when in fact those studies do not establish that proposition. She also asserted that the Tran, Zamarin, and Schwarz articles presented a plausible mechanism explaining A.I.'s neurological deterioration, despite acknowledging that she did not know whether the impact of an attenuated strain such as found in the FluMist vaccine would be the same as the wild flu virus studied in those papers.

Thus, on the whole, I found that Dr. Kendall's testimony was *far* less persuasive than that of Dr. McCandless. (*See, e.g.*, *Cedillo v. HHS*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (holding that special masters may properly conclude under a *Daubert* analysis that "there is simply too great an analytical gap between the data and the opinion proffered."); *Caves v. HHS*, 100 Fed. Cl. 119, 134 (2011), *aff'd*, 463 Fed.Appx. 932 (2012)(quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136 (1997) for the proposition that "*Daubert* does not require a trial court 'to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert.'"); *see also Hennessey v. HHS*, 2009 WL 1709053, at * 42 (Fed. Cl. Spec. Mstr. May 29, 2009) ("When experts disagree, many factors influence a fact-finder to accept some testimony and reject other contrary testimony. Objective factors, including the qualifications, training, and experience of the expert witnesses and the extent to which their proffered opinions are supported by reliable medical research, other testimony, and the factual basis for their opinions, are all significant in determining what testimony to credit and what to reject.").)

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articles, she does not otherwise know the mechanism at work in A.I.'s case, and that these articles were deliberately presented as a plausible explanation for A.I.'s condition. (Tr. 66.)

VIII

PETITIONER'S CASE FAILS THE *LOVING /ALTHEN* TEST

In this part of my Decision, I will explain how this case fits specifically within the interpretive standards set forth in the *Althen* and *Loving* decisions. The short answer is that I find that Petitioner's case clearly does *not* satisfy the standards presented in either *Althen* or *Loving*.

In this regard, as previously noted, Petitioner has argued that A.I.'s FluMist vaccination *significantly aggravated* a preexisting mitochondrial disorder, known as Leigh Disease. Accordingly, I will analyze Petitioner's case under the six-part *Loving/Althen* test for "significant aggravation" claims.

A. Analysis of a "significant aggravation" issue is guided by the ruling in Loving.

The Vaccine Act states that "[t]the term 'significant aggravation' means any change for the worse in a preexisting condition which results in markedly greater disability, pain or illness accompanied by substantial deterioration of health." §300aa-33(4).

The elements of an off-Table significant aggravation case were set forth in *Loving v. HHS*, 86 Fed. Cl. 135, 144 (2009). The United States Court of Appeals for the Federal Circuit acknowledged that "the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims," in *W.C. v. HHS*, 704 F.3d 1352, 1357 (Fed. Cir. 2013). Thus, the Federal Circuit Court of Appeals, which sets binding precedent for decisions by the Office of Special Masters, endorsed the use of a six-part test for significant aggravation, which was first elaborated in *Loving*. A petitioner must prove by preponderant evidence that a vaccination caused significant aggravation by showing:

> (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

W.C., 704 F.3d at 1357.

B. Analysis of this case, under the six-part Loving/Althen test

In this Section, I will discuss whether Petitioner has satisfied the six-part *Loving* test to establish the existence of vaccine-related *significant aggravation* of a preexisting condition.

1. What was A.I.'s condition prior to the administration of the vaccination in question?

During her childhood, A.I. had experienced developmental delay. (Ex. 1, pp. 94, 98, 102.) On January 11, 2008, when she received her FluMist vaccination, she had an upper

respiratory infection. (*Id*., pp. 39-40.) She also was already afflicted, since birth, with a mitochondrial disorder known as Leigh Disease. However, on January 11, beyond the upper respiratory illness, she did not seem especially ill.

2. What was A.I.'s condition soon after the vaccination in question?

Tragically, in the three months after January 11, 2008, A.I.'s condition worsened terribly, and eventually she died, as set forth on pp. 7-9 above. Her decompensation and death were related to her Leigh Disease.

3. A.I.'s condition and death in the three months post-vaccination legally constitutes a "significant aggravation" of her prior condition.

In part 3 of the *Loving/Althen* formulation set forth in *W.C.* and quoted above, one question posed is whether the vaccinee's condition soon after the vaccination in question constitutes a "significant aggravation" of the vaccinee's condition prior to vaccination. *W.C.*, 704 F.3d at 1357. (I understand "significant aggravation," in this context, to simply mean a "significant worsening," without any implication as to the *cause* of the worsening.) As to that question, my conclusion is that A.I.'s condition in the three months post-vaccination obviously was "significantly worse" than her condition appeared immediately prior to the vaccination in question. Therefore, following the standard set forth in *Loving* and *W.C.*, A.I.'s condition during those three months and her death *do* amount to a "significant aggravation" of her Leigh Disease (though the worsening has definitely *not* been shown to have been related to her *vaccination*).

