In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 03-0632V
Originally filed September 28, 2015
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For Publication

R.K., on behalf of A.K., a Minor,	*	Autism; Entitlement;
	*	Mitochondrial
Petitioners,	*	Disorder;
	*	Influenza Vaccine;
	*	Diagnosis; ASD
SECRETARY OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES,	*	
	*	
Respondent.	*	

John F. McHugh, New York, N.Y. for petitioners.
Heather L. Pearlman, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

Vowell, Special Master:

On March 26, 2003, petitioners [*] filed a Short-Form "Petition for Vaccine Compensation"[2] for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §300aa-10, *et*

[1] [* This ruling was originally issued on September 28, 2015. In this public Ruling, the family name of the petitioners has been redacted, pursuant to their request.]

[2] By electing to file a Short-Form Autism Petition for Vaccine Compensation, petitioners alleged that:

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

Autism General Order #1, filed July 3, 2002, Exhibit A, Master Autism Petition for Vaccine Compensation at 2.

seq[3] ["Vaccine Act" or "Program"] on behalf of their son ["A.K."], thereby joining the Omnibus Autism Program ["OAP"]. An amended petition was filed on February 28, 2011, and a second amended petition [hereinafter "2d Am. Pet"], which now constitutes the operative petition for petitioners' vaccine injury claim on behalf of A.K., was filed on April 17, 2013, just days prior to the causation hearing.

In their second amended petition,[4] petitioners claimed that A.K.'s two influenza vaccinations "either resulted in an encephalopathy or significantly aggravated an existing condition related to prior vaccinations or otherwise." Petition at 1 (ECF No. 237). In ¶¶ 74-76, petitioners specified that the "existing condition" is a mitochondrial disorder.

Petitioners here, like the petitioners in the vast majority of the autism spectrum disorder ["ASD"] cases on my docket since 2007, have a firm, fixed belief that vaccinations have caused or significantly aggravated their child's neurodevelopmental disorder. Since the OAP test case decisions were issued (and affirmed on appeal),[5] most of the petitioners who elected to proceed on new theories (or old theories readdressed) have eschewed the autism diagnoses that appear in their children's medical records, asserting that their children have various other conditions which resulted in behavioral symptoms that led to or looked like ASD, using terms like "encephalopathy" or "encephalitis" as euphemisms for ASD. They have also asserted that their children have metabolic or mitochondrial disorders that either look like an ASD or to explain that, notwithstanding the test case decisions, their children were vulnerable

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[3] The National Vaccine Injury Compensation Program ["Vaccine Program"] is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. § 300aa-10 et seq. (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

[4] Hereinafter, unless the context clearly indicates otherwise, any references to "petition" are to this Second Amended Petition.

[5] Decisions in each of the three test cases pertaining to the first theory of causation ["Theory 1"] presented by the Petitioners' Steering Committee ["PSC"] rejected the petitioners' causation theories. *Cedillo v. Sec'y, HHS*, No. 98-916V, 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009) ***aff'd***, 89 Fed. Cl. 158 (2009), ***aff'd***, 617 F.3d 1328 (Fed. Cir. 2010); *Hazlehurst v. Sec'y, HHS*, No. 03-654V, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), ***aff'd*** 88 Fed. Cl. 473 (2009), ***aff'd***, 604 F.3d 1343 (Fed. Cir. 2010); *Snyder v. Sec'y, HHS*, No. 01-162V, 2009 WL 332044 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), ***aff'd***, 88 Fed. Cl. 706 (2009). Decisions in each of the three "test cases" pertaining to the PSC's second theory ["Theory 2"] also rejected the petitioners' causation theories, and the petitioners in each of those three cases chose not to appeal. *Dwyer v. Sec'y, HHS*, No. 03-1202V, 2010 WL 892250 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); *King v. Sec'y, HHS*, No. 03-584V, 2010 WL 892296 (Fed. Cl. Spec. Mstr. Mar 12, 2010); *Mead v. Sec'y, HHS*, No. 03-215V, 2010 WL 892248 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). These "test case" decisions were deliberately written comprehensively, in anticipation that the evidence set forth therein would be available to resolve the thousands of cases remaining in the OAP. They thus analyzed in detail all of the evidence presented on both sides. The three test case decisions in Theory 1 totaled more than 600 pages of detailed analysis, and were solidly affirmed in many more pages of analysis in three different rulings by three different judges of the United States Court of Federal Claims, and in two rulings by two separate panels of the United States Court of Appeals for the Federal Circuit. The three decisions concerning Theory 2 were similarly comprehensive; no motions for review were filed. Thus, 11 lengthy written rulings by the special masters, the judges of the U.S. Court of Federal Claims, and the panels of the U.S. Court of Appeals for the Federal Circuit unanimously rejected the petitioners' claims.

to the side effects of a vaccine by virtue of these underlying genetic conditions. Thus, they have claimed that various vaccines significantly aggravated these underlying conditions, resulting in an ASD diagnosis.

For nearly nine years, several of my colleagues and I have had the unenviable task of hearing these heart-wrenching cases.[6] If sympathy alone could provide a basis for judgment in their favor, they would have that judgment. This case is rendered even more difficult because of the severity of A.K.'s condition and because petitioner [R.K. * * * *] is a well-respected attorney who appears frequently in Vaccine Act cases, including many similar to A.K.'s.

Nevertheless, I am charged with deciding this causation in fact case based on the requirements of the Vaccine Act and the binding precedents of the Federal Circuit interpreting the Act's provisions. The Act requires preponderant evidence that a vaccine actually caused or significantly contributed to A.K.'s condition before compensation may be awarded. Petitioners failed to produce preponderant evidence that the two influenza vaccinations they now claim were responsible[7] can or did cause or significantly aggravate A.K.'s condition. Their petition is therefore dismissed.

I. Abbreviated Procedural History.

This case has had a long and complicated procedural history. Indeed, petitioners initially advanced this case as a test case for the OAP with regard to the second causation theory – *i.e*., that thimerosal-containing vaccines cause autism. Ultimately, petitioners withdrew as an OAP test case and filed an amended petition which changed

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[6] A small minority of the autism petitioners have elected to continue to pursue their cases, seeking other causation theories and/or other expert witnesses. All of the causation in fact and significant aggravation decisions issued to date have rejected petitioners' claims that vaccines played a role in causing their child's autism. *See*, *e.g.*, *Holt v. Sec'y HHS*, No. 05-136V, 2015 WL 4381588 (Fed. Cl. Spec. Mstr. June 24, 2015) (mitochondrial disorder), *Miller v. Sec'y HHS*, No. 02-235V, 2015 WL 5456093 (Fed. Cl. Spec. Mstr. Aug. 18, 2015) (encephalopathy and mitochondrial disorder), *Nuttall v. Sec'y, HHS*, No. 07-810V, 2015 WL 4934583 (July 31, 2015), *Brook v. Sec'y, HHS*, No. 04-405V, 2015 WL 3799646 (Fed. Cl. Spec. Mstr. May 14, 2015) (autoimmune encephalopathy), *Blake v. Sec'y, HHS*, No. 03-31V, 2014 WL 2769979 (Fed. Cl. Spec. Mstr. May 21, 2014) (autism not caused by MMR vaccination); *Henderson v. Sec'y, HHS*, No. 09-616V, 2012 WL 5194060 (Fed. Cl. Spec. Mstr. Sept. 28, 2012) (autism not caused by pneumococcal vaccination); *Franklin v. Sec'y, HHS*, No. 99- 855V, 2013 WL 3755954 (Fed. Cl. Spec. Mstr. May 16, 2013) (MMR and other vaccines found not to contribute to autism); *Coombs v. Sec'y, HHS*, No. 08-818V, 2014 WL 1677584 (Fed. Cl. Spec. Mstr. Apr. 8, 2014) (autism not caused by MMR or varicella vaccines). In addition, some causation autism claims have been rejected without trial, at times over the petitioner's objection, in light of the failure of the petitioner to file plausible proof of vaccine-causation. *See, e.g., Waddell v. Sec'y, HHS*, No. 10-316V, 2012 WL 4829291 (Fed. Cl. Spec. Mstr. Sept. 19, 2012) (autism not caused by MMR vaccination); *Geppert v. Sec'y, HHS*, No. 00-286V, 2012 WL 2500852 (Fed. Cl. Spec. Mstr. Sept. 6, 2012); *Fesanco v. Sec'y, HHS*, No. 02-1770, 2010 WL 4955721 (Fed. Cl. Spec. Mstr. Nov. 9, 2010); *Fresco v. Sec'y, HHS*, No. 06-469V, 2013 WL 364723 (Fed. Cl. Spec. Mstr. Jan. 7, 2013); *Pietrucha v. Sec'y, HHS*, No. 00-269V, 2014 WL 4338058 (Fed. Cl. Spec. Mstr. Aug. 22, 2014). Judges of this court have affirmed the practice of dismissal without trial in such a case. *E.g.*, *Fesanco v. Sec'y, HHS*, 2011 WL 1891701 (May 16, 2011) (Judge Braden). No judge or special master has found, post the test case decisions, that any vaccine can contribute to or cause autism.

[7] When this claim was filed, the influenza vaccines they now claim were causal were not on the Vaccine Injury Table, and thus no claim of injury caused by them could be brought. *See* 42 C.F.R. § 100.3(c)(6) ("Trivalent influenza vaccines (Item XIV of the Table) are included on the Table as of July 1, 2005").

their theory to allege that two doses of A.K.'s influenza vaccination were the cause of his injury.[8]

The history of this case is also noteworthy for a dismissal of the petition in 2011 for failure to prosecute and failure to comply with court orders and a granted motion to reconsider the dismissal; scattershot and untimely filing of medical literature; and a number of motions *in limine* filed on the eve of the entitlement hearing. Thus, due to the unusually protracted procedural history in this case, I have issued a separate ruling addressing the numerous motions and evidentiary issues raised prior to and after hearing. *See* Motions Ruling, filed on Sept. 28, 2015 (ECF No. 319). A more complete procedural history of this case appearing in that ruling is incorporated here by reference. Only those matters necessary to the understanding of events at the hearing and the entitlement determination process will be repeated here. This abbreviated procedural history is provided to place the lengthy delays leading to resolution of this 12-year-old claim in context.

By filing their short-form petition, petitioners opted into the OAP.[9] Cases in the OAP remained "on hold" for an extended period at petitioners' request, while discovery proceeded. In early 2008, A.K.'s case was identified as one of the three test cases to be heard on the second theory of causation in the OAP. This theory was that thimerosal-containing vaccines caused ASD.

While this case was one of the test cases, petitioners filed some expert reports and medical records.[10] They also filed some of A.K.'s medical and school records. *See, e.g.*, filings of Feb. 14, 2008.

On April 10, 2008, approximately a month before the OAP was to begin, petitioners filed a motion requesting to withdraw A.K.'s case as a test case and to withdraw from the OAP.[11] They explained that they intended to pursue another theory of causation not addressed in the OAP, while specifically reserving the right to present evidence on the thimerosal theory along with their new theory. *See* Motion, filed Apr. 10, 2008. Respondent did not object and I granted petitioners' motion. *See* Order, filed

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[8] At the time the original petition was filed in this case, other vaccines were alleged as causal. The influenza vaccine was not added to the Vaccine Injury Table, 42 C.F.R. § 100.3, until 2005.

[9] A detailed explanation of the creation of the OAP and the effects of opting into it can be found in *Dwyer,* 2010 WL 892250, at *3.

[10] These expert reports by Drs. Elizabeth Mumper, Richard Deth, Sander Greenland, and H. Vasken Aposhian were filed in support of the thimerosal causation theory. With the exception of Dr. Mumper's report, they were not tailored to A.K.'s specific case, and presented only general causation evidence. In *Dwyer*, 2010 WL 892250, based on these same reports and subsequent testimony, I rejected the hypothesis that thimerosal-containing vaccines can cause ASDs.

[11] In a status conference on November 3, 2008, petitioners indicated their desire to return the case to the OAP, largely because I was pressing them to obtain and file an expert report on causation and, as the OAP test case decisions were still pending, they would have the benefit of the extended period of delay afforded to the OAP petitioners until the test case decisions were finalized. I directed them to file a written motion so requesting. *See* Order filed November 7, 2008. Petitioners never filed such a motion.

Apr. 15, 2008. By withdrawing from the OAP, petitioners signaled their intent to proceed to a causation hearing on their new theory.[12]

However, soon after the withdrawal, it became apparent that petitioners were not yet prepared to proceed to a hearing. Petitioner [R.K.* * *] was substituted as the attorney of record for his son. Order, filed May 23, 2008. Although [R.K. * * * *] represented that he was actively seeking another attorney to pursue A.K.'s claim (*see* Order, filed Jun. 17, 2008) and that he was pursuing medical testing and opinions on causation, a new attorney, or did not enter an appearance for about 19 months. On January 5, 2010,[13] Mr. John McHugh filed a motion to be substituted in as counsel in this case.

On January 20, 2010, I held a status conference with the parties to discuss the next steps in this case. During this phone call, Mr. McHugh informed me he had not yet met with petitioners or familiarized himself with the case. *See* Order, filed Jan. 20, 2010, at 1. Over the next two months, there was little progress on the case, but in March 2010, Mr. McHugh informed me that he was reviewing A.K.'s medical records, that Dr. Marcel Kinsbourne had been retained as an expert,[14] and suggested that in 90 days, he would be able to participate in a status conference to set a schedule for further proceedings.

On June 8, 2010, I held a status conference with the parties. Reporting that financial constraints were hampering their ability to obtain experts, petitioners indicated they intended to file a request for interim costs. I directed that the interim fee application be filed by July 23, 2010, and that petitioners inform me of their progress in retaining additional experts by August 9, 2010. Order, Jun. 8, 2010. Petitioners did not file an interim fee application.

Instead, they filed an out of time[15] status report on August 13, 2010. In their status report, petitioners informed me that: (1) Dr. Kinsbourne was unable to complete his expert report as he was awaiting further diagnostic tests; (2) Dr. Kinsbourne could not specify when his expert report would be completed; and (3) petitioners were pursuing another unnamed expert as Dr. Kinsbourne might not be testifying in the case.

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[12] It later became apparent that their new theory was based on what they perceived as having happened in another OAP case. That case, *Poling v. Sec'y, HHS*, No. 02–1466V, is discussing in detail in Sections VIII.A.2-3, below, and in the motions ruling in this case. Petitioners here have asserted that the respondent is "judicially estopped" from contesting A.K.'s case based on how the *Poling* case was handled. *See* Motions Ruling, filed on Sept. 28, 2015 (ECF No. 319), at Section II.B.6.

[13] Mr. McHugh filed a defective motion to substitute on December 2, 2009.

[14] Doctor Kinsbourne, a frequent witness for Vaccine Act petitioners, had testified in both the Theory 1 and Theory 2 test cases. *Snyder*, 2009 WL 332044, at *11-12 (referencing Dr. Kinsbourne's participation in *Cedillo*, 2009 WL 331968, at *23 and *Dwyer*, 2010 WL 892250, at *16).

[15] Petitioners' status report was due on August 9, 2010. Petitioners were reminded how to request additional time under Vaccine Rule 19(b) and warned that future out of time filings would be struck from the record. *See* Order, filed Aug. 18, 2010, at 1, n.1.

Status Report, filed Aug. 13, 2010, at 1-2. Petitioners suggested that they file monthly status reports until their expert reports were filed. *Id.* at 2.

I rejected this suggestion and, instead, ordered petitioners: (1) to identify their potential new expert and outline the steps taken to contact him or her; (2) to file a status report informing me when Dr. Kinsbourne had received the medical records he needed and when his report could be filed; and (3) if Dr. Kinsbourne could not file his report within 75 days, to file a letter from Dr. Kinsbourne explaining why and giving a date when his report would be completed. Order, filed Aug. 18, 2010, at 1-2. The deadline set in this order was August 27, 2010.

My August 18 order, I was very clear that some progress in obtaining an expert report had to be demonstrated if the case was to continue, as the records filed to date had failed to suggest vaccine causation of A.K.'s condition. I noted that the geneticist who had been seeing A.K. had specifically recommended that he continue to receive vaccinations and indicated that he was a "good candidate" to receive seasonal vaccinations, such as influenza. Petitioners' Exhibit ["Pet. Ex."] 34, p. 6.[16] At this point, Dr. Kinsbourne had been reviewing A.K.'s case for about five months. The fact that no opinion from Dr. Kinsbourne had yet been filed, coupled with the suggestion that he might not be testifying, signaled to me that he was either unable or unwilling to opine favorably in A.K.'s case.

Petitioners failed to reply to both this order and likewise ignored an Order to Show Cause issued on September 3, 2010. Therefore, I dismissed the petition on October 13, 2010. However, petitioners filed a motion for reconsideration on October 26, 2010[17] which I granted on November 12, 2010.[18]

I subsequently ordered petitioners to file a status report informing me of the date a report from their new expert, Dr. Frye, would be filed and to file an "amended petition clarifying their theory of causation." Order, filed Nov. 15, 2010, at 1. In response, petitioners filed a motion requesting an enlargement of time to file their amended petition and seeking an award of interim costs in the amount of $5,000[19] to be paid as a

[16] In this decision, pin citations to medical records are made using a page number format. *E.g.*, "Pet. Ex. 34, p. 6." Pin citations to other documents, including affidavits, expert reports, medical journal articles, briefs, etc., are made using an "at" format. *E.g.*, "Pet. Ex. 23 at 3." Because medical journal articles are often publically available, citations to journal articles are usually made using the page numbers integral to the published article, rather than the page numbers assigned by counsel. The public has no access to articles filed by a party. *See* § 12(d)(4)(A).

[17] With their motion for reconsideration, petitioners also filed the much-delayed report from Dr. Marcel Kinsbourne, along with other evidence. *See* Pet. Exs. 37-56.

[18] Petitioners also filed motions requesting redaction of the October 13, 2010 decision and November 24, 2010 order granting the motion for reconsideration. *See* Motions, filed Oct. 29 and Nov. 24, 2010. I granted redaction of A.K.'s name and the medical references identified by petitioner but denied redaction of petitioners' names. Order, filed Jan. 10, 2011, at 3, 5.

[19] This amount was based on an hourly rate of $500 and thus constituted payment for ten hours of work. To the best of my knowledge, this decision was the first time any special master had authorized advance payment for an expert.

retainer to Dr. Frye. On January 28, 2011, I granted the motion for additional time to file an amended petition and awarded interim costs in the amount of $5,000.[20]

On February 28, 2011, petitioners informed me that Dr. Frye would not be opining in this case as he was changing institutions and "would no longer be able to provide services as an expert witness." Motion, filed Feb. 28, 2011, at 1.

In March 2011, petitioners identified their new expert, Dr. Yuval Shafrir, and requested an additional sixty days to file his report. Status Report, filed Mar. 9, 2011. I granted petitioners' unopposed request for additional time, ordering them to file Dr. Shafrir's expert report by May 9, 2011. Order, filed Mar. 9, 2011, at 1. Petitioners received one more enlargement of time before filing Dr. Shafrir's expert report on July 7, 2011.[21] *See* Order, filed Jun. 30, 2011.

Between July and December 2011, petitioners filed the report of an additional expert, Dr. Fran Kendall, and respondent filed a supplemental Vaccine Rule 4 report and several expert reports. At a January 13, 2012 status conference, petitioners indicated that they were looking for two additional experts, one in pediatric development and one in oxidative stress. As the report of petitioners' mitochondrial disease specialist had not been filed until December 21, 2011, I provided a new deadline for the report of respondent's mitochondrial disorder specialists. I indicated that, notwithstanding the indications that more expert reports were expected, the parties should confer on hearing dates, with a hearing to begin between November 2012 and February 2013.

The parties having eventually agreed to a hearing for the last two weeks of February 2013, on February 13, 2012, I set this case for a hearing on February 17-27, 2013 in Washington, DC. Additional experts were identified and reports filed between March and July 2012.[22]

On July 31, 2012, notwithstanding that the February 2013 hearing date had been set a year in advance, petitioners informed me that the hearing date would have to be moved. Petitioners explained that their attorney was lead counsel in an unrelated civil case in which the trial judge had "set a firm trial date" which conflicted with the hearing date for this case. Status Report, filed Jul. 31, 2012, at 1.

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[20] On February 7, 2011, respondent filed a motion for reconsideration which I denied. *See* Order, filed Feb. 23, 2011, at 5. However, I withdrew my decision awarding interim costs on February 28, 2011 after petitioners informed me that Dr. Frye was no longer opining in this case. *See* Order, filed Feb. 28, 2011.

[21] Petitioners did not seek interim fees for Dr. Shafrir until shortly before the hearing.

[22] On March 13, 2012, respondent filed expert reports from Bruce Cohen, M.D. and Kendall B. Wallace, Ph.D. Petitioners informed me that A.K.'s pediatrician, Dr. Heddy Zirin, would be testifying in this case but they still were seeking a medical expert in oxidative stress. Status Report, filed Jun. 1, 2012, at 1. On July 31, 2012, petitioners filed a status report, informing me that Richard Deth, Ph.D. would be testifying as an expert in oxidative stress and Mary Megson, M.D. would be testifying as a developmental pediatrician.

On August 1, 2012, I held a status conference to discuss this issue. *See* Order, filed Aug. 1, 2012, at 1. I reminded petitioners that I "deliberately set the hearing a year in advance to give the large number of experts who are expected to testify ample time to make the necessary arrangements in their clinical practices and research schedules to permit their presence at the hearing." *Id.* Furthermore, I "expressed my concern that petitioners' counsel failed to inform the trial judge of our previously set firm hearing date in this case when the jury trial date was being discussed." *Id.* (emphasis in the original). I ordered the parties to file a joint status report, discussing whether the entitlement hearing could be held from February 25, 2013 through March 5, 2013 and if a fact hearing could be scheduled in December 2012 or January 2013. *Id.*

Instead of a joint report, the parties filed separate status reports on August 15, 2012 indicating their preferred schedules. I then set a fact hearing in New York City, N.Y. from December 12-13, 2012 to take testimony from petitioners and fact testimony from two of A.K.'s treating physicians, Drs. Boris and Zirin (fact testimony only). Ultimately, only [A.K.'s parents] testified at the fact hearing. For reasons never clearly articulated, Dr. Zirin never testified; Dr. Boris appeared at the entitlement hearing as both a fact and as an expert witness.

I set the entitlement hearing for April 22-30, 2013. Order, filed Aug. 16, 2012, at 1. I also ordered petitioners to file all expert reports by September 14, 2012 and respondents to file all expert reports by November 13, 2012.[23]

This time the entitlement hearing went off as scheduled, notwithstanding a number of late filings by petitioners, including expert reports, motions, a second amended petition, and medical journal articles. Post-hearing, petitioners sought to file more medical journal articles, and requested and received several extensions for their post-hearing briefs. I declared the evidentiary record closed in 2013 (Order, issued Nov. 15, 2013 (ECF No. 282)), but petitioners filed many more medical journal articles thereafter, some of which I allowed and some of which I ordered to be stricken from the record. *See* Motions Ruling, filed on Sept. 28, 2015 (ECF No. 319), at Section II.C.

Although petitioners had requested the opportunity to present the testimony of either Dr. Megson or another physician with expertise in developmental pediatrics, ultimately they decided to rely on Dr. Megson's report. They withdrew their requests to file another expert report and conduct another session of the entitlement hearing. Motion *in Limine*, filed Apr. 8, 2013 (ECF No. 227). With the filing of the last post-hearing briefs on June 16, 2014, this case became ripe for resolution.[24]

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[23] Once again, the deadlines had to be extended. Petitioners filed expert reports from Drs. Megson and Boris on September 26, 2012 and from Dr. Deth on October 29, 2012. Since I had extended petitioners' deadlines at their request, I also adjusted respondent's deadline, ordering her to file all expert reports by December 13, 2012. *See* Order, filed Sept. 26, 2012.

[24] After this date, petitioners and respondent filed additional documents addressing various motions, which are discussed in greater detail in the in the motions ruling. *See* Motions Ruling, filed on Sept. 28, 2015 (ECF No. 319), at Section II.C.1.

The subsequent sections begin with a brief summary of the reasons for the decision in this case (Section II) followed by a summary of A.K.'s medical history (Section III). More detailed information about A.K.'s medical history is provided in the later sections dealing with A.K.'s diagnoses and the analyses of the various theories presented by petitioners' experts (Sections VI-IX).

II. Summary of Decision.

Although petitioners present multiple theories, this crux of all of them is whether A.K.'s two influenza vaccinations in November and December of 2001 significantly aggravated A.K.'s alleged underlying mitochondrial disorder, thereby causing-in-fact ASD or an encephalopathy presenting as ASD.

Because petitioners are not raising a "Table" injury claim, they must show by preponderant evidence a medical theory causally connecting the vaccinations to the injury, a logical sequence of cause and effect showing that the vaccination was the reason for the injury, and a showing of a proximate temporal relationship between the vaccinations and the injury.

After considering the record as a whole, I hold that petitioners have failed to establish by preponderant evidence that A.K.'s condition was caused or significantly aggravated by a vaccine or any component thereof. The evidence presented was both voluminous and extraordinarily complex. After careful consideration of all of the evidence, it was abundantly clear that petitioners' theories of causation were speculative and unpersuasive. Respondent's experts were far more qualified, better supported by the weight of scientific research and authority, and simply more persuasive on nearly every point in contention.

Petitioners have failed to show that A.K. had an underlying mitochondrial disorder. They have also failed to show that the onset of A.K.'s ASD was in any way related to his influenza vaccinations. Indeed, respondent persuasively presented significant evidence indicating that A.K.'s ASD onset predated his vaccinations. Nor did petitioners establish by preponderant evidence that A.K. experienced any regression of skills related to his ASD or his vaccinations. Thus, petitioners have failed to establish as a factual matter that either of A.K.'s two influenza vaccines of November and December 2001 either caused or aggravated his ASD or any other neurological condition. Moreover, even if I accepted petitioners' interpretation of the factual record, petitioners failed via their multiple theories to even establish that an influenza vaccine could have caused the type of injury they have alleged.

Therefore, I deny their petition for compensation.

III. Summary of A.K.'s Medical History.

Most of A.K.'s medical history is not in dispute. The portions that are in dispute primarily concern whether certain behaviors displayed on videos, and sometimes mentioned in medical records or other evidence, constituted early symptoms of ASD, when symptoms of developmental delay or ASD arose, the symptoms he displayed prior to and after the allegedly causal vaccinations, and whether some of the diagnoses

appearing in his records are correct. These contested issues are addressed in some detail in Sections VI – IX below. Thus, only an abbreviated medical history is provided below.

A.K. was born in early November 1999, after an uneventful pregnancy. *See generally*, Pet. Exs. 15, 19. He was a large baby, weighing about 10 ½ pounds, and because of his size, he was delivered early by caesarian section. Pet. Ex. 19, pp. 7-8. His Apgar scores were 9 and 9, reflective of a healthy newborn.[25] *Id*. A slight heart problem was noted before he was discharged from the hospital, but a pediatric cardiology consultation found no pulmonary stenosis.[26] Pet. Exs. 61, p. 178.

In his first 18 months of life, A.K. received the usual childhood vaccinations, without apparent ill effects.[27] These vaccinations are reflected on a handwritten summary sheet appearing in the records of Woodbury Pediatrics Associates ["Woodbury Pediatrics"], where A.K. received most of his primary care from his

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[25] The Apgar score is a numerical assessment of a newborn's condition (with lower numbers indicating problems), usually taken at one minute and five minutes after birth. The score is derived from the infant's heart rate, respiration, muscle tone, reflex irritability, and color, with from zero to two points awarded in each of the five categories. *See* DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (32d ed. 2012) ["DORLAND'S"] at 1682 (all citations to DORLAND'S will be to the 32d ed., unless otherwise noted).

[26] Subsequent evaluations in 2000 and 2001 also found that the murmur was essentially benign. *See* Pet. Ex. 61, pp. 176-77.

[27] A.K. received his initial hepatitis B vaccination on November 15, 1999, with subsequent doses on December 30, 1999 and May 2, 2000. Pet. Ex. 61, p. 4. This series of vaccinations was completed. His other vaccinations appear to have been spaced out to avoid receipt of more than two vaccinations at any one time. He received his first diphtheria, tetanus and acellular pertussis ["DTaP"] on December 20, 1999 when he was about six weeks old and his first Haemophilus influenza type B ["Hib"] and inactivated polio ["IPV"] vaccinations on January 27, 2000, when he was about two and one half months old. Pet. Ex. 61, p. 4. A.K. received a second DTaP on February 29, 2000, at not quite four months of age, and his second Hib and IPV vaccines on March 30, 2000 at not quite five months of age. The year of this Hib vaccination is incorrectly reflected on the summary sheet (Pet. Ex. 61, p. 4) as 2001, but it appears on another summary sheet and the vaccine administration record as 2000. *See id.*, p. 106; Pet. Ex. 16, p. 131. A.K. received his third DTaP vaccine on May 2, 2000 and his third Hib vaccination on June 6, 2000, when he was six and seven months of age, respectively. Pet. Ex. 61, p. 4. He did not begin receiving Prevnar vaccinations until September 20, 2000, when he was over 10 months of age, but this was likely because Prevnar was not licensed until February 2000. *Id.*; *see also* the vaccine administration schedule for 2001, cited below. The measles, mumps, and rubella ["MMR'] vaccines are ordinarily administered in a combined MMR vaccination, but A.K. received his in three separate vaccinations administered on December 1, 2000 (mumps); December 19, 2000 (measles), and January 2, 2001 (rubella), when he was between 13-14 months of age. *Id.* A.K. received his final Hib vaccination (the last in the four-shot series) and his second Prevnar vaccination on February 17, 2001and his last DTaP vaccination (short of completing the vaccine series) on May 9, 2001, along with his third Prevnar vaccination. *Id.* He received his last IPV vaccination on May 24, 2001, when he also received his only varicella vaccination. *Id.* At the time of these last vaccinations, A.K. was 18 months of age. The childhood vaccination schedule recommended by the Centers for Disease Control and Prevention ["CDC"] may be found at the following: http://www.cdc.gov/vaccines/schedules/past.html (listing recommended childhood vaccinations and time frames for administration for the years in question) (last visited Sept.14, 2015). The vaccination schedule in place in 2000 and 2001 indicates that a fourth dose of DTaP should have been administered between 15-18 months of age; as well as a fourth dose of Prevnar about six months after the last dose.

pediatrician, Dr. Marvin Boris.[28] *See* Pet. Ex. 61, p. 4 (summary sheet); *see also id*., p. 106 (American Academy of Pediatrics standard vaccine administration record). The dates of administration on the summary sheet are clearer and more complete than those on the vaccine administration record; therefore, most citations will be to the summary sheet.

Most vaccinations were also reflected in the pediatric visit notes (*see e.g.,* Pet. Ex. 61, pp. 93, 98, 99, 100, 101, 105), but not the two influenza vaccinations,[29] administered on November 2, 2001 and December 3, 2001, that petitioners claim are causal. These two influenza vaccinations are not reflected on the vaccine administration record (Pet. Ex. 61, p. 106) or in any office visit notes from Woodbury Pediatrics. A record of the second influenza vaccination was located in [A.K.'s mother's] medical records some time prior to the December 12, 2012 fact hearing and was filed on that date as Pet. Ex. 118.[30]

Notwithstanding the somewhat unusual pattern of vaccine administration reflected in n.27, *supra*, A.K. had routine well-child visits. *See, e.g*., Pet. Ex. 61, pp. 96 (six month well child visit), 98 (four month well-child visit), 100 (well-child visit at two and one half months of age) 101 (two month well child visit at seven weeks of age). At his twelve month well-child visit, he was in the 95th percentile for height and weight. Furthermore, he was noted to play "pat-a-cake," wave bye-bye, bang two blocks together, imitate vocalizations, say "Mama" and Dada," understand "no," cruise and stand alone for 2-3 seconds. *Id.* at 78.

A.K. was also seen and treated for various childhood illnesses, including conjunctivitis (Pet. Ex. 61, pp. 103), an upper respiratory infection ["URI"] (p. 98), congestion (p. 94), cough, congestion, and possible allergies (pp. 90-91), loose bowel movements (p.89), rash (p. 85), presumed viral infection (p. 82) and possible otitis media (p. 80), during his first year of life. When he received the rubella vaccination on January 2, 2001, the medical record from that date included a complaint that he had just experienced "5 miserable days" and an impression of "rhinitis, teething." Pet. Ex. 61, p. 75. Later in January 2001, A.K. vomited, had loose stools, was running a high fever,

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[28] Woodbury Pediatrics records were originally filed as Pet. Ex. 2. The copy of the immunization summary sheet in those records is blotchy and difficult to read. An updated (and clearer) copy of the Woodbury Pediatrics records was subsequently filed as Pet. Ex. 61, p. 4 in the updated version of the Woodbury records.

[29] These were the next two vaccinations chronologically on the summary sheet after the varicella vaccination. They are the only two on the summary sheet (Pet. Ex. 61, p. 4) for which there are no pediatric records ordering administration. Neither appears on the vaccine administration record (*id*., p. 106). The summary sheet lists November 2, 2001 for the first vaccination, but only the month and year ("12/01") for the second. *Id.*, p. 4.

[30] Doctor Boris, who served as one of A.K.'s pediatricians during A.K.'s first year, left Woodbury Pediatrics in January 2001 to start his own practice treating "adults and children with allergies or immunological conditions and children with developmental problems." Pet. Ex. 47 at 2. Doctor Boris also served as [A.K.'s mothers'] pediatrician since the age of three years old and he is married to her father's cousin. Tr. at 16.

had a runny nose, was holding his ears, and was constipated with a decreased appetite. *Id.* at 74.[31]

His medical records also reflect several telephone calls by his parents to the pediatric practice and returned calls by the practice to his parents. *See, e.g*., Pet. Ex. 61, pp. 87 (loose stools, diarrhea, and diet), 95 (teething advice and diet), 97 (eye discharge and teething). Although his parents reported low grade fevers after his vaccinations, no record of such fevers appears in A.K.'s medical records. Pet. Exs. 45 at 20; 46 at 3; Tr. 61-62. There was a report on May 11, 2001 that A.K. had redness at the injection site for his Prevnar and DTaP vaccinations, which he had received two days earlier. Pet. Ex. 61, p. 64. On June 4, 2001, after having received his only varicella and third polio vaccinations on May 24, 2001, he was he was diagnosed with pharyngitis (inflammation of the throat). Pet. Ex. 61, p. 63. Under the section titled physical exam, it was noted that A.K. was febrile at the time of the examination but his exact temperature was not recorded.[32] *Id.*

There are several telephone calls pertaining to fevers, but none in close proximity to his many vaccinations. *See, e.g*., Pet. Ex. 61, pp. 72 (fever and reported partial recovery around February 2001), 81 (two phone calls regarding fever in late October 2000, with the closest prior vaccination administered on September 20, 2000) (*id*., p. 4).

A.K.'s growth and development during his second and third year of life (from 12-36 months of age) are in dispute and are thus addressed elsewhere in this decision. He continued to have childhood illnesses during this period. They included a URI and some sleep problems, loose stools, and teething in July 2001. Pet. Ex. 61, p. 59. Both A.K. and his mother contacted a stomach virus in early September 2001. *Id.*, p. 58. On October 5, 2001, A.K. was diagnosed with a protracted URI after suffering from a cold for ten days. *Id.*, p. 57. He was prescribed amoxicillin and noted to be much better by October 9, 2001. *Id.*

As indicated above, the vaccine summary sheet reflected that A. K. received a vaccination for influenza on November 1, 2001. *See* Pet. Ex. 61, p. 4. However, there is no record of a visit on that date in the medical records from Woodbury Pediatrics.[33]

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[31] A.K was also seen by Dr. Heddy Zirin at Woodbury Pediatrics. Tr. at 16. Doctor Zirin had been [A.K.'s mother's] pediatrician since she was a teenager. *Id.*

[32] I note that the medical records from Woodbury Pediatrics did not contain entries giving actual temperatures or respiratory rates. These records often are unsigned or signed with a J or P, neither of which is indicative of A.K.'s pediatrician at that time, Dr. Boris.

[33] On February 24, 2011, petitioners filed additional medical records from Woodbury Pediatrics. These records covered the period from November 6, 2002 until August 29, 2007 and included an updated record of vaccinations. *See* Pet. Ex. 61. However, there is no notation of an office visit or this influenza vaccination administered on November 2, 2001 in the earlier medical records from Woodbury Pediatrics. Petitioners explained that A.K. received his second dose of the influenza vaccine from Dr. Boris at his new practice due to Woodbury Pediatrics' shortage of vaccine. *See infra* n.34. However, they indicated he received his first influenza vaccination on November at Woodbury Pediatrics. *See, e.g*., Pet. Ex. 46 at 3 (Declaration of [A.K.'s mother]).

See Pet. Exs. 2; 61. There are notes, perhaps reflecting telephone calls, on Oct 23, 2001 (reflecting that A.K. had a copiously runny nose) and on November 16, 2001 (reflecting nasal congestion and ear rubbing). According to Pet. Ex. 118, Dr. Boris administered influenza vaccinations to petitioners and both of their children on what appears to be "12/3/01." The date on the form was written over, and may have initially read "12/1/01," which was a Saturday. [34]

A.K.'s influenza vaccinations, and the events surrounding them, are discussed in greater detail in Sections VII.C.2-3, below. Petitioners claim that after A.K.'s second influenza vaccination, he became fatigued, irritable, unresponsive, and exhibited regression in his speech. Pet. Ex. 46 at 7; Petition at 13, 15, 18-22 (ECF 237). Over the course of late December 2001 through February 2002, A.K. suffered from a protracted URI, rhinitis, bilateral otitis media (infections in both ears), and experienced some fever for approximately three nights. Pet. Ex. 61, p. 49-52, 54.[35]

A.K. was formally diagnosed with ASD by a pediatric neurologist, Dr. Isabel Rapin, on April 22, 2004, at about four and a half years of age. Pet. Ex. 11, p. 3. However, Dr. Boris' records indicate his impression that A.K. had ASD on September 12, 2002. Pet. Ex. 3 at 142. Issues surrounding A.K.'s diagnosis, as well as A.K.'s speech delay are discussed in greater detail in Section VII.

Both before and after his formal ASD diagnosis by Dr. Rapin, A.K. received a variety of therapies and treatments for his condition, including a 2002 colonoscopy. During this period (2002-04), he primarily saw Dr. Boris and Dr. Arthur Krigsman.[36]

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[34] In a declaration filed in this case, [A.K.'s mother] indicated that sometime during the week of December 3, 2001, Dr. Boris, a relative and former pediatrician of both A.K. and his mother, accommodated the whole [*******] family by providing influenza vaccinations when Woodbury Pediatrics ran out of vaccine. Pet Ex. 46 at ¶¶ 14-16. Petitioners subsequently filed a single page of medical records from Dr. Boris recording that flu vaccines were administered to each of the members of the [* * * * *] family. Pet Ex. 118. Exhibit 118 is a page from [A.K.'s mother's] pediatric record. Tr. 190-91. Doctor Boris explained that when he left Woodbury Pediatrics to begin his allergy practice, he carried over the medical files for relatives who had been his patients, including [A.K.'s mother]. *Id*. He indicated that he recorded the influenza vaccinations in [A.K.'s mother's] file, because he did not have a file for A.K. at that time. Tr. 157-58. There was no mention of this record in Dr. Boris's declaration filed in this case in October of 2010 (*see* Pet Ex. 47) and the medical record was not filed until years later on December 12, 2012 (*see* Pet Ex. 118), the day of the fact hearing in this case. Doctor Boris indicated that he recalled the existence of the record only after petitioners' counsel suggested he may have recorded the vaccinations in someone else's file. Tr. 157. As a result of this, the question of whether A.K. received his second dose of influenza vaccine as alleged remained a disputed issue at the time of the hearing in this case. *See* Respondent's Prehearing Submission Regarding Disputed and Undisputed Issues (ECF No. 226) at 2. Subsequently, respondent amended her position, contending that although petitioner maintains the burden of establishing that the vaccinations occurred, the issue was no longer disputed. Tr. 942; ECF No. 295 at fn. 1.

[35] Doctor Zirin, A.K.'s primary pediatrician at that time, explained that the December 17, 2001 entry is from a telephone call with [A.K.'s mother]. Pet. Ex. 108, filed Sept. 26, 2012, at 3.

[36] Doctor Krigsman was an expert witness for petitioners in the Theory 1 OAP test cases. While he was an attending physician at Lenox Hill Hospital in New York from 2000–2004, the hospital became concerned that he was performing medical procedures on autistic children for research purposes, rather than for medical necessity. He sued the hospital for what he viewed as a restriction on his privileges. He testified that the pathology findings supported his decision to perform the colonoscopies. His professional

Doctor Krigsman treated A.K. for various gastrointestinal problems in 2002-03. *See generally*, Pet. Ex. 8. He performed a colonoscopy in November 2002 for "abdominal pain and diarrhea." *Id.*, pp. 60-61.

Over the course of his treatment of A.K., Dr. Boris ordered a wide variety of tests. *See generally*, Pet. Ex. 3, pp. 148-398. Doctor Boris treated him with intravenous gammaglobulin infusions ["IVIG"] (*see, e.g.*, pp. 320),[37] secretin infusions (p. 142), glutathione and vitamins (p.140), chelating agents (pp. 138-39 (prescribing a chelating agent and noting completion of first chelation course)) and methylcobalamin injection (p. 137). Doctor Boris recorded many different diagnoses, including communication delay, allergic rhinitis, hypotonia, ASD, autoimmune neurological disorder, autism, colitis, metabolic/nutritional disorder, malabsorption, toxic metals, "allergic autism," and "chronic inflam[matory] neuropathy," among others. *See, e.g.*, *id.*, pp. 120, 125, 128, 144, 146. According to Dr. Boris' notes, virtually every treatment resulted in improvement, but overall, A.K.'s condition remained about the same, according to therapy records. *See, e.g.*, Pet. Exs. 17 (Early Intervention Records 2002); 18 (school records from Roslyn School in 2003); 14 (School for Language and Communication Development records from January to June 2003).

A brain MRI ordered by Dr. Boris in 2004 was read as "unremarkable." Pet. Ex. 3, p. 264. A test measuring A.K.'s "skeletal age" as "approximately six years" was performed in September 2005, when A.K. was not quite six years of age. *Id*., p. 237. A number of urine tests for toxic metals were performed by Doctors' Data laboratory during A.K.'s treatment by Dr. Boris. *See, e.g*., *id*., pp. 259, 354-55, 359-60, 367, 372. The results varied widely. For example, A.K.'s tin levels varied from 2.6 to 30 to 86 µg/g creatinine in tests performed just months apart. *Id*., pp. 359-60, 367, 372.

Doctor Boris continued to treat A.K. through 2006. Tr. 170. None of the treatments he pursued appear to have been particularly successful in addressing A.K.'s behavioral symptoms, although therapies for some of his gastrointestinal problems may have provided some relief.

During the December 2012 fact hearing, [A.K.'s mother] testified that A.K. continued to currently experience gastrointestinal problems, including severe constipation and a diagnosis of colitis from Dr. Krigsman, which required that he maintain a very

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record also reflected a 2005 fine imposed by the Texas State Board of Medical Examiners for an advertisement that he was available to see patients at a time before he was licensed to practice medicine in Texas. *Snyder*, 2009 WL 332044 at *16.

[37] Funding for these IVIG infusions was denied by A.K.'s insurance in March 2003 as there was no evidence that he had low immunoglobulin levels or immunodeficiency. Pet. Ex. 3, pp. 340-43. An appeal was denied in April 2003, as the stated basis for use of IVIG (mercury and lead poisoning), did not meet the criteria for use of IVIG. *Id.*, pp. 324-25. In June 2003, Dr. Boris wrote a letter supporting a further appeal, stating that A.K. had evidence of "an autoimmune neuropathy," "positive autoantibodies to the thyroid and active colitis. He also fails to respond to measles vaccinations, not producing any antibodies. This is a selective immunodeficiency." *Id.*, p. 316. As A.K. had only one measles vaccination, the plural "measles vaccinations" was incorrect. This appeal was denied as well. *Id.*, p. 311

restrictive diet. Tr. 20-21. [A.K.'s mother] testified that "A.K. does not speak. He's had speech return and disappear several times through the years." *Id*. at 52. She also testified that A.K. is currently being homeschooled because of his constantly changing condition. *Id.* at 80. A.K. plays the piano and takes musical therapy. *Id.* at 52, 81.

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

When petitioners allege an off-Table injury, eligibility for compensation is established when, by a preponderance of the evidence, petitioners demonstrate that the vaccinee received, in the United States, a vaccine appearing on the Table and sustained an illness, disability, injury, or condition caused by the vaccine or experienced a significant aggravation of a preexisting condition. They must also demonstrate that the condition has persisted for more than six months.[38] Vaccine Act litigation rarely concerns whether the vaccine appears on the Table, the geographical location of administration, or whether the symptoms have persisted for the requisite time. In the very small minority of Vaccine Act cases that proceed to a hearing, the most common issue to be resolved by the special master is whether the injury alleged was caused by the vaccine.