4. Petitioner has failed to establish Prong 4 of Loving/Prong 1 of Althen.

As discussed above, Prongs 4, 5, and 6 of the *Loving* test are, in effect, the same as Prongs 1, 2, and 3 of the *Althen* standard. Under Prong 4 of *Loving* and Prong 1 of *Althen*, a petitioner must provide a medical theory demonstrating that the *type* of vaccine in question can cause a significant worsening of the *type* of preexisting condition of the vaccinee. In this case, however, for the reasons stated at length above, the Petitioner has *failed* to show that the vaccination in question *can* aggravate the type of mitochondrial disorder from which A.I. suffered.

a. Relationship between Althen Prongs 1 and 2 (Loving Prongs 4 and 5)

One interpretive issue with the *Althen* test concerns the relationship between the first two elements of that test. The first two prongs of the *Althen* test, as noted above, are that the petitioners must provide "(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." Initially, it is not absolutely clear how the two prongs differ from each other. That is, on their face, each of the two prongs seems to require a demonstration of a causal connection between "the vaccination" and "the injury." However, a number of Program opinions have concluded that these first two elements reflect the analytical distinction that has been described as the "can cause" vs. "did cause" distinction. That is, in many Program opinions issued prior to *Althen* involving "causation-in-fact" issues, special masters or judges stated that a petitioner must demonstrate (1) that the *type* of vaccination in question *can* cause the *type* of injury in question, and also (2) that the *particular* vaccination received by the specific vaccinee *did* cause

the vaccinee's *own* injury. *See, e.g., Kuperus v. HHS*, 2003 WL 22912885, at *8 (Fed. Cl. Spec. Mstr. Oct. 23, 2003); *Helms v. HHS*, 2002 WL 31441212, at *18 n. 42 (Fed. Cl. Spec. Mstr. Aug. 8, 2002). Thus, a number of judges and special masters of this court have concluded that Prong 1 of *Althen* is the "can cause" requirement, and Prong 2 of *Althen* is the "did cause" requirement. *See, e.g., Doe 11 v. HHS*, 83 Fed. Cl. 157, 172-73 (2008); *Nussman v. HHS*, 83 Fed. Cl. 111, 117 (2008); *Banks v. HHS*, 2007 WL 2296047, at *24 (Fed. Cl. Spec. Mstr. July 20, 2007); *Zeller v. HHS*, 2008 WL 3845155, at *25 (Fed. Cl. Spec. Mstr. July 30, 2008). And, most importantly, the *Federal Circuit* confirmed that interpretation in *Pafford*, ruling explicitly that the "can it?/did it?" test, used by the special master in that case, was equivalent to the first two prongs of the *Althen* test. *Pafford v. HHS*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006). Thus, interpreting the first two prongs of *Althen* as specified in *Pafford*, under Prong 1 of *Althen* a petitioner must demonstrate that the *type* of vaccination in question can cause the *type* of condition in question; and under Prong 2 of *Althen* that petitioner must then demonstrate that the particular vaccination *did* cause the *particular* condition of the vaccinee in question.

Moreover, there can be no doubt whatsoever that the *Althen* test ultimately requires that, as an overall matter, a petitioner must demonstrate that it is "more probable than not" that the particular vaccine was a substantial contributing factor in causing the particular injury in question. That is clear from the statute itself, which states that the elements of a petitioner's case must be established by a "preponderance of the evidence." § 300aa-13(a)(1)(A). And, whatever is the precise meaning of Prongs 1 and 2 of *Althen*, in this case the overall evidence falls far short of demonstrating that it is "more probable than not" that the vaccine that A.I. received contributed to the causation of her tragic death.

b. Petitioner has failed to establish Prong 1 of Althen (Loving Prong 4) in this case.

As explained above, under Prong 1 of *Althen* a petitioner must provide a medical theory demonstrating that the *type* of vaccine in question can cause the *type* of condition in question. Petitioner's theory in this case is that metabolic demand placed on A.I.'s system by her FluMist vaccination, coupled with her upper respiratory infection, caused a metabolic decompensation that ultimately, through a cascade of neurologic cell death, resulted in her death. For all of the reasons described above, however, Petitioner has failed to make this showing. That is, Petitioner's reliance on certain postmarketing evidence was shown to be ineffectual. (Section VII(A)(3) above.) Petitioner's reliance on the Poling and Shoffner articles, among other articles, and on the *Paluck* opinion, was also shown to be without merit. (Section VII(B)(1) above.) Petitioner additionally sought to establish that the flu virus is capable of causing cell death, but failed to demonstrate that the type of *attenuated* viral strain contained in the FluMist vaccine at issue would have the same effect on the body as an infection from a *wild* flu virus. (Section VII(B)(2) above.) Thus, Petitioner was unable to explain persuasively how the FluMist vaccine might have caused or contributed to the type of decompensation that A.I. sustained. Petitioner has therefore failed to meet her burden under the first *Althen* prong.[27]

[27] In this case, it does not matter whether Petitioner's burden under Prong 1 of *Althen* is merely to show that her "general causation" theory is "plausible," or to show that it is "more probable than not." I find that Petitioner did not establish *Althen* Prong 1/*Loving* Prong 4 under *either* standard of proof, for all the reasons set forth above.