To establish legal causation in an off-Table case, Vaccine Act petitioners must establish by preponderant evidence: (1) a reliable medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. *Althen v. Sec'y, HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *see de Bazan v. Sec'y, HHS*, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); *Caves v. Sec'y, HHS*, 100 Fed. Cl. 119, 132 (2011), *aff'd per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012) (specifying that each *Althen* factor must be established by preponderant evidence). Where a petitioner in an off-Table case is seeking to prove that a vaccination aggravated a pre-existing injury, petitioners must establish three additional factors. *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 petitioners to demonstrate aggravation by showing: (1) the vaccinee's condition prior to the administration of the vaccine, (2) the vaccinee's current condition, and (3) whether the vaccinee's current condition constitutes a "significant aggravation" of the condition prior to the vaccination. *Id*.

The applicable level of proof is the "traditional tort standard of 'preponderant evidence.'" *Moberly v. Sec'y, HHS*, 592 F.3d 1315, 1322 (Fed. Cir. 2010) (citing *de Bazan,* 539 F.3d at 1351; *Pafford v. Sec'y, HHS*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Capizzano v. Sec'y, HHS*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *Althen*, 418 F.3d at 1278). Although special masters are not bound by the formal rules of evidence

[38] Section 13(a)(1)(A). This section provides that petitioner must demonstrate "by a preponderance of the evidence the matters required in the petition by section 300aa–11(c)(1) . . . ." Section 11(c)(1) contains the factors listed above, along with others not relevant to this case.

generally applicable in federal courts, they are required to find evidence reliable before they may consider it. *Knudsen v. Sec'y*, *HHS,* 35 F.3d 543, 548-49 (Fed. Cir. 1994) (Petitioner has the burden to present a reliable and reputable medical theory, which must be "legally probable, not medically or scientifically certain."); *Daubert v. Merrell Dow Pharmaceuticals,* 509 U.S. 579, 590 (1993) (holding that scientific evidence and expert opinions must be reliable to be admissible). The preponderance standard "requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence." *In re Winship*, 397 U.S. 358, 371 (1970) (Harlan, J., concurring) (internal quotation and citation omitted).

Another formulation of the causation requirement in off-Table cases is the "Can it cause?" and "Did it cause?" inquiries used in toxic tort litigation. These queries are also referred to as issues of general and specific causation. Prong 1 of *Althen* has been characterized as an alternative formulation of the "Can it cause?" or general causation query. Prong 2 of *Althen*, the requirement for a logical sequence of cause and effect between the vaccine and the injury, has been characterized as addressing the "Did it cause?" or specific causation query. *See Pafford v. Sec'y, HHS*, No. 01-165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (2006). Prong 3 of *Althen*, the requirement that the injury sustained occur within a medically appropriate interval after vaccination, is subsumed into the other inquiries. Even if a particular vaccine has been causally associated with an injury, petitioner must still establish facts and circumstances that make it more likely than not that this vaccine caused the particular injury. Timing may be one of those circumstances.

Whether a case is analyzed under *Althen* or the "Can it cause?" formulation, petitioners are not required to establish identification and proof of specific biological mechanisms, as "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. Petitioners need not show that the vaccination was the sole cause, or even the predominant cause, of the injury or condition; showing that the vaccination was a "substantial factor"[39] in causing the condition, and was a "but for" cause, are sufficient for recovery. *Shyface v. Sec'y, HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999); *see also Pafford,* 451 F.3d at 1355 (petitioners must establish that a vaccination was a substantial factor and that harm would not have occurred in the absence of vaccination). Petitioners cannot be *required* to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect" (*Capizzano*, 440 F.3d at 1325), but the special master may certainly consider such evidence when filed. *Andreu v. Sec'y, HHS,* 569 F.3d 1367, 1379 (Fed. Cir. 2009) (Special masters may consider medical literature and

[39] The Restatement (Third) of Torts has eliminated "substantial factor" in the factual cause analysis. § 26 cmt. j (2010). Because the Federal Circuit has held that the causation analysis in the Restatement (Second) of Torts applies to off-Table Vaccine Act cases (*see Walther v. Sec'y, HHS*, 485 F.3d 1146, 1151 (Fed. Cir. 2007); *Shyface*, 165 F.3d at 1352), this change does not affect the determination of legal cause in Vaccine Act cases: whether the vaccination is a "substantial factor" is still a consideration in determining whether it is the legal cause of an injury.

epidemiological evidence, when it is submitted, in "reaching an informed judgment as to whether a particular vaccine likely caused a particular injury."). Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen,* 35 F.3d at 548. Close calls regarding causation must be resolved in favor of petitioners. *Althen*, 418 F.3d at 1280; *but see Knudsen*, 35 F.3d at 550 (when evidence is in equipoise, the party with the burden of proof fails to meet that burden).

In Vaccine Act cases, special masters are frequently confronted by expert witnesses with diametrically opposing positions on causation. When experts disagree, many factors influence a fact-finder to accept some testimony and reject other contrary testimony. As the Federal Circuit noted, "[a]ssessments as to the reliability of expert testimony often turn on credibility determinations, particularly in cases . . . where there is little supporting evidence for the expert's opinion." *Moberly*, 592 F.3d at 1325-26. Objective factors, including the qualifications, training, and experience of the expert witnesses; the extent to which their proffered opinions are supported by reliable medical research and other testimony; and the factual basis for their opinions are all significant factors in determining what testimony to credit and what to reject. *Lalonde v. Sec'y, HHS,* 746 F.3d 1334, 1340 (Fed. Cir. 2014) (noting that "as the finder of fact, the special master was responsible for assessing the reliability of [the expert's] testimony by looking for reliable medical or scientific support" (citing *Moberly*, 592 F.3d at 1324-25)).

Congress contemplated that special masters would weigh and evaluate opposing expert opinions in determining whether petitioners have met their burden of proof. Congress clearly specified petitioners' burden of proof in off-Table cases as the preponderance of the evidence standard. It directed special masters to consider the evidence as a whole, but stated that special masters are not bound by any particular piece of evidence contained in the record.[40] In weighing and evaluating expert opinions in Vaccine Act cases, the same factors the Supreme Court has considered important in determining their admissibility provide the weights and counterweights. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 149-50 (1999); *Terran v. Sec'y, HHS*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). As the Supreme Court has noted, a trial court is not required to accept the *ipse dixit* of any expert's medical or scientific opinion, because the "court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

Although special masters are not bound by the formal rules of evidence generally applicable in federal courts, the Federal Rules of Evidence and cases interpreting them can guide special masters in their decisions. *Daubert*, which interpreted Rule 702 of the Federal Rules of Evidence provides a useful framework for evaluating scientific evidence in Program cases. *Terran*, 195 F.3d at 1316 (concluding that it was reasonable for the special master to use *Daubert* to evaluate the reliability of an expert's testimony); *Cedillo,* 617 F.3d at 1339 (noting that special masters are to consider all

[40] *See* § 13(a)(1)(A) (preponderance standard); § 13(a)(1) ("Compensation shall be awarded . . . if the special master or court finds on the record as a whole . . . ."); § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation and special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record).

relevant and reliable evidence filed in a case and may use *Daubert* factors in their evaluation of expert testimony); *Davis v. Sec'y, HHS*, 94 Fed. Cl. 53, 67 (2010) (describing the *Daubert* factors as an "acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted . . . by special masters in vaccine cases"); *see also Snyder*, 88 Fed. Cl. at 718 (quoting *Ryman v. Sec'y, HHS*, 65 Fed. Cl. 35, 40-41 (2005) (special masters perform gatekeeping function when determining "whether a particular petitioner's expert medical testimony supporting biological probability may be admitted or credited or otherwise relied upon" and as a "trier-of-fact [a special master] may properly consider the credibility and applicability of medical theories")).

The special master's use of *Daubert's* factors to evaluate the reliability of expert opinions in Vaccine Act cases has been cited with approval by the Federal Circuit more recently in *Andreu,* 569 F.3d at 1379 and *Moberly,* 592 F.3d at 1324. *See also Vaughan v. Sec'y, HHS,* 107 Fed. Cl. 212, 222 (2012) ("The Federal Circuit has repeatedly stated that the Special Master may refer to *Daubert* to assess reliability of expert testimony in vaccine cases."). Special masters decide questions of credibility, plausibility, probability, and reliability, and ultimately determine to which side the balance of the evidence is tipped. *See Pafford*, 451 F.3d at 1359.

Bearing all these legal standards in mind, I now turn to the causation evidence presented in this case, beginning with the qualifications of the experts and a summary of their opinions.

V. Expert Testimony.

In this case I heard extensive expert testimony from eleven witnesses. These experts have diverse qualifications and represent a number of different scientific or medical disciplines, including psychology, pediatric neurology, immunology, biochemistry, and pharmacology. While the experts' opinions cover the breadth of issues in this case, they do so in overlapping and conflicting ways. Certain aspects of these expert opinions will be highlighted because they illuminate the analysis to follow, but each expert's opinion was carefully considered in full. In this section, I will therefore separately summarize each expert's qualifications and opinions.

A. Petitioners' Experts.

Petitioners presented three expert witnesses, and one witness who testified as a treating physician, fact witness, and expert, Dr. Marvin Boris.[41] The first of the three expert witnesses to testify was Dr. Frances Kendall, a pediatrician and biochemical geneticist who has focused much of her career on diagnosing and treating mitochondrial disorders. Doctor Kendall argued that A.K. has a mitochondrial disorder and presented a theory that such disorders can be aggravated by oxidative stress from the influenza vaccine. She was joined by Dr. Shafrir, a pediatric neurologist, and Dr. Deth, a pharmacologist. Doctor Shafrir argued that A.K.'s ASD resulted from the combined

[41] Doctor Boris's expert opinions are discussed in conjunction with Dr. Shafrir's causation theory with regard to Dr. Shafrir's reliance on A.K.'s MTHFR polymorphisms as well as Dr. Shafrir's contention that A.K. had an abnormal immune system. *See* Sections VIII.B.2.b and B.2.c, below.

effects of an autoimmune attack coupled with other vulnerabilities, such as A.K.'s alleged mitochondrial disorder and "MTHFR" (i.e., methylenetetrahydrofolate reductase) mutation. Doctor Deth postulated a mechanism whereby the influenza vaccine could create injurious oxidative stress in the manner suggested by Drs. Kendall and Shafrir.

1. Frances Kendall, M.D.

a. Doctor Kendall's Qualifications.

Doctor Kendall has been practicing medicine with a special attention to mitochondrial diseases for 20 years. Pet. Ex. 65 at 1. 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. Pet. Ex. 65 at 1; Tr. 236-37. She considers herself one of "only a handful" of mitochondrial experts in the country. Pet. Ex. 65 at 1; Tr. 416.

Doctor Kendall received a biology degree from Temple University before attending medical school. Pet. Ex. 232 at 1; Tr. 237. She completed her residency in pediatrics at Thomas Jefferson University Hospital and fellowships in genetics at the Children's Hospital in Boston and Harvard Medical School. *Id*. Doctor Kendall has past university affiliations with Harvard and Emory Universities and has been on the staff of Boston Children's Hospital as well as director and chairman of the genetics department at Scottish Rite Children's Hospital. Pet. Ex. 232 at 1-3; Tr. 237, 241. She is currently on staff at the Children's Hospital of Atlanta. *Id*.

For approximately the last five years, Dr. Kendall has operated her own private practice. Tr. 241. Her current practice, Virtual Medical Practice, is devoted to the care of patients with mitochondrial and other rare genetic disorders. Pet. Ex. 65 at 1. She estimates that she has over one thousand patients and that at least one hundred of them have both autism and mitochondrial disorders. Tr. 373. Her patients come to her both for diagnosis and for ongoing management of their symptoms. Tr. 372-73. She recently published an article in the JOURNAL OF PEDIATRIC BIOCHEMISTRY that sets out an overview of mitochondrial disease and testing and which has been submitted in this case. Tr. 238; Pet. Ex. 172.

b. Doctor Kendall's Opinion.

Doctor Kendall's opinions extended to A.K.'s diagnosis and causation of his injury. She opined that A.K. met the diagnostic criteria for a mitochondrial disorder. She also opined that immunizations can act as metabolic stressors that can cause a child with a mitochondrial disorder to decompensate or regress. In A.K.'s case, she contended that his influenza vaccinations of November and December of 2001 aggravated his underlying mitochondrial disorder, triggering an autistic regression.

She explained that there is no "gold standard" test for diagnosis of mitochondrial disease that can be applied in every case, and that each diagnosis depends on the expertise of the clinician, who must look at a collection of different data points. Tr. 248-49, 425-27. A mitochondrial diagnosis is typically made by considering biochemical, genetic, and clinical features. Tr. 249-51. Although there is no universally accepted diagnostic standard for mitochondrial disorders, she opined that A.K. exhibited enough

signs and symptoms of mitochondrial dysfunction to be so diagnosed.[42] Pet. Ex. 65 at 7; Tr. 285.

Specifically, Dr. Kendall felt that A.K.'s biochemical tests showed elevated levels of lactate and "AST" that are consistent with mitochondrial disease.[43] Tr. 244. She also noted A.K.'s enzymology indicated a "Complex I" defect.[44] Tr. 250-51. She contended that these findings, combined with his clinical presentation of autistic features, developmental delays, dysautonomia (*i.e.*, temperature intolerance), gastrointestinal issues, fatigability, and hypotonia, were sufficient to support a diagnosis of mitochondrial disease. *Id*. She acknowledged that there were no genetic findings in A.K.'s case to support her diagnosis. Tr. 251; *see also* Pet. Ex. 33.

Having concluded that A.K. had a mitochondrial disease, Dr. Kendall further opined that this left him susceptible to mitochondrial regression following episodes of metabolic (or oxidative) stresses. Tr. 253-54. Doctor Kendall opined that, based on her own experience, A.K.'s influenza vaccine could have been such a stressor. Tr. 253-54. Based on her interpretation of A.K.'s complete medical history, the onset of his developmental delays and ASD-like symptoms were temporally related to the two doses of influenza vaccine he received in November and December of 2001.[45] Tr. 285.

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[42] In her report, Pet. Ex. 65 at 1, Dr. Kendall explained that her diagnosis of A.K. was based on the "Bernier" criteria. *See* F. Bernier, et al., D*iagnostic criteria for respiratory chain disorders in adults and children*, NEUROL. 59(11):1406-11 (2002), filed as Pet. Ex. 90, Res. Ex. SS, Tab 1, and Res. Ex. UU, Tab 1 [hereinafter "Bernier, Pet. Ex. 90"]. Application of the Bernier criteria results in diagnoses at different confidence levels, rated as definite, probable, or possible. Pet. Ex. 90 at 1407. She opined that based on these criteria, A.K.'s mitochondrial diagnosis could be considered "definitive or highly probable." Pet. Ex. 65 at 7. However, after being questioned extensively by respondent's counsel about her application of the Bernier criteria to A.K.'s case, Dr. Kendall acknowledged that A.K.'s diagnosis is not "definitive" under that criteria and instead characterized it as "probably probable." Tr. 317-19. On further questioning, Dr. Kendall became somewhat critical of the Bernier criteria, arguing that they are "not comprehensive" and stressing that there are other, more recent diagnostic criteria available, and that there is no consensus on what criteria to use. Tr. 423-25. She re-emphasized this point in her supplemental report filed on October 3, 2013. *See* Pet. Ex. 269.

[43] According to Dr. Kendall, "AST" is a liver function test, but she contended that AST elevation can be a sign of a mitochondrial disorder. Tr. 244-45. "AST" stands for "aspartate aminotransferase," an enzyme "found in very high concentrations within highly metabolic tissue." When injury or disease occurs in these tissues, the serum level of AST rises, remaining elevated for several days after injury. If the "injury is chronic, levels will be persistently elevated." K. Pagona & J. Pagona, MOSBY'S MANUAL OF DIAGNOSTIC AND LABORATORY TESTS (5th ed. 2014) at 119 [hereinafter "MOSBY'S LABS"].

[44] Mitochondria function via five protein complexes (typically numbered with Roman numerals) which make up what is called the electron transport chain or respiratory chain. These concepts are discussed in greater detail in Section VI.A, below. Doctor Kendall acknowledged that the muscle biopsy enzymology findings were open to debate. She indicated that the lab that tested A.K.'s tissue for respiratory chain function did not perform calculations designed to account for the difficulty of measuring function of Complex I of the respiratory chain in tissue. Tr. 247-48. She argued, however, that there is no single standard by which to evaluate the validity of the results, and, at least initially, considered the results valid. *Id*. This issue is discussed in more detail in Section VI.C.1, below.

[45] I questioned Dr. Kendall's recitation of the facts of A.K.'s medical history within her report, noting that her report was misleading regarding his medical history at several points. Tr. 341-55. Doctor Kendall's testimony was also confused about A.K.'s medical history. On direct examination she contended that video clips of A.K. at about 18-19 months of age supported her view regarding the temporal association

Doctor Kendall was not aware of any study that found that the influenza vaccine could aggravate a mitochondrial disorder or cause regression. Tr. 332. Nonetheless, citing to three medical journal articles (Poling, Shoffner, and Weissman),[46] she contended that these "recent studies have documented the association of developmental regression and autism in patients with mitochondrial disease following exposure to immunizations." Pet. Ex. 65 at 7-8; Tr. 376-78. When challenged, Dr. Kendall acknowledged that A.K.'s presentation did not fit within the parameters of these studies, but contended that the studies establish that "there are other factors that impact these children that can cause autistic regression."[47] Tr. 369-71. She argued that they established a "precedent" for an association between A.K.'s influenza vaccinations and his condition. Pet. Ex. 65 at 8; Tr. 288-90. She therefore opined, particularly in the absence of any other explanation, that the two doses of influenza vaccine more likely than not caused A.K.'s condition. *Id*.

2. Yuval Shafrir, M.D.

a. Doctor Shafrir's Qualifications.

Doctor Yuval Shafrir received his medical degree from the Sackier School of Medicine in Tel Aviv, Israel, in 1982. Pet. Ex. 62 at 1. From 1982 to 1992, Dr. Shafrir continued post graduate medical training, including pediatric residencies with a neonatology rotation, as well as fellowships in pediatric neurology and pediatric neurophysiology and epileptology. *Id*. Doctor Shafrir is currently licensed to practice in the state of Maryland. He has previously been licensed in Israel, Virginia, Oklahoma, Pennsylvania, and the District of Columbia. *Id*. at 2. Doctor Shafrir is board certified in

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between the onset of A.K.'s condition and his influenza vaccines. Tr. 270-72. During subsequent questioning, however, she appeared unsure whether the video had any significance, stating that "I looked at that with a question mark. You know, does this mean anything?" Tr. 411.

[46] Three medical journal articles are addressed extensively in the analysis below. The first, J. Poling, et al., *Developmental Regression and Mitochondrial Dysfunction in a Child with Autism*, J. CHILD NEUROL., 21(2):1-3 (2006), was filed as Pet. Exs. 40; 63, Ref. 18; 91 and as Res. Exs. MM, Tab 14 and UU, Tab 9 [hereinafter "Poling, Res. Ex. MM, Tab 14"]. The second, J. Shoffner, et al., *Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression*, J. CHILD NEUROL., 25: 429-434 (2010), filed as Pet. Exs. 42; 63, Ref. 15; 92 and as Res. Exs. MM, Tab 16 and UU, Tab 10 [hereinafter "Shoffner, Res. Ex. MM, Tab 16"]. The third extensively discussed article, J. Weissman, et al, *Mitochondrial Disease in Autism Spectrum Disorder Patients: A Cohort Analysis*, PLoS ONE 3(11): e3815 (2008) was filed as Pet. Exs. 39 and 63, Ref. 3 and as Res. Exs. MM, Tab 15; SS, Tab 18, and UU, Tab 14.[hereinafter "Weismann, Pet. Ex. 39"]. Doctor Kendall did not cite the Weissman paper in her report, although it was discussed to some extent during her testimony. The Poling and Shoffner articles were cited in Dr. Kendall's report, Pet. Ex. 65, as references 26 and 27. My usual practice is to cite to petitioners' exhibit numbers when an article is filed by both parties. However, during the hearing, I indicated that the copy of the Shoffner article filed with Dr. Kendall's report was incomplete and that I intended to rely on a copy of that article filed by respondent as Exhibit MM, Tab 16. The copies of the Poling article filed as petitioners' exhibits were an on-line version; I therefore cite to the print publication version filed by respondent. Because the evidence filed in this case is not publically available, I cite to these (and other) journal articles by the page numbers that appear in the published versions of the article to enable any readers to more easily find the references that appear throughout this decision

[47] During the hearing I questioned Dr. Kendall closely regarding her exaggeration of the findings of the Shoffner study in her report. Tr. 369-71. The Shoffner study and what Dr. Kendall claimed about it are discussed in more detail in Section VIII.A.2.a, below.

neurology and clinical neurophysiology and was formerly board certified in pediatrics.[48] Pet. Ex. 62 at 2; Tr. 450.

Doctor Shafrir has held several clinical positions, including attending child neurologist at Georgetown University Hospital from 1995 to 1999 and at Oklahoma University Health Science Center from 1999 to 2000. Pet. Ex. 62 at 3. In addition, he has held assistant professorships in neurology and pediatrics at the U.S. University of the Health Sciences, Georgetown University, and the University of Oklahoma. Pet. Ex. 62 at 3; Tr. 451. Since 2000 Dr. Shafrir has operated a full-time private practice in pediatric neurology where he sees about 60 patients a week. Tr. 451-52. He estimated that in private practice he has treated at least 1,000 children with autism. Tr. 452. In addition to his private practice, Dr. Shafrir also serves as a clinical assistant professor at the University of Maryland. Tr. 451.

Doctor Shafrir's curriculum vitae listed seven journal articles relating to child neurology, none of which were related to autism or mitochondrial disorders, three letters to the editor, ten abstracts, and numerous conference lectures.[49] Pet. Ex. 62 at 4-8. However, he is not a member of any professional societies and does not review for any professional journals. Pet. Ex. 62 at 3; Tr. 517-18.

b. Doctor Shafrir's Opinion.

Although he does not believe that autism itself is genetically caused, Tr. 481-84, Dr. Shafrir opined that A.K. had genetic factors that left him vulnerable to environmentally induced autistic regression.[50] Pet. Ex. 63 at 12, 16-18; Tr. 554-55. That is, Dr. Shafrir argued that the presence in A.K. of both a Complex I mitochondrial disorder[51] and a double mutation in the MTHFR gene left A.K. susceptible to mechanisms of brain injury including apoptosis, oxidative stress, and other unspecified mechanisms. Pet. Ex. 63, p. 18-19. On cross examination, Dr. Shafrir conceded that there is no basis for contending that either the mitochondrial disorder or the MTHFR gene mutation actually caused A.K.'s autism. Tr. 547, 560-61. Rather, he opined that each of these conditions was a "risk factor" for autistic regression. *Id*.

Doctor Shafrir contended that, when A.K. received his influenza vaccinations, these genetic factors, combined with an "abnormal, rare, genetically determined

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[48] Doctor Shafrir's curriculum vitae was last updated in 2005. He confirmed during the hearing that his certifications in neurology and neurophysiology are not time limited, but that he opted not to renew his board certification in pediatrics when it expired in 2005. Tr. 450, 515-18.

[49] At the hearing, Dr. Shafrir indicated that he had published one additional article since his curriculum vitae was last updated in 2005. Tr. 517-18. The article, on the subject of spinal cerebral ataxia type 2, was published in NEUROLOGY in 2011. *Id*.

[50] Doctor Shafrir contended that autism and autistic regression were overlapping, but distinct, entities. Pet. Ex. 63 at 12; Tr. 519-22. I have previously rejected this contention (*see Dwyer* 2010 WL 892250, *37 *and Synder*, 2009 WL 332044, *39) and do so here as well, for the reasons set forth in Section VIII.B.1, below.

[51] Significantly, while Dr. Shafrir assumed the presence of a mitochondrial disorder for purposes of his theory, he noted that he is not a mitochondrial expert and deferred to the other experts in this case regarding the question of whether A.K. in fact had any mitochondrial disorder. Tr. 513-14, 546.

structure of his immune system,"[52] resulted in an autoimmune attack on A.K.'s brain which caused an encephalopathy leading to autistic regression. Pet. Ex. 63 at 15-16; Tr. 458, 556. Doctor Shafrir contended that what happened to A.K. was an example of the "triple hit theory," which he said explains the relationship between genetic and environmental factors in autism. Pet. Ex. 63 at 18; Tr. 549-54. He argued by analogy that abnormal immune responses in cases regarding chicken pox, Guillain-Barre Syndrome ["GBS"], acute disseminated encephalomyelitis ["ADEM"], and narcolepsy showed that a vaccine could activate a neuroimmune reaction among vulnerable populations. Pet. Ex. 63 at 14-16; Tr. 484-89, 502-04, 542.

Significantly, however, Dr. Shafrir acknowledged that there is no evidence in this case that A.K. experienced any immune reaction within his brain. Tr. 541-42. Instead, he argued that his theory is supported by the nature and timing of A.K.'s autistic regression, which he claimed demonstrated a clear challenge-rechallenge response[53] to the two doses of influenza vaccine at issue in this case.[54] Tr. 491, 502-04. In that regard, although he cautioned that regression is a process and cannot necessarily be pin-pointed, Dr. Shafrir placed the onset of A.K.'s autistic regression at about two years of age. Tr. 528.

Initially, Dr. Shafrir opined that "there is excellent documentation of appearance of regression of language and behavioral changes typical for the autistic regression such as loss of eye contact appearing after the first, and worsening after the second influenza vaccine." Pet. Ex. 63, p. 12. At the hearing, however, Dr. Shafrir indicated that A.K.'s medical records were "sketchy" (Tr. 461), and added that it was difficult to rely on A.K.'s pediatric records alone, particularly with regard to his speech development (Tr. 529-30). He explained that his opinion was based on a combined reading of A.K.'s medical records and [the affidavits of A.K.'s parents], which he said indicated that A.K. had some speech prior to vaccination which he lost after the vaccination. Tr. 531, 534, 538-39. He contended that there is no evidence in the record to suggest that A.K. was *not* developmentally normal up until November 9, 2001. Tr. 528-29. Doctor Shafrir argued in particular that video clips of A.K. shown during the hearing demonstrated a dramatic change in behavior between November 9, 2001, and November 10, 2001.[55] Tr. 470-71, 478-79. He testified that A.K.'s regression was apparent, because A.K. acted "more or less normal" in the first video, but his autistic symptoms were "absolutely striking" in the second.[56] Tr. 470-73.

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[52] Doctor Shafrir's claim that A.K. has an abnormal immune system appears to be based on his diagnosis at three years of age with Hashimoto Thyroiditis, a type of autoimmune hypothyroidism. Tr. 556-57.

[53] A challenge-rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine." *Cappizano,* 440 F.3d at 1322. This concept is discussed in greater detail in Sections VII.D and VIII.B.3.b, below.

[54] Doctor Shafrir also contended that A.K.'s regression occurred within the medically accepted time frame for an autoimmune reaction, as evidenced by the recognized time frame for other adverse immune reactions such as GBS. Pet. Ex. 63 at 15; Tr. 478-79.

[55] Doctor Shafrir had not yet viewed the videos at the time he wrote his report for this case. Tr. 458-59.

[56] Despite drawing this comparison, Dr. Shafrir testified that you cannot diagnosis a child with autism from video footage. Tr. 467-69. In particular he indicated that he "really feel[s] that you cannot make

3. Richard Deth, Ph.D.

a. Doctor Deth's Qualifications.

Doctor Richard Deth is a professor of pharmacology at Northeastern University in Boston, Massachusetts, a position which he has held since 1976. Tr. 599-600; Pet Ex. 117 at 4. He received his undergraduate degree in Pharmacy at the State University of New York at Buffalo in 1970, and earned a Ph.D. in Pharmacology from the University of Miami in 1975. Tr. 599; Pet. Ex. 95 at 1. He also completed one year of post-graduate training at the University of Leuven in Belgium. *Id*.

Doctor Deth claimed more than eighty peer-reviewed publications, including a monograph entitled "Molecular Origins of Human Attention: The Dopamine-Folate Connection." Pet. Ex. 95 at 4-11. He also serves as a journal referee for a number of publications, including the JOURNAL OF PHARMACOLOGY, EXPERIMENTAL THERAPEUTICS, CIRCULATION RESEARCH, SCIENCE MAGAZINE, and MOLECULAR PSYCHIATRY. Tr. 604; Pet. Ex. 95 at 3. He is a member of the Society for Neuroscience, the International Society for Autism Research, the American Society of Pharmacology and Experimental Therapeutics, and the Society for Biological Psychiatry. Pet. Ex. 95 at 1.

Doctor Deth's professional history is noteworthy in that his original background and training focused on the cardiovascular system rather than the neurological system. Tr. 601. He did not begin his current research focus on oxidative stress and brain disorders until approximately 1998. Tr. 608. Doctor Deth testified that for the past eight to ten years he has focused his attention on studying autism and working with autism support groups. Tr. 601-02. In 2008, Dr. Deth testified in the Vaccine Program's Omnibus Autism Proceeding with regard to the theory that the thimerosal component of certain vaccines could cause autism. Tr. 609.

b. Doctor Deth's Opinion.

Doctor Deth summarized his opinion in this case[57] thusly: "vaccinations promote inflammation and oxidative stress as integral components of the immune response, and individuals with limited capacity to recovery are at higher risk of long term adverse consequences, including developmental regression in the case of young children." Tr.

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comments about thing[s] that you expect to see but you don't see." Tr. 470. Doctor Shafrir's argument appears to be that analysis of video footage is not ordinarily a valid method of diagnosis, but that it can be used in this case to determine the timing of A.K.'s regression due primarily to the presence of "dramatic" features of autism in the second video which cannot be seen in the first video, marking a stark contrast between the two. Tr. 467-69, 537-38. In that regard, Dr. Shafrir's assessment of the first video seemed to hinge on the argument that there was no "*obvious* evidence for autistic behavior." Tr. 473 (emphasis added). It is noteworthy then that Dr. Shafrir's stance on this issue appears to be largely informed by the fact that he was highly pessimistic about the efficacy of autism evaluation guidelines (Tr. 495-98, 522-24) and in fact rejected the idea that "subtle" signs of autism should even be considered for diagnostic purposes at all, regardless of whether they appear on video. Tr. 473-74, 483-84.

[57] Petitioners' counsel indicated that petitioners did not intend for Dr. Deth's opinion to be considered as a separate causation theory, but rather that he was opining with regard to the mechanism by which A.K.'s injury might have occurred. Tr. 597. I found Dr. Deth's testimony to be highly problematic and not at all helpful in resolving this case. A more detailed discussion of the problems with Dr. Deth's testimony is contained in Section IX, below.

751. That is, Dr. Deth argued that "oxidative stress" is one phenomenon that can impact gene expression, and ultimately human development, through epigenetic regulation.[58] Tr. 615-16.

As Dr. Deth explained, oxidative stress can occur when cells metabolize oxygen via mitochondrial function. Tr. 640-41. In mitochondrial oxygen metabolism, electrons are lost and harmful "reactive oxygen species" ["ROS"] molecules are created. *Id*. Under normal conditions, cells use existing antioxidants to provide additional electrons in order to neutralize the ROS and maintain balance (i.e., a normal "redox" state). Tr. 640-42. When cells lack sufficient antioxidants to neutralize the harmful ROS, oxidative stress results. Tr. 642.

Two antioxidants central to Dr. Deth's theory, methionine[59] and cysteine,[60] are amino acids that are absorbed through the terminal ilium of the small intestine. Tr. 713-15. Doctor Deth argued that inflammation of the intestinal tract, and the terminal ilium in particular, depresses the uptake of these antioxidants due to the presence of a pro-inflammatory cytokine called "tissue necrosis factor alpha" ["TNF-α"]. Tr. 707, 713, 723. According to Dr. Deth, TNF-α has been shown to both inhibit methionine synthase and reduce the uptake of cysteine. Tr. 708-09. Thus, Dr. Deth contended that since the terminal ilium of the intestinal tract is the primary source of these antioxidants, inflammation of the gastrointestinal ["GI"] tract can lead to a whole body deficit of antioxidants and increase susceptibility to oxidative stress.[61] Tr. 715-16, 721-23.

In A.K.'s case, Dr. Deth argued that evidence of terminal ilium inflammation upon endoscopy, coupled with multiple findings of low cysteine and the presence of antibodies to gliaden, casein, and casomorphin, supported the conclusion that A.K. experienced a depressed antioxidant status and an abnormal immune response. Tr.

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[58] Doctor Deth contended that epigenetics, *i.e.,* the impact of non-genetic factors on gene expression (*see* n. 288, *infra*), is key to understanding autism in that autism is caused by a combination of genetic and environmental factors. Tr. 613, 621, 644-46. Although he acknowledged that epigenetics operates in all phases of human development from pre-conception through adulthood, Dr. Deth stressed that epigenetic changes occurring in earlier development have a larger impact. Tr. 628-31, 813-14. In particular, he argued that epigenetic changes occurring in early childhood, when significant brain and immune development is occurring, were the most critical. Tr. 628-31. He maintained that the acute inhibition of deoxyribonucleic acid ["DNA"] methylation (a process whereby enzymes control gene expression by attaching single carbon molecules to specific DNA sites) by oxidative stress could have long-term consequences for growth and development. Tr. 622-25.

[59] Doctor Deth identified the enzyme methionine synthase as being one of the enzymes that controls DNA methylation. He stressed that it is particularly sensitive to oxidative stress. Tr. 646-48.

[60] Doctor Deth contended that while the neuronal activity of the brain is of a higher-energy and demands a higher rate of aerobic metabolism than the rest of the body, the cerebral spinal fluid surrounding the brain is particularly low in antioxidants. Tr. 659-61. Thus he opined that the brain is particularly dependent upon cystine (the oxidized form of cysteine) crossing the blood/brain barrier. Tr. 663-66.

[61] I warned at multiple points during the hearing that Dr. Deth's opinions regarding the impact of inflammation on the intestinal tract were beyond his area of expertise. *See, e.g.*, Tr. 747, 751. Doctor Deth is not a physician, and has no training in gastroenterology or immunology, and thus many of his opinions are entitled to little weight.

745-749. He therefore contended that A.K. was at a higher risk of experiencing long-term adverse consequences due to oxidative stress.[62] Tr. 751.

Doctor Deth also opined that vaccines create increased metabolic need as a result of the activation of "T cells" to initiate an immune response, requiring additional antioxidants. Tr. 733-34. Doctor Deth claimed that, as a result of additional inflammatory responses created by the aluminum adjuvant in vaccines, TNF-α is released, possibly in the brain; methylation is decreased; and available antioxidant pathways are modified.[63] Tr. 737, 741-44. That is, Dr. Deth claimed that vaccines both increase metabolic need and decrease the availability of the antioxidants necessary to counteract the reactive oxygen species generated by that excess metabolic activity.

Thus, Dr. Deth contended that among those—like A.K., allegedly—who have difficulty maintaining redox, the result is neural inflammation which can ultimately lead to encephalopathy or other brain injury. Tr. 744-45. He argued that the brain is particularly susceptible to changes brought about by oxidative stress[64] and that studies have linked signs of oxidative stress within the brain to autism. [65] Tr. 705-08; Pet. Ex. 117 at 12. More specifically, he hypothesized that when the brain is subjected to oxidative stress, it impairs the development of "D4" dopamine receptors, which he argued are necessary to the "gamma" frequency brain activity associated with the capacity for attention. Tr. 686-87. He argued that the decreased gamma activity is a characteristic of autism. Tr. 686-89. Significantly, however, Dr. Deth's opinion in this case was severely limited in that he has acknowledged that he does not know how much oxidative stress is created by an influenza vaccination, nor the amount of oxidative stress necessary to cause autism or how long the onset period would be. Tr. 773-74.

4. Marvin Boris, M.D.

a. Doctor Boris's Qualifications.

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[62] Doctor Deth also argued that A.K.'s MTHFR polymorphism was an additional factor contributing to A.K.'s vulnerability in that it, too, leads to impaired methylation. Tr. 721-23, 749-50.

[63] Doctor Deth acknowledged, however, that the effect of vaccination on methylation "has not been extensively studied," and indicated that "that's a serious problem." Tr. 736.

[64] For example, he contended that the presence of oxidative stress would determine epigenetically whether brain development favored the growth of neurons or astrocytes. Tr. 651-54. And again, as noted above, he stressed that the cerebral spinal fluid surrounding the brain is relatively antioxidant poor. Tr. 660-61.

[65] Doctor Deth presented his own post-mortem brain study which he described as showing lower levels of the messenger RNA ["mRNA"] necessary for creating methionine synthase among autistic individuals. Tr. 705-07. He posited that the messenger RNA was inhibited by TNF-α. Tr. 708. On cross-examination, he acknowledged that the post-mortem study did not find that the hydroxyl guanosine biomarker for oxidative stress was elevated in the autistic population. Tr. 781-82. On redirect, Dr. Deth explained that he thought that the low levels of methionine synthase mRNA is evidence of a coping mechanism which allowed the autistic individuals to keep the biomarkers of oxidative stress low. Tr. 827.

Related to [A.K.'s mother] by marriage, Dr. Boris treated A.K. and interacted with his family socially.[66] He originally was scheduled to testify at both the fact and entitlement hearings. Due to scheduling difficulties, petitioners opted instead to have Dr. Boris testify at the entitlement hearing as both a factual and expert witness. *See* Status Report, filed Nov. 16, 2012 (ECF No. 185).

In 2010, petitioners filed a declaration containing factual assertions from Dr. Boris as an attachment to their motion for reconsideration. *See* Pet. Ex. 47. His expert opinion was filed on September 26, 2012, and he testified about the manifestation and cause of autism during the entitlement hearing. Tr. at 146-48. He opined as to the cause of A.K.'s autism in his declaration. *See* Pet. Ex. 47 at 8-9.

Doctor Boris earned his medical degree from the New York University, College of Medicine in 1958. Tr. at 142, 145; Pet. Ex. 47 at 10. His post graduate medical training included a one year internship at Bellevue Hospital and residency at New York Hospital, Cornell Medical Center, both in New York City. Tr. at 142-43. He then spent two years at the CDC in Atlanta, Georgia, in the Epidemic Intelligence Service. When he left the CDC, he entered private practice in the areas of pediatrics, allergy and immunology. Tr. at 143.

Doctor Boris is board certified in both pediatrics and allergy and immunology. Tr. at 143-44; Pet. Ex. 47 at 10. He has held teaching positions at Cornell University, School of Medicine and the New York University, School of Medicine and has published approximately 28 articles regarding infectious disease, allergy, immunology and autism. Tr. at 144. He is a member of the American College of Allergy Immunization, American Board of Allergy, American Academy of Pediatrics and Defeat Autism Now! (DAN!).[67] Tr. at 144-45; Pet. Ex. 47 at 10.

While affiliated with Woodbury Pediatrics, he was the pediatrician for A.K.'s sister and A.K. for the first year of A.K.'s life. Tr. at 149, 154-55; Pet. Ex. 47 at 1-2. In early 2001, he left Woodbury Pediatrics to focus on allergy and immunology. Tr. at 154; Pet. Ex. 47 at 1-2. During this period, however, Dr. Boris still saw [A.K.'s family] socially. Tr. at 149; Pet. Ex. 47 at 2. He and petitioners testified that he administered influenza vaccinations to all family members in early December 2001 after Woodbury Pediatrics ran out of the vaccine.[68] Tr. at 156-57.

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[66] Doctor Boris's wife is a second cousin of [A.K.'s mother's] father. Tr. at 148; Pet. Ex. 47 at 2. When she was a child, [A.K.'s mother] was a patient of Dr. Boris's. Tr. at 148. Doctor and Mrs. Boris socialized with [A.K.'s family], along with A.K.'s grandparents, on multiple occasions (Tr. at 149) and Dr. Boris's wife is A.K.'s godmother (Tr. at 151).

[67] Defeat Autism Now ["DAN!"] physicians subscribe to treatment protocols developed by the Autism Research Institute. These treatments may include chelation and other therapies not vetted as efficacious by controlled clinical studies. *Dwyer*, 2010 WL 892250 at *20, 178.

[68] A. K. received his first vaccination for influenza on November 1, 2001. *See* Pet. Ex. 61, p. 4. According to Pet. Ex. 118, Dr. Boris administered influenza vaccinations to petitioners and both of their children on what appears to be "12/3/01." The date on the form was written over, and may have initially read "12/1/01," which was a Saturday.

Doctor Boris described his practice as "80 percent allergy immunology, and 20 percent developmental" (Tr. at 209) consisting of "30 percent children and 70 percent adults" (Tr. at 210). He testified that he has treated over two thousand patients who have been diagnosed with autism or autistic-like symptoms. Tr. at 146. When he began treating A.K. again in June 2002, he used treatments he employed with other autistic children such as a gluten-free, casein-free diet and chelation of heavy metals. Tr. at 207-209. I regarded Dr. Boris as a treating physician, factual witness, and expert.

b. Doctor Boris's Opinion.

Doctor Boris described his opinion as "personal" indicating it was based on his experience with over two thousand autistic patients. Tr. at 146. Labeling autism's cause as "a biomedical reason secondary to genetics," Dr. Boris testified that he believes autism develops in an individual with a genetic biomedical defect who experiences an immunological insult, "environmentally or otherwise." Tr. at 146. He emphasized that both the genetic defect and environmental trigger were required for autistic symptoms to manifest. Tr. at 147-48.

The only specific cause mentioned by Dr. Boris was a MTHFR deficiency which he claimed was more prevalent in autistic children. He testified that, along with a noted specialist in the field, Dr. Jill James, he found "a higher statistical preponderance of this MTHFR deficiency in autistic children."[69] Tr. at 166-67. He theorized that this deficiency could cause autism or at least make the person who is unable to methylate properly more susceptible. Tr. at 167.

In his declaration, Dr. Boris attributed A.K.'s autism to the two doses of the influenza vaccine he received in November and December 2001. He theorized that A.K. exhibited the phenomena termed challenge-rechallenge when he suffered adverse effects after each dose of the influenza vaccine. Pet. Ex. 47 at 8-9. In making this assertion, Dr. Boris relied on the "close temporal proximity" of A.K.'s symptoms to vaccination. *Id.* at 9. During his testimony, however, Dr. Boris indicated he did not see evidence of challenge-rechallenge in A.K.'s medical records. Tr. at 165. After further questioning from petitioner's counsel, he noted the speech problem reported in A.K.'s medical records in mid-November 2001 as evidence of an adverse effect following the first influenza dose. Tr. at 165; *see also* Pet. Ex. 2, p. 20.

Most of Dr. Boris's testimony concerned the manifestation of A.K.'s symptoms. He maintained that A.K. was "a perfectly developing, normal boy" during his first year of life receiving all childhood vaccinations and suffering only normal childhood illnesses. Tr. at 154-55; *accord.* Pet. Ex. 47 at 2-3. After leaving Woodbury Pediatrics, Dr. Boris still saw A.K. on social occasions and saw no evidence of any developmental issues. He described him as acting like a normal developing child, reacting, and coming when called. Tr. at 155-56, 183-84. In particular, he indicated nothing struck him as abnormal when, as a favor to petitioners, he administered the second dose of the influenza vaccine to A.K. in his office in early December 2001. Tr. at 158; Pet. Ex. 47 at

[69] *See*, Pet. Ex. 55, M. Boris, et al, *Association of MTHFR Gene Variants with Autism,* J. AM. PHYSICIAN & SURGEONS**,** 9(4): 106-08 (2004) filed as Pet. Ex. 55 [hereinafter "Boris, Pet. Ex. 55,"]. This article is addressed in Section VIII.B.2.b, below.

4-5. Doctor Boris could not remember many of the details associated with that visit, but he did remember speaking to each family member including A.K. Although he testified that he did not remember the content of these conversations (Tr. at 191-195), he indicated in his declaration that he remembered [A.K.'s mother] telling him "that she had developed in the previous weeks some concerns about [A.K.'s] speech." Pet. Ex. 47 at 5.

Doctor Boris next saw A.K. at a Hanukkah party at A.K.'s grandparent's house in early December 2001. Tr. at 158-59. After observing A.K. not responding to his name, not speaking, not smiling, and not reacting to others, Dr. Boris told [A.K.'s mother] that A.K.'s behavior was abnormal and recommended she get A.K.'s hearing tested. [70] Tr. at 159. On cross examination, Dr. Boris could not recall many of the details regarding the party and clarified that he did not feel A.K.'s behavior warranted a visit to the hospital. Tr. at 198-200.

Over the next six months, he communicated with [A.K.'s mother] on multiple occasions regarding A.K.'s abnormal behavior. Tr. at 202; Pet. Ex. 47 at 5. After learning A.K.'s hearing test results were normal,[71] Dr. Boris encouraged [A.K.'s mother] to bring A.K. in for an evaluation. Tr. at 202; Pet. Ex. 47 at 5. [A.K.'s mother] did so in late June 2002 and Dr. Boris assessed him as hypotonic and a typical autistic child. Tr. at 160, 202; *see also* Pet. Ex. 47 at 5. Doctor Boris claimed A.K. had indicators of metabolic problems "as well as problems related to immune function and autoimmunity." Pet. Ex. 47 at 5. In his testimony, he cited abnormal lab results, he claimed showed abnormal metabolism and thyroid function. Tr. at 173.