5. Petitioner has failed to establish Prong 2 of Althen (Loving Prong 5) in this case.

Under Prong 2, the Petitioner needs to show that it is "more probable than not" that A.I.'s FluMist vaccine *did* cause A.I.'s *own* death. But this she has failed to do. Again, for all the reasons discussed above, Petitioner has failed to demonstrate that A.I.'s vaccine created additional metabolic demand, or that it created any after-effect that in turn created such demand. Moreover, Petitioner admitted that even if a vaccine could create metabolic demand, such metabolic demand cannot be measured in a clinical setting. And in any event, for that same reason, Petitioner's expert conceded that she was unable to opine that the upper respiratory infection, which A.I. was experiencing at the time of her vaccination, was not itself capable of causing A.I.'s injury regardless of the vaccination. In that regard, it was also significant that the only medical literature cited by either expert that addressed the *timing* of such deterioration (Edmonds, *et al*.) better supported Respondent's theory of the case than Petitioner's. For all of these reasons, I find that Petitioner has failed to establish that it is more likely than not that A.I.'s FluMist vaccine did aggravate A.I.'s own Leigh Disease. Thus, Petitioner has also failed to meet her burden under the second *Althen* prong.

6. Petitioner has failed to establish Prong 3 of Althen (Loving Prong 6) in this case.

Since I have explained why Petitioner has failed to satisfy both the first and the second prongs of *Althen*, I need not discuss why Petitioner's case also fails to satisfy the third prong. However, I will note that, as described in Section VII(A)(1) above, I found that the timing of A.I.'s first symptom of neurodegeneration (*i.e*., the staring spells), as alleged by Petitioner herself, made the vaccination an unlikely explanation for A.I.'s metabolic decompensation. That is, the evidence did not make it appear likely that the vaccine could have caused that symptom in less than a single day. Therefore, Petitioner failed to establish a proximate temporal relationship between the vaccination and A.I.'s metabolic decompensation, and thus failed to satisfy the third *Althen* prong.

7. Summary: Petitioner has failed the Loving/Althen test.

To obtain a Program award under the *Loving/W.C.* test, a petitioner must succeed in demonstrating *all four* of Prongs 3, 4, 5, and 6 of *Loving*. However, in this case, as explained above, Petitioner has succeeded on Prong 3, but failed to demonstrate Prongs 4, 5, and 6. Therefore, Petitioner has *failed* to demonstrate entitlement to an award in this case.

C. This is not a close case.

As noted above, in *Althen* the Federal Circuit indicated that the Vaccine Act involves a "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." 418 F.3d at 1280. Accordingly, I note here that this case ultimately is *not* a close case. For all the reasons set forth above, I found that Dr. Kendall's theory was not at all persuasive, while Respondent's expert was far more persuasive.[28]

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[28] Petitioner argued in one of her briefs (ECF 114, pp. 86-90), that Respondent failed to carry "Respondent's burden" of demonstrating that A.I.'s decompensation and death were caused by "factors unrelated to the administration of the vaccine." *See* § 300aa-13(a)(1)(B). Petitioner is mistaken. Petitioner never carried *her burden* of demonstrating that the vaccination

IX

CONCLUSION

The record of this case demonstrates plainly that Petitioner and her family have been through a tragic ordeal. Petitioner has my deepest sympathy on account of the tragic loss of her daughter.

However, I must decide this case not on sentiment, but by analyzing the evidence. Congress designed the Program to compensate only the families of those individuals whose injuries or deaths can be linked causally, either by a Table Injury presumption or by a preponderance of "causation-in-fact" evidence, to a listed vaccine. In this case, the evidence advanced by the Petitioner has fallen far short of demonstrating such a link. Accordingly, I conclude that the Petitioner in this case is *not* entitled to a Program award as a result of A.I.'s death.[29]

/s/ George L. Hastings, Jr.

George L. Hastings, Jr.
Special Master

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aggravated A.I.'s Leigh Disease, or harmed her in any way. Therefore, no burden relating to a "factor unrelated" ever passed to Respondent in the first place.

In any event, as explained above, I conclude that Dr. McCandless *did* show it to be "more probable than not" that A.I.'s tragic decompensation and death likely were caused by a combination of (1) her *inborn Leigh Disease* and (2) the *infectious illness* that afflicted A.I. just prior to the vaccination in question.

[29] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.