Doctor Boris recommended a gluten-free, casein-free diet for A.K. and began therapies such as chelation, supplements to counteract the effects of his MTHFR gene defect, and autoimmune medications. Tr. at 168-69. He testified that A.K. "did not respond very well to most of the treatments [he] administered." Tr. at 169. During cross examination, Dr. Boris was unable to produce the low immunoglobulin G ["IgG"]) level he thought he had seen prior to administering intravenous immunoglobulin ["IVIG"] treatment to A.K. (Tr. at 215-221) and agreed that "there was no real definite immunoglobulin deficiency" (Tr. at 231).[72] In his declaration, Dr. Boris indicated he continues to treat A.K. "for his developmental problems and various other symptoms." Pet. Ex. 47 at 2.

B. Respondent's Experts.

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[70] He testified that it was Mrs. Boris who noticed A.K.'s behavior and prompted him to make his observations. Tr. 199; Pet Ex. 47 at ¶12.

[71] Doctor Boris did not remember exactly how he learned A.K.'s hearing test results were normal. Tr. at 201.

[72] Doctor Boris originally testified that A.K. did not have an "ordinary common variable immunodeficiency, but [fell] into that category" indicating that he based his assessment on a low IgG level. Tr. at 215. When asked to find this test result, Dr. Boris could point only to a test result showing deficiencies of "the side chains of Kappa Lambda and Kappa Lambda combinations." Tr. at 220 (referencing Pet. Ex. 3, p. 375). He indicated that record was the only one which supported the immunodeficiency he diagnosed in A.K. Tr. at 220-21.

Respondent presented testimony by seven experts. Doctor Judith Miller, a psychologist, addressed the onset and diagnosis of A.K.'s ASD, arguing that the onset of this condition predated the implicated vaccinations. Doctor Kendall Wallace, a biochemist, disputed the laboratory data upon which A.K.'s diagnosis of mitochondrial disorder was based, while Dr. Bruce Cohen, a pediatric neurologist and mitochondrial disease specialist, disputed the overall diagnosis of mitochondrial disorder, including both the laboratory results and clinical symptoms. Doctor Christine McCusker opined, contrary to Dr. Shafrir's theory, that A.K.'s immunological status was normal, and Drs. Gerald Raymond, Dean Jones, and Jeffrey Johnson, with expertise in neurology and genetics, biochemistry, and pharmacology respectively, each countered various aspects of Dr. Deth's presentation.

1. Judith Miller, Ph.D.

a. Doctor Miller's Qualifications.

Doctor Judith Miller received an M.S. in Psychology from the University of Utah in 1996, followed by a Ph.D. in Clinical Child and Family Psychology from the same institution four years later in 2000. Tr. 849; Respondent's Exhibit ["Res. Ex."] PP at 1. After graduation, she completed a postdoctoral fellowship at the Emery Autism Resource Center at Emory University in Atlanta, Georgia. *Id*. Thereafter, Dr. Miller served as an assistant professor of Psychiatry at the University of Utah from 2002 to 2008 and as an associate professor from 2008 to 2010, before moving to her current position with the Children's Hospital of Philadelphia ["CHOP"]. Tr. 849-50; Res. Ex. PP at 1.

Currently, Dr. Miller is the Clinical Training Director and Co-Director at the Center for Autism Research at CHOP. Tr. 847-48; Res. Ex. PP at 1. In that capacity she oversees an assessment clinic that completes diagnostic assessments of between 15-20 children per week who are suspected of having autism. Tr. 847. In addition, Dr. Miller serves as Autism Director for Leadership Education in Neurodevelopment Disabilities ["LEND"], an interdisciplinary training program at CHOP, and as Planning Manager for CHOP's Autism Integration Committee. Tr. 848-49; Res. Ex. PP at 1.

Doctor Miller is licensed in both Utah and Pennsylvania. Res. Ex. PP at 2. She is a founding member of the Autism Council of Utah and maintains membership in both the American Psychological Association and the International Society for Autism Research. Tr. 850-52; Res. Ex. PP at 2. In addition to being a regular reviewer for PEDIATRICS and the JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY (*id.*), her curriculum vitae listed 29 peer reviewed research publications which deal almost exclusively with subjects relating to autism spectrum disorders. Res. Ex. PP at 4-7. She is also a frequent lecturer. Tr. 851-52; Res. Ex. PP at 3-4.

b. Doctor Miller's Opinion.

Doctor Miller testified at length regarding the diagnosis and assessment of autism spectrum disorders.[73] Tr. 860-95. In particular, she described the proper

[73] In their post-hearing brief, petitioners argued that Dr. Miller's testimony in this case should be stricken in its entirety because it lacked foundation. *See*, Pet. Post Hearing Brief (ECF No. 297) at 31, n.17. I

application of standard diagnostic tools such as the Autism Diagnostic Interview ["ADI"] and Autism Diagnostic Observation Schedule ["ADOS"], which correspond to the Diagnostic and Statistical Manual of Mental Disorders ["DSM"] criteria for autism spectrum disorders.[74] Tr. 857-95. Doctor Miller concluded that A.K. met 11 of the 12 DSM-IV criteria, far more than necessary, for diagnosing ASD.[75] Tr. 937-38.

Doctor Miller opined that the early signs and symptoms of A.K.'s autism could be observed long before he received either of his influenza vaccinations and that he did not experience any regression after them.[76] Tr. 939; Res. Ex. OO at 2. Specifically, Dr. Miller noted that there were references in A.K.'s early pediatric record which suggested early signs of autism that were not recognized as such at the time.[77] Tr. 928-37. She testified at length about signs of ASD in video footage of A.K. as early as 14 months of age. Tr. 896-919. Doctor Miller stressed that, even if the videos occasionally showed "good" moments, "based on the totality, he has extremely few moments that look good, and at his age and across the number of hours of video we have, we should see hundreds of examples of that kind of moment that we saw maybe two or three of." Tr. 1041-42.

Significantly, Dr. Miller specifically disagreed with Dr. Shafrir's contention that the video footage in this case showed a dramatic change in A.K.'s behavior between November 9 and 10, 2001. Tr. 907. Doctor Miller described distraction, limited social interaction, and object focus during the November 9 footage, which she argued were "the same exact behaviors" that A.K. demonstrated in the video footage of the next

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ruled against petitioners on this issue. *See* Motions Ruling, filed on Sept. 28, 2015 (ECF No. 319), at Section II.F.4.

[74] At the time of Dr. Miller's testimony (April 25, 2013), the DSM was in its fourth edition ["DSM-IV-TR"]. Doctor Miller noted in her testimony, however, that the fifth edition of the DSM ["DSM-V"] was soon to be released. Tr. 889. Doctor Miller explained the changes coming in the DSM-V (Tr. 889-95) and opined that A.K. met the criteria for ASD under either version (Tr. 895-96).

[75] According to Dr. Miller, A.K.'s symptoms included: limited eye contact, lack of facial expressions or gestures to communicate, failure to initiate or share social interaction, appearing as if "in his own world," not responding to or having emotional reciprocity, delayed language, lack of conversational approximation, having repetitive sounds, lack of pretending or imitating, circumscribed interest, mannerisms such as ear holding or hand flapping, and preoccupation with objects or parts of objects. Tr. 937-38. Doctor Miller did not observe any rigid routines, which is the one DSM-IV criteria she noted was absent. Tr. 938.

[76] Although there are parental reports of regression of certain skills in the medical records, Dr. Miller argued that there was no indication that A.K. ever developed these skills "to any kind of significant level" such that they could be considered to have been lost and noted that these regressions were first documented in the records at age 3 years and 5 months. Tr. 938-39; Res. Ex. OO at 2.

[77] Doctor Miller did not fault A.K.'s pediatricians for not recognizing these signs. Rather, her critique spoke to the state of the field of autism assessment and diagnosis during the period at issue in this case. That is, she argued that the available screening techniques have improved significantly since that time. Tr. 1036-38, 1047-50. At the time A.K. was diagnosed, children were not routinely referred for autism evaluations until about three or four years of age. Tr. 1048. Now, however, reliable and stable diagnosis of autism is possible at two years of age. Tr. 870-71. Much of the change has to do with a better understanding of social and non-verbal communication skills which should develop before speech. Tr. 871-72.

day,[78] Tr. 904-07, albeit that the November 10 video was a more dramatic presentation of A.K.'s relative abnormality in behavior given that, due to the setting, A.K.'s behavior stood out starkly when compared to the other children.

2. Kendall Wallace, Ph.D.

a. Doctor Wallace's Qualifications.

Kendall Wallace, Ph.D., is a professor of biochemistry and molecular biology at the University of Minnesota School of Medicine. Tr. 1057; Res. Ex. VV at 1. He earned a B.S. in Biochemistry from Michigan State University in 1975, followed by an M.S. and Ph.D. in Physiology from the same university in 1977 and 1979 respectively. Tr. 1056; Res. Ex. VV at 1. From 1979 to 1981, he completed a two year postdoctoral fellowship in toxicology at the University of Iowa. *Id*.

Doctor Wallace has been a professor at the University of Minnesota at Duluth since 1981. Tr. 1056; Res. Ex VV at 1. Prior to joining the Department of Biochemistry and Molecular Biology in 1996, he was a professor of pharmacology and director of graduate studies for the school's toxicology program. Ex VV at 1. He was also director of the school's Chemical Toxicology Research Center. *Id*. In his current position, Dr. Wallace teaches courses in mitochondrial biology and molecular regulation, cardiac pharmacology and clinical toxicology, as well as conducting clinical training on differential diagnosis. Tr. 1057.

Doctor Wallace's primary role, however, is laboratory-based research. Tr. 1059. He has published 100 peer-reviewed publications, including five book chapters. Tr. 1059-60; Res. Ex. VV at 17-23. Doctor Wallace indicated that the majority of his publications were based on his own laboratory research relating to mitochondrial biology and toxicology. Tr. 1060. He is also a reviewer for a number of academic journals, including the JOURNAL OF PHARMACOLOGY and EXPERIMENTAL THERAPEUTICS, CANCER RESEARCH, MITOCHONDRION, TOXICOLOGICAL SCIENCES, and TOXICOLOGY AND APPLIED PHARMACOLOGY. *Id*. He has been a co-editor of the journal TOXICOLOGY since 2001. Tr. 1060; Res. Ex VV at 9.

Doctor Wallace is board certified in toxicology by the American Board of Toxicology and is a fellow of the Academy of Toxicological Sciences. Tr. 1061; Res. Ex VV at 7. He is a member and past president of both the Society of Toxicology and the Mitochondrial Research Society. Tr. 1061; Res. Ex. VV at 7-8.

b. Doctor Wallace's Opinion.

Doctor Wallace opined that the metabolic, biochemical and genetic laboratory test results generated in A.K.'s case did not support a diagnosis of mitochondrial

[78] Doctor Miller also disagreed with Dr. Shafrir's broader criticism of using videos to diagnosis ASD. She testified that studies have shown that home video footage can be used to assess a child in his or her home environment to identify early signs of autism that are more difficult to observe clinically. Tr. 919-21. She also noted that this is a practice currently used by clinicians. Tr. 921. In this case, Dr. Miller noted that although the medical records do include some "red flags," the nature of developmental screening at that time was such that A.K.'s social behaviors prior to age two were not well documented. Tr. 921-22. She observed that the videos illustrated behaviors not noted in the medical records. Tr. 922.

disorder.[79] Tr. 1064; Res. Ex. UU at 19. Specifically, Dr. Wallace reviewed the findings of Dr. John Shoffner's 2008 evaluation of A.K., *see* Pet. Ex. 32, and concluded that "the original diagnosis of a Complex I defect by Dr. Shoffner on November 20, 2008, was, in my opinion, tentative and contingent on confirmation by subsequent genetic tests, all of which were negative and not supportive of the original diagnosis."[80] Res. Ex. UU at 19; Tr. 1115.

After reviewing Dr. Shoffner's enzymology results, Dr. Wallace contended that the raw data for the two Complex I enzyme assays presented should have been normalized over citrate synthase, and that when that calculation was performed, the assay results fell within the normal range to a 95% confidence level.[81] Tr. 1106-07. Doctor Wallace also noted that Dr. Shoffner further supported his Complex I finding by citing "correlative protein chemistry changes."[82] Tr. 1113; Pet. Ex. 32, p. 3. He explained that the protein chemistry changes were tested using a method called "Western blot" and argued that, although Dr. Shoffner listed a "possible" decrease in the ND6 subunit within Complex I, the actual numbers generated by the Western blot support a "normal" finding for ND6. Tr. 1077, 1112. Doctor Wallace further noted that Dr. Shoffner's interpretation of the ND6 finding as potentially decreased was not supported by subsequent genetic testing which found no mutation to the ND6 gene. Tr. 1113-15.

Moreover, even taking the reported enzymology values at face value, Dr. Wallace argued that Dr. Shoffner's respirometry results—a measure of the functioning of the complete respiratory chain rather than a single enzyme complex—were equivocal, meaning the results were insufficient to demonstrate an abnormality. Tr. 1110-11. Doctor Wallace contended that this finding cast doubt on Dr. Shoffner's diagnosis, even in the face of a depressed Complex I finding, because the respirometry results showed that the mitochondria were functioning "just fine" overall and that the

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[79] Doctor Wallace was careful to note that he is not a physician or a clinician and that his opinion does not extend to A.K.'s overall clinical diagnosis. Tr. 1072.

[80] Significantly, Dr. Wallace indicated that he was not challenging the underlying data gathered by Dr. Shoffner. Tr. 1115.

[81] Doctor Wallace acknowledged, as Dr. Kendall asserted, that there was no agreement among laboratories regarding the proper interpretation of enzyme assays. Tr. 1120-22. He did not know why Dr. Shoffner chose not to normalize over citrate synthase and characterized it as "his professional judgment." Tr. 1125. Nonetheless, Dr. Wallace was clearly of the opinion that normalizing the Complex I results over citrate synthase was a superior approach. He argued that because Complex I enzymes are the most unstable enzymes, normalization over citrate synthase is an important means to narrow the resulting variations among different laboratories when handling the enzyme. Tr. 1102-04. To the extent that he acknowledged that citrate synthase is also difficult to accurately measure, he noted that Complex I can also be normalized over Complex II as an alternative approach. Tr. 1104-05. Significantly, Dr. Wallace further noted that the Bernier criteria upon which Dr. Kendall relied (*see, e.g.,* n. 42, *supra*.) recommend normalizing Complex I assays over either citrate synthase or Complex II. Tr. 1100-01. He contended that A.K.'s results would remain normal within a 95% confidence level if normalized over Complex II rather than citrate synthase. Tr. 1108-09.

[82] Additional protein chemistry findings relating to Complexes II and IV were reported as "reduced" (Pet. Ex. 32, p. 36), but Dr. Shoffner did not report any correlating Complex II or IV defects among his enzymology results (Pet. Ex. 32, p. 35).

respirometry results were consistent with the blood, urine and cerebral spinal fluid metabolic profile. *Id*. Doctor Wallace also observed that Dr. Shoffner's own findings indicated that blood, urine, and cerebral spinal fluid tests showed metabolites that were within a normal range.[83] Tr. 1097-98.

To the extent Dr. Kendall pointed to instances of elevated lactic acid as an indication of mitochondrial disorder, Dr. Wallace noted that although there was one instance of elevated lactic acid on one occasion within A.K.'s medical records, testing on five additional occasions resulted in normal or below normal lactic acid.[84] Tr. 1116. Doctor Wallace therefore argued that the weight of the evidence was against a finding of elevated lactic acid. *Id*. He also pointed out that A.K.'s medical records included four reports showing normal urine organics and nine reports of normal acylcarnitines. Tr. 1118-19. He disputed Dr. Kendall's contention that AST and ALT, bio-indicators of liver dysfunction, could be considered evidence of a mitochondrial disorder. Tr. 1116-17.

3. Bruce Cohen, M.D.

a. Doctor Cohen's Qualifications.

Bruce Cohen, M.D., earned his undergraduate degree in Chemistry from Washington University in St. Louis, Missouri, in 1978 and his M.D. at the Albert Einstein College of Medicine at Yeshiva University in New York, New York, in 1982. Res. Ex. TT at 1; Tr. 1134. After medical school, Dr. Cohen completed both a pediatric residency and a pediatric neuro-oncology fellowship at the Children's Hospital of Philadelphia as well as a pediatric neurology residency at Columbia Presbyterian Medical Center. Res. Ex. TT at 1.

Currently, Dr. Cohen serves as the director of neurology at the Children's Hospital Medical Center of Akron and as a professor of pediatrics at Northeast Ohio Medical University where he specializes in mitochondrial disease, brain tumors, and chemotherapy complications. Res. Ex. TT at 2; Tr. 1134-35. His practice is "heavily weighted towards mitochondrial disease," an area in which he first became interested in 1983. Tr. 1135-36. He estimated that he has evaluated over 2,000 patients with suspected mitochondrial diseases. Tr. 1137.

Doctor Cohen is also a member of the medical consulting staff for the department of pediatrics at Hillcrest Hospital, part of the Cleveland Clinic Health System. Res. Ex. TT at 2. Previously, Dr. Cohen served as staff physician for the Neurological Institute of the Cleveland Clinic and as chairman of the Cleveland Clinic's pediatric neurology section. *Id*. He was a professor at Case Western Reserve University for approximately 22 years. Tr. 1139-40; Res. Ex. TT at 2.

Doctor Cohen is licensed to practice medicine in the state of Ohio. Res. Ex. TT at 2. He is a fellow of the National Board of Medical Examiners and the American

[83] The results were characterized by Dr. Shoffner as "unremarkable." Pet. Ex. 32, p. 1.

[84] Doctor Wallace noted that elevated lactate—or lactic acidosis—can be a marker for a number of metabolic disorders. He also stressed that its instability makes accurate measurement difficult. For that reason, he noted that elevated lactic acid was normalized by reporting it as a ratio to pyruvate. Tr. 1115-16.

Board of Psychiatry and Neurology with special competence in child neurology. Res. Ex. TT at 2; Tr. at 1134. He is a member of the American Academy of Neurology, the Child Neurology Society, Professors of Child Neurology, the Mitochondrial Research Society, and the Mitochondrial Medicine Society. Res. Ex. TT at 3; Tr. 1141-42. He is a past president of both the Professors of Child Neurology and the Mitochondrial Medicine Society. *Id*. He has served on a multitude of committees and advisory groups both nationally and at the Cleveland Clinic and is on the editorial board of seven academic journals, including NEUROLOGY and MITOCHONDRIAN. Res. Ex. TT at 3-5. Doctor Cohen listed numerous peer-reviewed and frequently cited articles on his curriculum vitae, as well as 29 peer-reviewed book chapters and an edited journal volume. Res. Ex. TT at 33-40. He co-authored several of the medical journal articles extensively discussed in this case.

b. Doctor Cohen's Opinion.

Like Dr. Kendall, Dr. Cohen acknowledged that there was disagreement among experts regarding the diagnosis of mitochondrial disorders. Res. Ex. SS at 13. He agreed with her that there was no single test to confirm a mitochondrial diagnosis and that such diagnoses are made in the judgment of clinicians looking at a number of factors. Tr. 1179-80, 1319-23. He cited the Bernier criteria, however, as an authoritative standard that brings some certainty to the analysis and stressed that a firm diagnosis requires "a lot" of evidence supported by a patient's medical records. *Id*. Applying these standards, Dr. Cohen disagreed with Dr. Kendall's ultimate conclusion that A.K. had a mitochondrial disorder, and further disagreed that A.K.'s influenza vaccinations would have aggravated that disorder.[85] Res. Ex. SS at 16; Tr. 1147-48, 1220.

Doctor Cohen disagreed with both Dr. Kendall and Dr. Shafrir's assessments of A.K.'s clinical history. Res. Ex. SS at 15-16. He argued that A.K.'s clinical course was consistent with the classic pattern of autism and was not consistent with mitochondrial encephalopathy. Res. Ex. SS at 9-10. In particular, he noted that the video footage in evidence in this case showed signs of autism as early as 15 or 16 months of age and did not support parental reports of regression. Res. Ex. SS at 6, 8; Tr. 1383-87. He further pointed out that the records of A.K.'s medical treatment in the months immediately following A.K.'s vaccinations (*i.e.,* November and December of 2001) did not include any expressing of concern regarding regression and did not reflect a course of treatment consistent with such a concern.[86] Moreover, Dr. Cohen contended that

[85] To the extent petitioners argued that A.K.'s medical records showed opinions by other mitochondrial specialists, including Drs. Korson, Sims and Alvarez, Dr. Cohen argued that his opinion should still control. Tr. 1330. He said that there is insufficient evidence to show that either Drs. Sims or Alvarez conducted any independent assessment of A.K. Tr. 1222-23, 1323. Rather, he contended they simply reiterated Dr. Shoffner's conclusion, which he challenged. *Id.* He also argued that, although Dr. Korson did a thorough exam of A.K., his report did not reflect any analysis of A.K.'s medical records or the video footage filed in this case. Tr. 1326-27. For those reasons, Dr. Cohen argued that his opinion is better informed. Tr. 1330.

[86] More specifically, Dr. Cohen contended that a sudden and complete loss of speech such as petitioners are alleging would constitute a medical emergency for which immediate diagnostic tests such as MRI, EEG or spinal tap would be necessary. Tr. 1154-55, 1369-70. Doctor Cohen indicated that possible

A.K.'s clinical features of fatigue, autism, developmental delay, and gastrointestinal problems—relied upon by Dr. Kendall in her diagnosis—were too non-specific, absent additional findings, to be indicative of mitochondrial disorder.[87] Tr. 1182-91. He also questioned the validity of notations indicating that A.K. experienced autonomic dysfunction and hypotonia. Tr. 1190-91, 1193-94.

Like Dr. Wallace, Dr. Cohen also challenged the significance of Dr. Shoffner's enzymology results and disputed his resulting diagnosis of mitochondrial encephalomyopathy.[88] Tr. 1220-21. Echoing Dr. Wallace, Dr. Cohen asserted that normalizing the Complex I assay result over citrate synthase was preferable and noted that when that calculation was performed, the results were normal. Res. Ex. SS at 13; Tr. 1206-12. He additionally noted that the normal finding for the combined Complex I and III measurement cast significant doubt on the separate Complex I finding, Res. Ex. SS at 13; Tr. 1212, as it was unlikely the combined finding would be normal where one of its components was decreased. Moreover, he stressed that the combined Complex I and III measure was considered a more robust finding and is more commonly used. *Id*. Taking the rest of Dr. Shoffner's findings into account, which were either normal or equivocal, Dr. Cohen argued that a diagnosis could not be made based on the Complex I finding alone, since it represented incongruent data at best. *Id*. He stated that the test results for lactic acid, AST, or ammonia, conducted on other occasions did not have any diagnostic significance. Tr. 1197-1206.

Doctor Cohen disagreed with the assertions by both Dr. Kendall and Dr. Shafrir that A.K.'s influenza vaccine could be linked to a regression through several papers.[89] Doctor Cohen argued that these papers did not stand for the proposition that vaccines

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causes for abrupt speech loss could include stroke, seizure, or meningitis. Tr. 1369-70. Doctor Cohen further testified that, even if one were to consider a regression occurring over the course of two months, a full battery of tests would still be advisable for detection of other disorders, such as Landau-Kleffner Syndrome, which also result in lost speech. Tr. 1155-56. Doctor Cohen noted in his expert report that those presenting with mitochondrial regression often present with acute or sub-acute loss of function, ataxia, blindness, loss of speech, and other symptoms that "result in a shocking change to parents and physicians." Res. Ex. SS at 9-10. Doctor Cohen indicated, however, that such presentations typically result in emergency evaluation, including neuroimaging. Res. Ex. SS at 10.

[87] Doctor Cohen claimed that the type of GI distress usually associated with mitochondrial disorders was a type of non-physical intestinal blockage called a "pseudo-obstruction," which A.K. did not have. Tr. 1186-88. Although he indicated that some mitochondrial patients do exhibit constipation, Dr. Cohen argued that a course of alternating diarrhea and constipation, such as A.K. experienced, would not be diagnostic of a mitochondrial disorder absent other classic mitochondrial disorder findings such as large fiber neuropathy, cardiac conduction defect, or other clinical or laboratory findings not present in A.K.'s history. Tr. 1188, 1303-04. Doctor Cohen opined that A.K.'s GI distress was more likely linked to his autism than to any mitochondrial disorder. Tr. 1220-21.

[88] To the extent Dr. Shoffner's assessment is based on his clinical summary in addition to his own test results, Dr. Cohen noted that there is no evidence to suggest Dr. Shoffner conducted any independent clinical evaluation. Rather, Dr. Cohen argued that it appears that Dr. Shoffner reported a clinical summary provided to him by Dr. Boris. Tr. 1220-21. In any event, Dr. Cohen stated, in essence, that it was not a lab technician's place to make an overall clinical diagnosis. Tr. 1221-22; Res. Ex. SS at 12.

[89] Referring to the Shoffner, Res. Ex. MM, Tab 16; Weissman, Pet. Ex. 39, R. Hass, *Autism and Mitochondrial Disease*, Dev. Disabil. Res. Rev., 16:144-53 (2010), filed as Pet. Ex. 63, Ref. 17 and as Res. Ex. MM, Tab 13 [hereinafter "Hass, Pet. Ex. 63, Ref. 17"]; and Poling, Res. Ex. MM, Tab 14, papers.

incited mitochondrial regression that petitioners' experts contended they do, and that even if they did, the studies were not good evidence of such a link, because they were not controlled studies and had other methodological flaws.[90] Res. Ex. SS at 15; Tr. 1226-30, 1356-59.

4. Christine McCusker, M.D.

a. Doctor McCusker's Qualifications.

Christine McCusker, M.D., received her M.S. and her M.D. from McMaster University in Hamilton, Ontario, in 1988 and 1993, respectively. Res. Ex. RR at 1; Tr. 1396. From 1993 to 1999 she completed a residency training program in pediatrics and a clinical fellowship in allergy and immunology at McGill University in Montreal, Quebec. Res. Ex RR at 2; Tr. 1396.

Currently, Dr. McCusker is an associate professor of allergy and immunology in the department of Pediatrics at the Montreal Children's Hospital and McGill University. Res. Ex. RR at 3; Tr. 1396-97. She is also a research director for Meakins-Christie Laboratories and a staff physician and director of the Clinical Immunology Laboratory at Montreal Children's Hospital. Res. Ex. RR at 4; Tr. 1397. Additionally, Dr. McCusker serves on a number of committees, including the Hereditary Angioedema Society and Primary Immunodeficiency Network, the Canadian Immunodeficiency Patient Organization Scientific Advisory Committee, and the Examination Committee for Allergy and Immunology of the Royal College of Physicians and Surgeons of Canada. Res. Ex. RR at 13. She is Co-Chair of the Immunology Interest Section of the Canadian Society for Allergy and Clinical Immunology. *Id*.

As well as being licensed by the Medical Council of Canada, Dr. McCusker is board certified by the American Board of Pediatrics. Res. Ex. RR at 2; Tr. 1397. She is a Fellow of the Royal College of Physicians and Surgeons of Canada, recognized in pediatrics as well as allergy and immunology. Res. Ex. RR at 3. She is licensed by the Collège des Médecins du Québec. Res. Ex. RR at 2-3; Tr. 1397. Doctor McCusker is also a member of the Canadian Medical Protective Association, the Federation of Medical Specialists of Quebec, the Quebec Allergy and Immunology Association, and the Clinical Immunology Society. Res. Ex. RR at 14.

In addition to her clinical and teaching duties, Dr. McCusker is an active researcher, listing numerous research grants on her curriculum vitae as well as three pending patent applications. Res. Ex. RR at 17-19. Doctor McCusker has published 25

[90] Doctor Cohen's testimony regarding methodological flaws of the Weissman article was particularly noteworthy in that he was a listed author of that study. Tr. 1227-29. Among Dr. Cohen's concerns regarding that paper are the fact that the authors did not know how many patients were ultimately screened to arrive at the study's population, leaving them without any "denominator" to assess the significance of their findings. Tr. 1357-59. He was also concerned that some potential subjects were screened out of the study based on the results of chromosomal microarray, but that this test was not consistently conducted on all of the subjects. Tr. 1356-57. Perhaps most significantly, Dr. Cohen indicated that he objected to the inclusion of the Poling case within the report. *Id*. He indicated that this objection resulted in negotiated language among the authors stating that the Poling case did not prove causation. He further argued that this article does not otherwise speak to vaccination, as the focus was a cohort analysis regarding mitochondrial disorders and autism. Tr. 1227-29, 1356-57, 1379-80.

articles and one book chapter on topics relating to allergy and immunology. *Id*. at 19-22. She is also a reviewer for a number of academic journals, including the JOURNAL OF IMMUNOLOGY, the JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, CLINICAL AND EXPERIMENTAL ALLERGY, CLINICAL AND EXPERIMENTAL IMMUNOLOGY, and IMMUNOBIOLOGY. Tr. 1400; Res. Ex. RR at 12.

b. Doctor McCusker's Opinion.

Doctor McCusker opined, based on a review of A.K.'s medical history,[91] that there is no evidence that A.K. had any immune disorder or deficiency. Tr. 1401, 1426-27. Rather, contrary to the opinions of Drs. Boris and Shafrir, she opined that A.K. has a normal immune system. Tr. 1426-27. She explained that A.K. had only "usual childhood illnesses" during his first two years of life, from which he recovered well, and that the isolated finding of antibodies, such as the myelin basic protein antibodies found in A.K., did not support any finding of immune dysregulation in the absence of correlating clinical symptoms. Res. Ex. QQ at 3; Tr. 1402, 1411, 1439-40. She also disputed that there was any evidence to suggest that A.K. had an abnormal adverse reaction to his influenza vaccines or that these vaccines contributed to his developmental delays.[92] Res. Ex. QQ at 3-5; Tr. 1411-12, 1426-27.

Doctor McCusker testified that the laboratory results relied upon by Dr. Boris to diagnose A.K. with common variable immunodeficiency ["CVID"] did not support that diagnosis, as they showed normal immunoglobulin levels. Tr. 1404 (evaluating Pet. Ex. 3, p. 375). She further opined that, even if A.K. did have low immunoglobulin, a diagnosis of CVID also required a corresponding functional deficiency, which A.K did not demonstrate. *Id*. That is, a definitive feature of CVID is that patients cannot produce antibodies when their immune system is stimulated. A.K., however, did form antibodies, as evidenced by the testing of the response to his mumps vaccine.[93] Tr. 1403-04, 1406.

In addition, Dr. McCusker disputed both Dr. Shafrir's contention that A.K. had autoimmune hypothyroidism as well as his assertion that such a condition was indicative of an abnormal immune system. Res. Ex. QQ at 3; Tr. 1407-08, 1410-11. Doctor McCusker explained that autoimmune hypothyroidism occurs where the formation of autoantibodies against the thyroid gland prevent the production of thyroid hormones such as "T4". Res. Ex. QQ at 3; Tr. 1407. Looking at A.K.'s lab results, Dr. McCusker acknowledged that A.K. did show autoantibodies, but noted that his thyroid

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[91] Doctor McCusker did not review the video footage filed in this case. Tr. 1401.

[92] Although Dr. McCusker acknowledged that [A.K.'s mother] reported that A.K. experienced a low grade fever following his influenza vaccination, she stressed that there is no indication of any abnormal immune response. Res. Ex. QQ at 4; Tr. 1412. She testified petitioners' reliance on the immunological concept of challenge-rechallenge and the so called "triple hit" theory to explain how A.K.'s vaccines could have led to developmental delays was misplaced. Res. Ex. QQ 3-5; Tr. 1419-26, 1440-41.

[93] Although Dr. McCusker acknowledged that A.K.'s test results were equivocal with regard to his immunity to measles and mumps, she noted that he did not receive the recommended second "booster" vaccine against the diseases. Tr. 1406. Doctor McCusker stated that although a booster could have improved his protection against these diseases, A.K.'s results show that he *did* make antibodies in response to vaccines. Tr. 1407.

function tests showed levels of T4 and TSH that were both normal.[94] *Id*. She argued that absent an abnormal T4 finding, A.K.'s tests did not support a diagnosis of autoimmune hypothyroidism. Tr. 1408. Moreover, occurring at a rate of eight per one thousand males per year, Dr. McCusker stated that autoimmune hypothyroidism is "not an uncommon problem" and is not an indication of general immune dysfunction. Tr. at 1411; Res. Ex. QQ at 3.

5. Gerald Raymond, M.D.

a. Doctor Raymond's Qualifications.

Doctor Gerald Raymond earned his undergraduate degree in biology from Fairfield University in 1980. He subsequently earned an M.D. from the University of Connecticut in 1984 and completed postdoctoral training from 1984 to 1993, including an internship and junior residency in pediatrics at Johns Hopkins Hospital and a neurology residency at Massachusetts General Hospital. He also completed fellowships in developmental neuropathology and genetics and teratology. Res. Ex. NN at 1; Tr. 1442-43.

Currently, Dr. Raymond is director of pediatric neurology and a professor of neurology at the University of Minnesota School of Medicine in Minneapolis where he maintains a clinical practice devoted to neurology and genetics. Tr. 1443-46; Res. Ex. NN at 1. Prior joining that faculty, he was a professor of neurology at Johns Hopkins University, director of neurogenetics research at the Kennedy Krieger Institute, and a staff physician in pediatrics and neurology at Johns Hopkins Hospital. Res. Ex. NN at 1-2; Tr. 1443.

Doctor Raymond is licensed to practice medicine in both Minnesota and Maryland and was previously licensed to practice in Massachusetts. Res. Ex. NN at 11. He is board certified in both clinical genetics and neurology, with special qualifications in child neurology, and was formerly board certified in pediatrics. Res. Ex. NN at 11; Tr. 1444. Doctor Raymond is a reviewer for a number of peer-reviewed academic journals, including the ANNALS OF NEUROLOGY, NEUROLOGY, LANCET, TERATOLOGY, the AMERICAN JOURNAL OF HUMAN GENETICS, and the AMERICAN JOURNAL OF MEDICAL GENETICS. Res. Ex. NN at 12; Tr. 1446. His curriculum vitae listed 98 peer-reviewed original articles, one book, and 16 book chapters. Res. Ex. NN at 2-6, 9-11.

b. Doctor Raymond's Opinion.

Doctor Raymond's opinion in this case focused principally on the epigenetic aspects of Dr. Deth's theory as well as the significance of A.K.'s MTHFR mutation, which was raised by both Dr. Deth and Dr. Shafrir.[95] Although it is undisputed that A.K.

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[94] Doctor McCusker did note that A.K. occasionally showed mildly elevated TSH. She indicated, however, that such mild elevations could happen transiently and were not concerning unless accompanied by elevated T4. She explained that TSH is a signal for the production of more thyroid hormone. Tr. 1407-08.

[95] Doctor Raymond's report was the first to be filed by respondent as among respondent's testifying experts. Tr. 1447-49. His report also spoke to broader issues in this case that were subsequently addressed by other of respondent's experts and which were not addressed during his direct examination.

has two variants in his gene coding for MTHFR, a heterozygous C677T alteration and a heterozygous A1298C alteration, Dr. Raymond disputed that these gene variants could have had the impact on A.K.'s condition that petitioners claim. Pet. Ex. 3, p. 301; Tr. 1449, 1454-57. He also contended that Dr. Deth's theory was implausible and premised on a fundamentally flawed understanding of the different ways in which epigenetic changes manifest in prenatal and postnatal development. Tr. 1460, 1464-69, 1472-73.

According to Dr. Raymond, the specific MTHFR alterations at issue are known as "polymorphisms," because they are found in a significant portion of the general population. Tr. 1450. Most people who have these polymorphisms have no issues related to the condition and are "perfectly fine." Tr. 1452-53. Among those who are impacted, the chief concern is a slowing of metabolic processes resulting in elevated homocysteine. Res. Ex. MM at 4; Tr. 1453-55. He explained that these metabolic consequences appear among those with nutritional folate deficiency and can ultimately lead to vascular health concerns later in life, but these polymorphisms are not linked to autism. Tr. 1455-57. Although Dr. Raymond acknowledged that some medical literature has posited an association between the MTHFR polymorphisms and conditions such as autism, Down syndrome and other developmental delays, these studies have been "all over the place" and did not present reliable evidence of a causal relationship. Res. Ex. MM at 5; Tr. 1456-57. Doctor Raymond also noted that the reports were only looking at prenatal embryonic development. *Id*.

Doctor Raymond had very definite and focused disagreements with Dr. Deth's presentation on epigenetics. Doctor Deth contended that early childhood is an important period for epigenetic regulation, but Dr. Raymond noted that Dr. Deth ignored the critical distinction between pre- and postnatal development.[96] Doctor Raymond explained that during early prenatal development, epigenetic activity occurs in the context of cell differentiation, regulating the process by which early cells begin to create different kinds of tissue. Tr. 1461-64. At that stage, epigenetic changes resulting from methylation can be carried on by the further replicating cells. *Id*. Postnatally, however, when epigenetic regulation acts on non-dividing cells, the changes are not carried forward as they would have been during early prenatal development. Tr. 1464-68. Doctor Raymond therefore asserted that Dr. Deth's theory was implausible, because the type of disruption in methylation Dr. Deth described—occurring at around 2 years of age on non-dividing neural cells—would have to be systematic to have such a significant impact to the brain. *Id*. Doctor Deth could not account for the "impossible" chance occurrence necessary for the methylation disruption he posits to impact a specific phenotype in the context of that type of systemic whole body deficit. Tr. 1467-68. That

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My summary of his opinion will address his more focused testimony. I do note, however, that Dr. Raymond indicated that despite the apparent reduction in the scope of his opinion, he still maintained that Dr. Deth's theory overall was "a striking oversimplification of a number of biochemical pathways" and that he had "numerous issues" with Dr. Deth's theory aside from its epigenetic aspects. Tr. 1474-75.

[96] Although Dr. Raymond agreed that epigenetic regulation occurs throughout life, he noted that epigenetic activity is critically important from conception through the second trimester of gestation. Tr. 1457-59.

is, Dr. Raymond asserted that Dr. Deth could not explain how his theory would result in autism, and only autism, without impacting other body tissues.[97] Tr. 1468-69.

6. Dean Jones, Ph.D.

a. Doctor Jones' Qualifications.

Dean Jones, Ph.D., is a professor at Emory University in the department of medicine with appointments in the departments of biochemistry, ophthalmology, and pediatrics. Res. Ex. YY at 1; Tr. 1610. In addition, he is the director of the Emory Clinical Biomarkers Laboratory and co-director of the Center for Clinical and Molecular Nutrition. Res. Ex. YY at 1. Doctor Jones focuses his research on two areas—personal medicine and oxidative stress—and considers himself an expert in oxidative stress. Tr. 1611-12. He listed a number of currently active research grants on his curriculum vitae, including three National Institutes of Health ["NIH"] grants for research on reactive oxygen species and antioxidants. Res. Ex. YY at 3; Tr. 1610. He has been affiliated with Emory University since 1979. Res. Ex. YY at 37; Tr. 1608.

Doctor Jones earned his undergraduate degree with majors in chemistry and biochemistry from the University of Illinois Champaign-Urbana, in Urbana, Illinois, in 1971. Res. Ex. YY at 2; Tr. 1608. Five years later, he earned a Ph.D. in biochemistry at the Oregon Health Sciences University in Portland, Oregon. *Id*. Thereafter, Dr. Jones completed a postdoctoral fellowship in nutritional biochemistry at Cornell University in Ithaca, New York. *Id*. He spent a further two years as a guest scientist in biochemical toxicology at the Korolinksa Institute department of forensic medicine in Stockholm, Sweden, and as a postdoctoral research associate in physiological chemistry at the Oregon Health Sciences University School of Medicine. *Id*.

Doctor Jones is a member of several academic societies, including the Society of Toxicology, the Society for Free Radical Biology and Medicine, and the Association for Advancement of Science. Res. Ex. YY at 2. He serves as a peer reviewer for a number journals, and provides special expertise in oxidative stress as a member of the National Institutes of Health Basic Mechanisms of Center Therapeutics Study Section. Res. Ex. YY at 37; Tr. 1609. He listed 270 peer-reviewed original publications on his curriculum vitae, over half of which he estimated are on subjects relating to oxidative stress, as well as numerous reviews and book chapters. Res. Ex YY at 11-36; Tr. 1612.

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[97] Doctor Raymond argued in particular that Dr. Deth's reliance on a recently published medical journal article was misplaced. *See* C. Wong, et al., *Methylomic analysis of monozygotic twins discordant for autism spectrum disorder and related behavioral traits*, MOL. PSYCHIATR., 23 April 2013 (advance online publication) [hereinafter "Wong, Pet. Ex. 240"]. is misplaced. Tr. 1470. While Dr. Deth relied on this paper to support a relationship between epigenetics and autism (Tr. 621), Dr. Raymond pointed out that the article addresses epigenetic changes occurring during very early embryonic development (Tr. 1470-74), because the studies were done on blood. The primogenitor cells that result in the cells that create blood are formed in the first few days or weeks of gestation. For an epigenetic difference between identical twins to occur and be identified in blood cells, it must have occurred when the blood producing cells were generated. Doctor Raymond argued that the paper therefore does not support the idea of vaccine-caused epigenetic dysregulation. Tr. 1470. I note that the study was filed after the deadline I imposed for filing medical literature, but because it was published April 23, 2013, I allowed it to be considered as evidence.

In addition, he has edited two books and registered six patents with an additional patent pending. Res. Ex. YY at 36.

b. Doctor Jones' Opinion.

Doctor Jones asserted that Dr. Deth's testimony and written opinion relied on an outdated understanding of the concept of "oxidative stress" and advanced a more nuanced understanding of the term. Thiol is the most reduced form of sulfur in the biological system, common in proteins. The traditional way of thinking about oxidative stress—as any imbalance in redox state favoring oxidation—failed to capture the reality that the different "thiol systems"[98] (such as cysteine vs. glutathione) do not exist in equilibrium with one another, but rather in "a nonequilibrium steady state." Tr. 1613-17. Any discussion of an overall whole-body redox balance is inadequate. *Id*. He noted the necessary role of oxidation in healing and immune responses. He explained that vaccinations do produce oxidation, but only to the extent of impacting redox signaling as part of the normal immune response. Vaccinations do not cause oxidative damage. [99] Tr. 1621, 1679-80. Doctor Jones pointed out that Dr. Deth's own study[100] showed that there is no association between markers of oxidative stress and autism. The study showed that markers of oxidative stress were not significantly different between subjects with autism and a control group.[101] Tr. 1651.

With regard to A.K.'s case specifically, Dr. Jones testified that Dr. Deth's theory lacked evidence to support four key components of the causal mechanism he proposed,[102] Tr. 1633-34, 1661,: (1) there is no credible evidence of oxidative stress; (2) no evidence of neuro-inflammation from oxidative stress,[103] *see* Res. Ex. ZZ at 2-6; Tr. 1650-52, 1659-61; (3) no evidence of impaired sulfur amino acid metabolism; and (4) no

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[98] I note that "thiol" is misspelled throughout the transcript as "thial." I will use the correct spelling within this decision, but will not further address each misspelling within the record.

[99] Doctor Jones questioned the thinking that oxidative stress is a central mechanism to understanding human disease. In this regard, Dr. Jones noted that studies have shown that administering antioxidants does not give a health benefit. Tr. 1617-18. He noted that, in addition to ill effects, "oxidative stress" also encompasses necessary redox signaling. Tr. 1620-21. Therefore not all oxidative stress is bad or causes damage. *Id*.

[100] Pet. Ex. 135, C. Muratore, et al, Age-Dependent Decrease and Alternative Splicing of Methionine Synthase mRNA in Human Cerebral Cortex and an Accelerated Decrease in Autism, PLoS ONE 8(2): e56927 (2013) [hereinafter "Muratore, Pet. Ex. 135"]. Doctor Deth was the last listed author on this journal article, the position usually used to designate the senior researcher.

[101] I note that, for his part, Dr. Deth confirmed that his study did not show elevated biomarkers for oxidative stress among autistic individuals. Tr. 827. He expressed surprise at that outcome, but hypothesized (without apparent support) the presence of a coping mechanism to explain the results. *Id*.

[102] Doctor Jones's hearing testimony refined his opinion in light of Dr. Deth's testimony. Tr. 1624, 1633-34. Therefore, I focus primarily on his hearing testimony.

[103] No test ever measured inflammatory cytokines in A.K., and that to the extent A.K. showed clinical signs of inflammation over the course of his medical history, such as upper respiratory infections, or coughing and sneezing, these kinds of symptoms are not indicative of neuroinflammation in particular. Tr. 1659-61.

evidence of impaired methionine synthase activity,[104] *see* Res. Res. Ex. ZZ at 6-8; Tr. 1657-59.

According to Dr. Jones, Dr. Deth relied solely on a finding of no detectable level of cystine in A.K.'s cerebral spinal fluid as evidence of the presence of oxidative stress. Tr. 1651-52. However, oxidative stress is associated with elevated cystine, and not low cystine, as Dr. Deth indicated. Tr. 1648-49. Moreover, regardless of its significance, Dr. Jones stated that the result of no detectable cystine was a misnomer in that the normal range for cystine in CSF was below the detection limits of the test used. Tr. 1643-45. Measurements of cystine are incredibly unreliable absent specific protocols, and cystine values vary by both time of day and diet. Tr. 1645-48. For these reasons, as well as the absence of information regarding the lab's handling of the samples, Dr. Jones did not trust the reported cystine values. Thus, even under Dr. Deth's erroneous view of low cysteine as a marker for oxidative stress, this test was inadequate as supporting evidence.[105] *Id*.

With regard to the claim of impaired sulfur amino acid metabolism, Dr. Jones contended that such an impairment could manifest in one of two ways. If an impairment occurred at the level of conversion of homocysteine to methionine, then one would expect to see a build-up of homocysteine. Alternatively, if impairment occurred at the level of the transsulfuration pathway, then one would expect to see an increase in methionine along with a decrease in both cystathionine and taurine. Tr. 1638-39. Doctor Jones pointed out, however, that in A.K.'s case, testing showed that all four of these components were normal. Tr. 1639, 1642-43. Moreover, Dr. Jones noted that Dr. Deth's own citation[106] indicated that the impact of vaccination on transsulfuration and methylation was only a fraction of the impact demonstrated between fasting and fed subjects. Thus, Dr. Jones noted that the capacity of the vaccine to impact sulfur amino acid metabolism is actually quite small. Tr. 1639-42.

With regard to the claim of impaired methionine synthase activity, Dr. Jones indicated that Dr. Deth was wrong to characterize the $EAAT_3$ transporter[107] as the primary transporter for cysteine and cystine in the intestine. Tr. 1654-57. While he was unable to state whether $EAAT_3$ is the primary transporter in the brain, Dr. Jones testified that $EAAT_3$ does not appear to be a major transporter for cysteine in the intestine and, thus, questioned the validity of Dr. Deth's focus on that transporter. Tr. 1655-56.

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[104] In addition, for reasons similar to respondent's other experts, Dr. Jones also thought there was insufficient evidence to show that A.K. had any mitochondrial dysfunction. Tr. 1626-33.

[105] In rebuttal testimony, Dr. Deth argued that Dr. Jones has no basis to discount the reported cystine values. He did not, however, specifically address Dr. Jones's actual criticisms. Instead, he simply argued that Dr. Jones was "shooting the messengers." Tr. 1743.

[106] Pet. Ex. 132, S. Mercier, et al., Methionine Kinetics are Altered in the Elderly Both in the Basal State and After Vaccination, AM J. CLIN. NUTR 83:291-98 (2006) [hereinafter "Mercier, Pet. Ex. 132"].

[107] In *Dwyer,* I explained the $EAAT_3$ transporter's function thusly: "Cysteine, like other amino acids, is transported across cell membranes by transporter proteins." *Dwyer*, 2010 WL 892250, at *121, n.517. Quoting Dr. Deth's testimony in that case, "in neurons, the transport is accomplished by the excitatory aminio acid transporter-3 ["$EAAT_3$"], which also transports glutamate, the primary excitatory amino acid." *Id.* (citations omitted).

Doctor Jones also indicated that an impairment in methionine synthase activity would increase levels of homocysteine. Tr. 1653-54. Turning again to Dr. Deth's own study,[108] however, Dr. Jones noted that, contrary to Dr. Deth's hypothesis in this case, homocysteine was lower among subjects with ASDs. Tr. 1652-54.

7. Jeffrey Johnson, Ph.D.

a. Doctor Johnson's Qualifications.

Jeffrey Johnson, Ph.D., is a professor of pharmaceutical sciences at the University of Wisconsin, Madison School of Pharmacy. The majority of his time there is spent engaged in laboratory research focused on "molecular aspects in regulation of gene transcription and neurodegeneration." Res. Ex. WW at 1; Tr. 1688-1690. More specifically, his research addresses redox biology in the context of chronic neurodegenerative diseases. Res. Ex. XX at 1. Prior to his appointment at the University of Wisconsin, Dr. Johnson was an assistant professor in the department of pharmacology, toxicology and therapeutics at the University of Kansas Medical Center in Kansas City, Kansas. Res. Ex. WW at 1.

In 1984, Dr. Johnson completed an undergraduate degree with a major in biology at the University of Minnesota, Duluth. Res. Ex. WW at 2; Tr. 1688-89. He later completed a master's degree in pharmacology at the same institution in 1986 before pursuing his Ph.D. in molecular environmental toxicology at the University of Wisconsin, Madison, from 1986 to 1992. Res. Ex. WW at 2; Tr. 1689. Doctor Johnson then completed a three-year postdoctoral fellowship in molecular neuroscience at the University of Washington in Seattle, Washington. Tr. 1689.

Doctor Johnson listed 82 peer-reviewed articles, seven reviews, and two book chapters on his curriculum vitae, along with numerous invited lectures. Res. Ex. WW at 2-12; Tr. 1690-91. He is a reviewer for numerous academic journals and currently holds three NIH grants. Tr. 1691. In addition, he is a member of the NIH study section on Neural Oxidative Metabolism and Death and an ad hoc member of the NIH study section on Neurotoxicology and Alcohol. Res. Ex. WW at 4; Tr. 1692. He is chair of the external advisory committee for Emory University's Parkinson's Disease-Collaborative Environmental Research Center and serves on multiple grant review panels. Res. Ex. WW at 4.

b. Doctor Johnson's Opinion.

Doctor Johnson disputed Dr. Deth's claim that vaccinations can cause neuroinflammation leading to oxidative stress and inhibited methionine synthase activity resulting in autism. Tr. 1732-33. Focusing on several specific studies cited by Dr. Deth, he contended that "there are a number of significant issues with the way these data were generated and interpreted" and that ultimately "Dr. Deth's hypothetical mechanism for how vaccines cause autism is fatally flawed" and lacks sufficient evidence. Res. Ex. XX at 3, 7.

[108] Muratore, Pet. Ex. 135.

Addressing Dr. Deth's citation of a study by Waly,[109] (Dr. Deth was a co-author of this study), Dr. Johnson contended that the study, which he characterized as "the whole foundation of Dr. Deth's theory," had a number of significant issues and had not been corroborated by any other laboratory.[110] Res. Ex. XX at 3-5. In addition to pointing out several technical deficiencies, Dr. Johnson asserted that the study failed to produce statistically valid data, and failed to test what impact, if any, the subject compounds had on global methylation. *Id*. at 5. He also noted that the study failed to actually examine neuronal methionine synthase activity and oxidative stress generation, both of which were "primary end points" for the paper's hypothesis. Res. Ex. XX at 3, 5; Tr. 1694. Doctor Johnson argued, therefore, that the hypothesis Dr. Deth based on the study lacks any sound scientific support. Res. Ex. XX at 5. Moreover, he noted that as a study based on neuroblastoma cells, any conclusion drawn from the test would be relevant only to the cell line and would not be indicative of actual neuronal activity. *Id*. at 3. These were all criticisms directed against the study in the OAP Theory 2 test cases and were cited there as reasons for rejecting Dr. Deth's opinions on how mercury in vaccines caused oxidative stress.

Doctor Johnson was also critical of Dr. Deth's attempt to rely on a study by James, et al.,[111] to link markers of oxidative stress among children with autism to vaccines. He noted that another study by Dr. Jill James[112] showed that these subjects have the same metabolic patterns as their mothers, strongly suggesting that the findings cited by Dr. Deth could not be attributable to vaccination. Tr. 1696-98.

In addition, Dr. Johnson pointed out that Dr. Deth selectively presented the results of his own study on methionine synthase mRNA splicing, and stated that the study actually presented contradictory data suggestive of a technical failure. Tr. 1708-14. Although Dr. Deth presented charts showing a lifetime decrease of MS "Cob" mRNA and MS "Cap" mRNA to zero by about age 70, Dr. Johnson pointed out that a figure from Dr. Deth's study showing the results of an ethidium[113] bromide-stained PCR gel showed that in a 76 year old patient, 95% of the MS mRNA was full length. Tr. 1708-10. Because the decrease of Cob and Cap to zero, as suggested by Dr. Deth, would require the deletion of those domains from the full mRNA, the finding of 95% full length mRNA in an aged subject was contradictory both to Dr. Deth's findings and to his hypothesis of a difference in methionine synthase activity between old, young and

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[109] Pet. Ex. 117, Ref. 9, M. Waly, et al., Activation of methionine synthase by insulin-like growth factor-1 and dopamine: a target for neurodevelopmental toxins and thimerosal, MOL. PSYCHIATR 9(4):358-370 (2004) [hereinafter "Waly, Pet. Ex. 117, Ref. 9"].

[110] This paper was discussed extensively in the OAP theory 2 test cases and is addressed in more detail in Section IX.C.

[111] Pet. Ex. 117, Ref. 38, S.J. James, et al, *Metabolic endotype and related genotypes are associated with oxidative stress in children with autism*, AM. J. MED. GENET. B. NEUROPSYCHIATR. GENET.; 141B(8): 947-56 (2006) [hereinafter, "James, Pet. Ex. 117, Ref. 38"].

[112] Pet. Ex. 117, Ref. 36, S.J. James, et al, *Abnormal transymethlation/transsfulfuration metabolism and DNA hypomethylation among parents of children with autism*, J. AUTISM DEV. DISORD.; 38(10:1966-1975 (2008) [hereinafter "James, Pet. Ex. 117, Ref. 36"].

[113] Misspelled in the transcript as "epithidium."

autistic. *Id*. Moreover, to the extent that Dr. Deth suggested that the presence of TNF-α explained how inflammation caused oxidative stress and inhibited methionine synthase activity, Dr. Johnson pointed out that Dr. Deth's underlying data, published elsewhere and not presented to the court, showed that the effects of TNF-α on methionine synthase activity were reversed within six hours, suggesting that the TNF-α has little-to-no long-term effect on methionine synthase activity.[114] Tr. 1714-19.

Finally, Dr. Johnson noted that the Wong study, Pet. Ex. 240, also contradicted Dr. Deth's theory. While Dr. Deth posited that autism is caused by depressed methylation, the Wong study showed that twins discordant for autism showed no overall difference in methylation. In fact, the study demonstrated that the discordant twins were variously over or under methylated. Doctor Johnson argued that Dr. Deth's theory cannot account for that outcome and that, contrary to Dr. Deth's hypothesis of depressed methylation, the Wong study showed that methylation was either increased or decreased among autistic subjects with a majority of the genes of the autistic twins becoming over-methylated. Tr. 1719-24, 1726. The Wong study showed that of the ten genes in the autistic twins with the largest changes in methylation, only three demonstrated decreased methylation. Tr. 1724.

VI. Petitioners Have Not Established That A.K. Actually Has an Underlying Mitochondrial Disorder or Dysfunction.

Petitioners' claim is that "one or more vaccines significantly aggravated an underlying mitochondrial disorder." 2d Am. Pet (ECF No. 237), ¶ 74. This petition, filed April 17, 2013, alleged that "the medical evidence establishing mitochondrial disorder . . . establishes that [A.K.] was vulnerable to vaccine injury, either directly due to oxidative stress caused by the vaccine or indirectly due to oxidative stress caused by the fever(s) which accompanied most of A.K.'s vaccinations." *Id*., ¶ 73. Moreover, petitioners explicitly stated in their post-hearing brief that "petitioners' claim relies on a diagnosis of A.K. with a mitochondrial defect based on enzyme assays of a muscle biopsy and other biomarkers." ECF No. 297 at 4. All three of petitioners' medical experts rely, *inter alia*, on the fact of A.K.'s mitochondrial disorder diagnosis. *See, e.g.,* Pet. Exs. 65 at 7-8; 117 at 2-3; 63 at 18. [115]

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[114] Moreover, Dr. Johnson further noted that the method of that study—*i.e*., directly injecting TNF-α into cells—resulted in a concentration of TNF-α an "order of magnitude" greater than one would see in cerebral spinal fluid after a vaccination. Thus, Dr. Johnson noted that if such a direct injection cannot produce a sustained inhibition of methylation, then a vaccine would not be able to produce enough oxidative stress to inhibit methylation. Tr. 1727.

[115] There is some uncertainty as to whether Dr. Deth considered a pre-existing mitochondrial disorder to be a condition precedent to his opinion. Despite his discussion of mitochondrial dysfunction, he indicated during cross-examination that he would still opine that A.K.'s injury was vaccine caused "with or without" a mitochondrial disorder being present, stating that he could still make "90% of the same connections." Tr. 799-800. This led respondent to state in her post-hearing brief that "evidence of impaired mitochondrial function is apparently not 'important' to Dr. Deth in this case." ECF No. 295 at 74. Petitioners argued in response that respondent mischaracterized Dr. Deth's opinion and that while oxidative stress is the damage-causing agent in Dr. Deth's theory, "mitochondrial malfunction adds to this mix." ECF No. 302 at 21. In arguing against the consideration of evidence from the OAP test cases, petitioners contended that this case is distinct from the OAP test cases precisely because it involves mitochondrial disease and "the

Thus, whether A.K. had a mitochondrial disorder is a threshold issue in this case. Petitioners contended that A.K.'s medical records established the mitochondrial disorder diagnosis, one made by multiple treating physicians. They also presented expert testimony by Dr. Kendall that A.K. meets accepted standards for a mitochondrial disorder diagnosis. Respondent countered with presentations by Drs. Cohen and Wallace, who both disputed the laboratory data on which A.K.'s mitochondrial disorder diagnosis was based. Additionally, Dr. Cohen's testimony disputed Dr. Kendall's interpretation of A.K.'s clinical history.

For the reasons discussed below, I find that respondent has made the more persuasive case and that petitioners have not established, more likely than not, that A.K. had any mitochondrial disorder or dysfunction.

A. Explaining Mitochondrial Disorders.

Mitochondria are small organelles (structures inside cells) that turn food and oxygen into the body's supply of chemical energy. According to the experts in this case, mitochondria's role within a cell can be analogized to the power plants that provide electricity to a city or the internal combustion engine that drives a car. Tr. 258-60, 1161-64. In addition to energy production, mitochondria are also responsible for maintaining proper functioning of various organs. *See e.g., Bast v. Sec'y, HHS,* No. 01-565V, 2012 WL 6858040 at *24 (Fed. Cl. Spec. Mstr. Dec. 20, 2012), *aff'd,* 117 Fed. Cl. 104 (2014).

Mitochondria use oxygen and food to produce adenosine triphosphate ["ATP"], the primary source of energy for all bodily functions, through a process labeled "the respiratory chain" or "electron transport chain" ["ETC"]. Res. Ex. UU at 6. Problems with energy production in the ETC can occur as the result of genetic defects in either the mitochondria's own DNA ["mtDNA"] or in the DNA found in the nucleus of cells themselves ["nuclear DNA"or "nDNA"]. Tr. at 1165; *see also* Res. Ex. UU at 8-11. The sole function of the mtDNA is to make proteins that are components of the ETC. Tr. at 1069-70*; see also* Res. Ex. UU at 6-7. The activity of the ETC, which takes place largely on the inner of the two membranes comprising the outer part of the mitochondria, consists of five protein complexes (Complexes I-V). Ex. UU at 6. A different biochemical step in the conversion of nicotinamide adenine dehydrogenase to ATP takes place in each complex. *Id*. This conversion process is referred to as "oxidative phosphorylation" or "OXPHOS." *Id.*

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role of oxidative stress in causing mitochondrial decompensation." *Id*. at 10. Notwithstanding this argument, Dr. Deth's testimony in this case, as well as the slides he used to illustrate it, overlapped considerably with his testimony and the slides he used in the OAP. Petitioners argued that Dr. Deth's hypothesis is supported, *inter alia*, by "extensive research establishing clear connections between mitochondrial disease and autism." *Id*. at 11. However, petitioners have also stated that Dr. Deth's opinion in this case does not constitute a separate theory of causation, but rather an explanation of the mechanism supporting their theory of the case, which is that A.K.'s underlying mitochondrial disorder was aggravated by his vaccinations. Tr. 597; 2d Am. Pet (ECF No. 237) ¶¶ 73-74. In that regard, I note that Dr. Deth characterized his opinion as answering the questions of "how a vaccine causes oxidative stress" and "how such oxidative stress can cause injury to a child with a mitochondrial disorder." Pet. Ex. 117 at 2. Thus, despite Dr. Deth's testimony on cross-examination, the centrality of a mitochondrial disorder to petitioner's claim is indisputable.

"Mitochondrial disease is not a single entity but, rather, a heterogeneous group of disorders characterized by impaired energy production due to genetically based oxidative phosphorylation dysfunction." Res. Ex. SS, Tab 6, R. Haas, et al, *Mitochondrial Disease: A Practical Approach for Primary Care Physicians,* PEDIATR.., 120(6) 1326-33, (2007) at 1326 [hereinafter "Haas, Res. Ex. SS, Tab 6"]. There is no "definitive biomarker that characterizes mitochondrial disease in all patients." *Id.* at 1331. "Mitochondrial diseases are usually progressive and multisystemic," typically affecting organs with "a high energy demand, including skeletal and cardiac muscle, endocrine organs, kidney, nonmucosal components of the intestinal tract, retina, and the central nervous system." *Id*. at 1327.

When a DNA defect results in clinical symptoms, a person is said to have a "primary" mitochondrial disease or defect. Other bodily processes including metabolic disorders, hypoxia, and some drugs may also affect the ETC, causing diminished ETC function, producing "secondary mitochondrial dysfunction." Tr. at 1165; *see also* Res. Ex. UU at 9. In the absence of an identified genetic defect or the presence of clusters of symptoms fitting a known mitochondrial syndrome, diagnosing a mitochondrial disorder is difficult.[116] *See e.g.*, Pet. Ex. 65 at 4-7 (expert report of Dr. Kendall); Res. Ex. SS at 11-14 (expert report of Dr. Cohen).

In this case, the allegation that A.K. has a mitochondrial disorder stems primarily from a report by Dr. John Shoffner, the medical director of a laboratory known as Medical Neurogenetics. *See* Pet Ex. 32. Doctor Shoffner completed what he termed "an oxidative phosphorylation disease evaluation," which included metabolic studies from blood, urine and cerebral spinal fluid as well as light microscopy of skeletal muscle, enzymology testing from muscle biopsy, and genetic testing. Pet Ex. 32, pp 1-2. He offered a diagnosis of "probably mitochondrial encephalomyopathy," based on an enzymology finding of a Complex I defect with correlative protein chemistry changes on Western Blot testing. Pet Ex. 32, p. 3. Although there is no evidence to suggest that Dr. Shoffner conducted any evaluation of A.K.'s medical history, his diagnosis was also

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[116] I have discussed mitochondrial disorders extensively in other recent decisions. *See Holt v. HHS*, 2015 WL 4381588, No. 05-236v (Fed. Cl. Spec. Mstr. June 24, 2015); *Miller v. HHS*, 2015 WL 5456093, No. 02-235v (Fed. Cl. Spec. Mstr. August 18, 2015). I note in particular that in *Holt*, a significant issue was the question of whether studies related to mitochondrial disorders or diseases (terms that can be used interchangeably) could be applied to a claim of mitochondrial dysfunction. In *Holt*, petitioner alleged that her minor child had mitochondrial dysfunction that did not rise to the level of severity of an actual mitochondrial disease or disorder. *Holt*, 2015 WL 4381588, *22-23. In this case, petitioners were consistent in their amended petition in alleging that A.K., having been diagnosed with mitochondrial encephalomyopathy, had a mitochondrial disorder that was aggravated by his vaccinations. *See* 2nd Am. Pet, (ECF No. 237), passim. In their post-hearing brief, petitioners referred variously to mitochondrial disorder (ECF No. 297 at 8), disease (ECF No. 297 at 39), susceptibility (ECF No. 302 at 25), defect (ECF No. 297 at 4), diagnosis (ECF No. 297 at 32, n.18), malfunction (ECF No. 302 at 21), and dysfunction (ECF No. 302 at 21). I find no instance in this case where petitioners have asserted or explained any intended distinction among those terms. In any event, the issue arose in *Holt* because respondent's expert conceded that there was laboratory evidence suggestive of a mitochondrial dysfunction, but that such dysfunction was not responsible for any of the petitioner's clinical symptoms, meaning no mitochondrial disorder was present. *Holt*, 2015 WL 4381588, *79. For the reasons described below, I have found that no such laboratory evidence exists for A.K. I find that A.K. had neither a mitochondrial disorder nor any mitochondrial dysfunction.

based on reported clinical symptoms including ASD, gastrointestinal dysfunction and pain, fatigue, and heat and cold intolerance. Ex. 32, p. 1. Genetic and metabolic tests were all "unremarkable." Ex. 32, pp. 1-2. As discussed below, petitioners contend that Dr. Shoffner's findings were subsequently confirmed by multiple treating physicians.

B. Diagnostic Standards for Mitochondrial Disorders.

Both of the clinical mitochondrial experts in this case (Drs. Kendall and Cohen)[117] agreed that the diagnosis of mitochondrial disorders involves the analysis of a number of signs and symptoms, including biochemical, genetic and clinical features. Tr. 248-51, 1322-23. Both also agreed that there is a great deal of uncertainty regarding the diagnosis of mitochondrial disorders and that the field has failed to standardize adequately the diagnostic criteria.[118] *See, e.g.*, Tr. 248-49, 1351. Each of these experts has published a review of other articles in which they address their own interpretations of the diagnostic criteria for mitochondrial disorders. *See* Ex SS, Tab 2, B. Cohen, et al, *The clinical diagnosis of POLG disease and other mitochondrial DNA depletion disorders*, METHODS, 51: 364-73 (2010); Pet. Ex. 172, F. Kendall, et al, *Mitochondrial disorders: Overview of diagnostic tools and new diagnostic trends*, J. PEDIATRIC BIOCHEM., 2: 193-203 (2012).

Nonetheless, Dr. Kendall relied on the Bernier criteria,[119] at least initially. Both parties agreed that the Bernier criteria were useful in diagnosing mitochondrial disorders. In her report, Dr. Kendall explained that:

> Because the diagnosis of mitochondrial disease is complicated and often required a multitude of clinical and laboratory findings for confirmation, a number of groups have developed diagnostic criteria to assist in evaluating suspected mitochondrial patients. In 2002, Bernier et al outlined these diagnostic criteria for respiratory chain disorders in adults and children in the journal Neurology.

Pet. Ex. 65 at 7 (citing Bernier, Pet. Ex. 90).

Although Dr. Kendall acknowledged that there are "other similar criteria," she used only the Bernier criteria in her expert report, concluding that "a review of [A.K.]'s clinical features and laboratory data collected to date provide support for a definitive or highly probable mitochondrial disease utilizing these diagnostic criteria. Pet. Ex. 65 at 7; *see also* Tr. 308. Doctor Cohen agreed that the Bernier criteria are authoritative,

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[117] Petitioners' experts, Drs. Shafrir and Deth, discussed mitochondrial disorders as part of their opinions, but both indicated that they deferred to other experts on the diagnosis of mitochondrial disorders. Tr. 513-14, 796. In addition, although respondent elicited testimony from two other experts (Drs. Wallace and Jones) regarding mitochondrial biology and supporting laboratory evidence, these experts indicated that they are not clinicians and that their opinions do not extend to the diagnosis of mitochondrial disorders. Tr. 1072, 1625-26.

[118] Doctor Cohen noted that some specific phenotypes of mitochondrial disorder are not subject to uncertainty, in that they have clearly identifiable genetic markers and accompanying clinical presentations, but he agreed that not all mitochondrial disorders can be so identified. Tr. 1319-22. In A.K.'s case, there is no genetic evidence of a mitochondrial disorder. Tr. 251.

[119] Bernier, Pet Ex. 90.

testifying that using the criteria "assigns a level of certainty to the diagnosis" where there is otherwise no certainty by requiring significant substantiated evidence. Tr. 1319-22. He characterized the Bernier criteria as a useful diagnostic tool and indicated that he uses them in his own practice. Tr. 1179-80. However, he disagreed with Dr. Kendall that, applying these criteria to the facts of A.K.'s case, he had a mitochondrial disorder. Tr. 1220.

On cross examination, Dr. Kendall was forced to acknowledge that she could not reach a "definite" mitochondrial disorder diagnosis by applying the Bernier criteria. On redirect, she began to question the efficacy of the Bernier criteria, implying that more recent diagnostic criteria, such as the Morava criteria,[120] were more diagnostically accurate. Tr. 317-19, 423-25. She also indicated that the Bernier criteria were less comprehensive than her own published criteria in terms of listing specific clinical symptoms, rather than broader categories. She then contended that A.K. had a mitochondrial disorder diagnosis under her own diagnostic criteria, based on his autistic features, developmental delays, dysautotonomia, hypotonia, gastrointestinal problems/dismotitlity, and fatigability. Tr. 423-24.

Doctor Cohen agreed that the Bernier criteria have been supplanted to some degree by other diagnostic methods, particularly the use of molecular genetics. However, he opined that these criteria remain a useful diagnostic tool—and one that he used in his own diagnostic practice. Tr. 1179-80. Moreover, he noted that, to the extent there are problems with the Bernier criteria, it is that the criteria are over-sensitive, rather than under-sensitive. Thus, application of the Bernier criteria will result in a mitochondrial disorder diagnosis for patients who actually have other identifiable disorders. The over-diagnosis using the Bernier criteria is something Dr. Cohen testified that he had experienced. *Id*.

Doctor Kendall did not address the over-inclusivity of the Bernier criteria in her testimony. She did testify that the reason for using the "basket" of clinical features that comprise various diagnostic criteria is to avoid false positives. Tr. 307.

Following the hearing in this case, I filed the "Nijmegen" or "Wolf" criteria[121] as Court Exhibit I and instructed the parties to submit supplemental reports regarding that article. *See* Order, 9/3/2013 (ECF No. 277). In response to my order, Dr. Cohen submitted a report indicating that he did not believe that A.K.'s case would even warrant

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[120] Referring to E. Morava, et al, *Mitochondrial disease criteria: Diagnostic applications in children*, NEUROL. 67:1823-26 (2006), filed as Res. Ex. SS, Tab 11, hereinafter simply "Morava" or "Morava criteria." This article was filed in conjunction with Dr. Cohen's expert report. The name of the principal author is incorrectly spelled in the transcript as "Morave." Tr. 424.

[121] N. Wolf & J. Smeitink, *Mitochondrial disorders, A proposal for consensus diagnostic criteria in infants and children*, NEUROL. 59 (9): 1402-05 (2002), filed as Court Ex. I; also filed as Res. Ex. SS, Tab 19. This study was a product of the Nijmegen Center for Mitochondrial Disorders, Nijmegen, the Netherlands, hence the shorthand reference to it as the "Nijmegen criteria." As I have previously noted, the Morava criteria are, in effect, the Nijmegen criteria, the Morava study having been performed to address the specificity of the Nijmegen criteria in identifying children with mitochondrial disorders established through genetic screening while screening out those with multi-system disease with other, non-mitochondrial genetic diagnoses. *Miller,* 2015 WL 5456093, *28.

full testing under the Nijmegen criteria. Res. Ex. KKK at 1. Nonetheless, applying the "scoring" system under the Nijmegen standards, Dr. Cohen opined that A.K.'s history would only generate one point, which makes a mitochondrial disorder diagnosis "unlikely."[122] *Id*. at 4. For his part, Dr. Wallace stressed that both the Nijmegen and Bernier criteria achieve "very similar results" in terms of diagnosing respiratory chain disorders. Res. Ex. LLL at 2-3. Ultimately, both of respondent's mitochondrial disorder experts opined that consideration of the Nijmegen criteria did not change their opinions originally rendered using the Bernier criteria. Res Ex. KKK at 5; Res. Ex. LLL at 3.

In her supplemental expert report (Pet. Ex. 269), Dr. Kendall explicitly argued that the Nijmegen criteria *cannot* be used to evaluate A.K.'s case. Specifically, Dr. Kendall noted that the Nijmegen criteria includes scoring based on additional biochemical tests not completed in A.K.'s case. Pet Ex. 269 at 1. Doctor Kendall stressed that the Bernier criteria fall short of a "gold standard," but noted again – as she did in her initial report – that the Bernier criteria were used to screen patients for inclusion in the only current clinical trial for mitochondrial patients. Pet. Exs. 269 at 2; 65, p. 7. Thus, although Dr. Kendall has been consistent in maintaining the lack of *any* gold standard diagnostic tool for mitochondrial disorders, her half-hearted references to other diagnostic criteria (made only after being challenged on the facts of this case) do not conceal her clear acceptance of, and reliance on, the Bernier criteria.

I am familiar with the other criteria for diagnosing mitochondrial disorders that have been cited, and indeed, I have addressed those criteria in other cases. *See, e.g., Holt v. HHS*, 2015 WL 4381588; *Miller v. HHS*, 2015 WL 5456093, No. 02-235v (Fed. Cl. Spec. Mstr. Aug. 18, 2015). In this case, however, petitioners have come forward with no expert opinion or other medical evidence analyzing the particulars of A.K.'s case under any generally accepted diagnostic rubric other than Bernier.[123] Although Dr. Kendall raised the existence of the Morava criteria, she did not actually opine that A.K. fit that criteria, and she argued explicitly against the application of the Nijmegen criteria. Moreover, her application on redirect examination of criteria from her own review article was cursory at best.[124]

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[122] Similar to the Bernier criteria described in greater detail below, Nijmegen seeks to categorize mitochondrial disorder diagnoses based on level of certainty, describing a diagnosis as either unlikely, possible, probable, or definite. Court Ex. I at 1403. Nijmegen "scores" patients based on clinical, metabolic, imaging, histopathologic and biochemical criteria. *Id*. at 1403. To avoid overemphasizing individual diagnostic categories, three general categories (clinical presentation, metabolic investigation and imaging, and histopathology) are capped at four points each. *Id*. at 1402-03. According to Dr. Cohen, whereas a probable or definite diagnosis ranges from five to twelve points, A.K.'s single point makes a diagnosis "unlikely." Rex. Ex. KKK at 5.

[123] As described in Section VI.D below, petitioners point to mitochondrial diagnoses contained in A.K.'s medical records as evidence that he does have a mitochondrial disorder. I note that none of those records reflect the use of any diagnostic instrument that reflects a systematic evaluation of A.K.'s documented clinical symptoms. Even Dr. Shoffner, the physician who first diagnosed A.K. with a probable mitochondrial encephalomyopathy (*see* Pet. Ex. 32, p. 3), did not identify the diagnostic criteria upon which his diagnosis was based (*id*.). Most of these later references merely repeat the history of an earlier diagnosis by Dr. Shoffner, rather than reaching an independent diagnosis.

[124] Although Dr. Kendall identified a number of symptoms she viewed as relevant, she did not specify how A.K.'s clinical history conformed to the symptoms she had identified within her own article. Although her

Ultimately Dr. Kendall testified that there is no diagnostic methodology that enjoys consensus and that each diagnosis depends on the particular experience of the diagnosing physician, opining in sum that the diagnosis of mitochondrial disorders is "as much an art as it is a science." Tr. 426. This alternative framing is wholly insufficient. "[I]t should be obvious to petitioner[s] that a scientific theory that lacks any empirical support will have limited persuasive force." *Caves*, 100 Fed. Cl. at 134 (quoting *Gen. Elec. Co. v. Joiner* 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.'").

In his expert report, Dr. Cohen also indicated that published diagnostic criteria "are not meant to account for all clinical and laboratory outcomes" and that "it is up to the clinician to offer a final determination if the laboratory data taken as a whole justify the diagnosis of a mitochondrial disorder or not." Ex. SS at 12. Nonetheless, he also indicated that the diagnostic criteria "compliment the opinion of the clinician." *Id*. In that regard, I stress that I am not adopting a strict application of the Bernier criteria in lieu of accepting Dr. Kendall's opinion, but rather assessing the credibility and persuasiveness of her opinion regarding the appropriate diagnosis for A.K. in light of, *inter alia*, her claimed application of the Bernier criteria. Where Dr. Kendall went too far is in expressing, by virtue of comparing diagnosis to an art, that there are no credible or limiting diagnostic standards *whatsoever*.[125] The lack of an agreed upon "gold standard" is not the same as having no standard at all.

Whatever the shortcomings of the Bernier criteria, the parties in this case agree that it is a valid diagnostic tool and that there is in fact no gold standard to be followed. Moreover, petitioners have provided no significant analysis under any other objective standard from which one could conclude A.K. in fact has a mitochondrial disorder.[126] Thus, my analysis will focus much of its attention on the Bernier criteria.

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article contains a chart of "possible" mitochondrial disease symptoms, which she cited in her testimony, neither the chart nor her testimony discuss what tests or thresholds are necessary to consider whether those symptoms match the typical presentations seen in mitochondrial disease, nor what number or combination of "possible" symptoms is supportive of a mitochondrial disease diagnosis under her particular criteria. Tr. 423; Pet. Ex. 172, at 195 (Table 1). For example, her chart lists "gastrointestinal problems," but does not define them. Other criteria, including Nijmegen, Morava, and even Bernier, require specific gastrointestinal symptoms reflective of dysmotility and that the gastrointestinal symptoms be unexplained. Her lack of detail may have been an attempt to avoid an extensive cross-examination similar to what she experienced when she was questioned in detail about whether A.K.'s clinical data in fact matched the Bernier criteria. *See* Tr. 308-319.

[125] Being careful not to reduce Dr. Kendall's entire opinion to one unfortunately worded utterance, I note that Dr. Kendall's suggestion that mitochondrial disorder diagnosis is "as much an art as it is a science" implied the lack of precision which is emblematic of her approach to this case. At multiple points, I found Dr. Kendall's grasp of the facts of this case to be tenuous or vague and her application of her own theory both cursory and problematic.

[126] The Bernier criteria are derived from adult diagnostic criteria, although they have been applied to pediatric patients. In contrast, the Nijmegen criteria were developed specifically to create a diagnostic standard more finely tailored to children and infants. The Wolf article noted, for example, that "[m]ost infants and children present with a nonspecific clinical picture, having neither histopathologic hallmarks like ragged red or COX-negative fibers nor mtDNA mutations. Applying a less restrictive approach to complex clinical pictures, we enabled nonclassic pediatric clinical presentations to achieve maximum

C. Applying the Diagnostic Criteria to A.K.'s Case.

The Bernier criteria were developed in an attempt to find consensus in diagnosis of mitochondrial disorders. Pet. Ex. 90 at 1406. A mitochondrial disorder diagnosis under these criteria is based on an aggregation of positive findings among clinical features, histology, enzymology, function (*i.e.* ATP synthesis rates), molecular pathogenicity, and metabolic indicators of impaired respiratory function. Pet. Ex. 90 at 1407, Table 1 & 2. Specific levels of impairment are specified for testing (i.e., ">3 SD [standard deviations] below mean" to consider fibroblast ATP synthesis rates as evincing a mitochondrial problem). For each type of feature (except metabolic features), "major" and "minor" diagnostic criteria are identified.[127] *Id.* Based on these indicators, a diagnosis can be characterized as either definite, probable, or possible.[128] *Id*. at 1407. Doctor Cohen contended that A.K. does not fit any of the Bernier criteria, major or minor. Tr. 1219-20. By contrast, Dr. Kendall initially argued that application of the Bernier criteria produced a diagnosis of a definite mitochondrial disorder. Pet. Ex. 65 at 7; Tr. 308.

During cross-examination, Dr. Kendall conceded that A.K. did not exhibit a number of the features listed under Bernier that she had previously scored as present. Tr. 308-14. These concessions ruled out any of the "major" criteria for clinical presentation, histology, function or molecular pathogenicity in A.K. *Id*. Ultimately, Dr. Kendall conceded that she could not reach the conclusion that A.K.'s diagnosis was "definite" under Bernier and instead argued that his diagnosis would be considered "probable" based on enzymology, metabolic indicators of impaired respiratory chain function, and clinical features compatible with a respiratory chain defect.[129] Tr. 314, 317-19.

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scoring." Court Ex. I at 1404. However, based on Dr. Kendall's reliance on Bernier, and her explicit statement that the Nijmegen criteria were inapplicable, and Dr. Cohen's concession to the application of the Bernier criteria, I will evaluate the experts' opinions and the facts of the case in the context of the Bernier criteria. Although the Nijmegen standard appears to be more applicable to the diagnosis of a child, to the extent it can be viewed as a more stringent standard, using it over petitioners' expert's objection is not warranted. And, it is unnecessary to consider the more specific and tailored Nijmegen criteria here, because I conclude that petitioners have not even established that A.K. has a mitochondrial disorder under the broader Bernier criteria.

[127] Metabolic indicators of impaired respiratory chain function are a minor finding only. Court Ex. I at 1404.

[128] A definite diagnosis requires a finding of either two major criteria or one major plus two minor criteria. A probable diagnosis includes either one major plus one minor criterion or at least three minor criteria. A possible diagnosis requires either a single major criterion or two minor criteria, at least one of which is clinical. Pet. Ex. 90 at 1407.

[129] Although she did not specify why she altered her diagnosis, Dr. Kendall's change from a definite to a probable diagnosis under Bernier was likely an indication that she did not believe that A.K. met the threshold for a "major" enzymology finding under Bernier. That is, having contended that A.K. demonstrated minor findings in two categories – clinical features and metabolic indicators – a major finding in enzymology would have been sufficient for her to maintain her position that A.K.'s diagnosis was definite. A minor enzymology finding, however, would support only a "probable" diagnosis, providing minor findings in three categories. In this regard it is also worth noting that, as described in more detail

Thus, the critical questions are whether Dr. Kendall's interpretation of A.K.'s enzymology results, clinical features and metabolic indicators can withstand scrutiny as a general matter and, if so, to what extent those features match the thresholds established by the Bernier criteria. For the reasons discussed below, I find that the Dr. Kendall's analysis largely falls short in both regards.

1. Enzymology.[130]

Under the Bernier criteria, enzymology results will support a mitochondrial disorder diagnosis as a "major" finding if the results show less than 20% of normal (*i.e*. mean) activity in any respiratory chain complex in a tissue, less than 30% of any respiratory chain complex in a cell line, or less than 30% of activity of the same respiratory chain complex in two or more tissues. Pet. Ex. 90 at 1407, Table 1. Enzymology will constitute a "minor" finding if the same tests show results of 20-30% for tissue or 30-40% for either a cell line or two or more tissues. Pet. Ex. 90 at 1407, Table 2.

In A.K.'s case, his enzymology results from Dr. Shoffner indicated results of 41 and 76 in two different assays (n-decyl CoQ and CoQ1)[131] of Complex I against means of 85 and 246.[132] Pet. Ex. 32, p. 35. This calculates to activity levels of approximately 48% and 31% of the reported mean respectively. Based on these figures, Dr. Shoffner concluded that a Complex I defect "appears likely." *Id*. These are the figures and conclusion on which Dr. Kendall relied when she claimed that A.K.'s enzymology results satisfied the Bernier diagnostic criteria. Tr. 245-48. Clearly, however, these results, though falling below the mean, do not fall low enough to be considered an abnormal finding under Bernier, either major or minor.[133]

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below, even using Dr. Kendall's preferred approach, Dr. Shoffner's enzymology results do not reach the threshold for a major finding under Bernier.

[130] Enzymology is a process of measuring the enzyme activity of an individual mitochondrial complex in isolation from the rest of the respiratory chain. Tr. 1078. The process involves mechanically breaking apart the mitochondria to extract the individual complex. The sample is then placed in a substrate medium optimized to that complex's function. *Id*. As time elapses the sample processes the surrounding substrate as it would within the respiratory chain. *Id*. The test results in a measure of velocity, or the rate of that processing over time. Tr. 1080-81. The concentration of substrate in the testing medium is increased until the velocity rate reaches maximum velocity, the point at which the concentration of the substrate is no longer a limiting factor. This leaves the complex itself as the limiting factor. Tr. 1083-84.

[131] Complex I's natural substrate is ubiquinone, also called CoenzymeQ or "CoQ"). Res. Ex. UU, Tab 6, D. Kirby, et al, *Biochemical Assays of Respiratory Chain Complex Activity*, Chapter 4, METHODS IN CELL BIOL., 80: 93-119 (2007), at 103 [hereinafter "Kirby, Res. Ex. UU, Tab 6"]. The most common form of CoQ in mammals is CoQ10; however, it is largely insoluble in aqueous assays. *Id*. Short chain coenzyme Q analogs, which are soluble, provide more reliable assays. *Id*. However, Dr. Shoffner's report did not explain why he used n-decyl CoQ and CoQ1. Pet. Ex. 32, p. 35.

[132] The unit of measure for enzyme activity is "nanomoles of substrate/minute/mg mitochondrial protein." Pet. Ex. 32, p. 35.

[133] The result for the CoQ 1 assay at 31% (based on the raw data) is very close to the 30% threshold for a minor finding under Bernier. The Bernier authors cautioned that there is "no clear cut-off between normal and abnormal activities" and that these percentages are "arbitrary." Pet. Ex. 90 at 1409. Doctor Cohen likewise acknowledged the "arbitrariness" of these figures, but noted that they generally conform to the

But even if Dr. Shoffner's raw data did fall below the Bernier threshold, there is a further issue with applying Dr. Shoffner's raw data to the Bernier criteria. The Bernier threshold is not based on raw numbers; it calls for an adjusted figure that is normalized against one of two other enzyme assays typically performed, either citrate synthase or Complex II. Pet. Ex. 90 at 1407, Tables 1-2. After performing that calculation, both Drs. Wallace and Cohen pointed out that that A.K.'s enzymology results are much higher than reflected in the raw data and would be considered normal under Bernier (within the 95% confidence interval) when the raw data is normalized over the citrate synthase finding. Tr. 1107-08, 1206-08. Although Dr. Kendall maintained that the use of raw numbers is a valid approach, she acknowledged on cross examination that the distinction means that A.K. did not, strictly speaking, meet the Bernier enzymology standard. Tr. 311-12.

The question of whether to normalize raw enzymology results is a professional judgment and one for which there is no consensus in the field. Tr. 1211-12. Respondent's experts, however, have persuasively argued that normalization is the superior approach and that it yields a more accurate result in this case in particular, in addition to being the methodology required under Bernier. Tr. 1100-04, 1210-11. They described Complex I as being the most complicated of the five respiratory (electron transfer) chain complexes, and the one most difficult to extract from the mitochondria. Tr. 1102-05, 1210-11. They indicated that as a result of that difficulty, Complex I assays often produce unreliable or highly variable raw data. *Id*. By measuring the Complex I results against citrate synthase (a water soluble enzyme of the Krebbs cycle), laboratories can account for the degree of loss caused by the extraction process. *Id*. This normalization provides more consistent results among different laboratories. *Id*. Doctor Cohen further explained that because citrate synthase is universally present in living cells and critically important to cellular function, it remains a good proxy for establishing how successful the extraction process was in any given case. Tr. 1210-11. Both Drs. Cohen and Wallace opined that the results are more reliably interpreted when normalized over citrate synthase and that in A.K.'s case those normalized results show no Complex I defect in A.K. Tr. 1107-08, 1209-12.

Doctor Kendall relied on the lack of consensus on the proper approach to interpreting enzymology results, but she did not advance any argument as to why using the raw data – in this case or in any case – would be a better approach.[134] Doctor

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level which divides symptomatic from non-symptomatic patients. Tr. 1208-09. Thus, he stated that he would still consider 31% as a result outside the abnormal range under Bernier. Tr. 1210.

[134] Doctor Kendall asserted that Dr. Shoffner reported raw data because of his position that the citrate synthase levels can be falsely decreased, making the normalized results unreliable. Tr. 312. She did not, however, explicitly adopt, defend or substantiate that view. In contrast to Dr. Kendall's apparent deference to the absent Dr. Shoffner, respondent's argument in favor of interpreting the enzymology in light of citrate synthase is supported not only by both Dr. Wallace and Dr. Cohen's explanations, but also by multiple studies in evidence in this case. *See, e.g.,* Bernier, Pet. Ex. 90; F. Gellerich, et al, *The problem of interlab variation in methods for mitochondrial disease diagnosis: enzymatic measurement of respiratory chain complexes*, MITOCHONDRION 4: 427-39 (2004), filed as Res. Ex. UU, Tab 3; Kirby, Res. Ex. UU, Tab 6. Each of these papers recommends using results calculated against citrate synthase. And it is, of course, highly significant that among these is the very Bernier criteria that Dr. Kendall relied upon and cited in her expert report.

Wallace did acknowledge that normalizing over citrate synthase is not a perfect approach in that citrate synthase can also be lost in the extraction process. Tr. 1104-5. He also noted, however, that the instability of citrate synthase can be accounted for by additionally or alternatively normalizing the enzymology results over Complex II and that when he performed that calculation in this case, A.K.'s results, when normalized over Complex II, still remain normal. Tr. 1104-05, 1108-09.

Furthermore, looking at the specifics of A.K.'s results in particular, respondent's experts also point out that, when compared to other findings made by Dr. Shoffner, the reported Complex I defect looks more like an aberration than a true defect, lending further credibility to the argument that the normalized results, which show no defect, are more accurate in this case. Specifically, Dr. Cohen pointed out that, even as a raw figure, A.K.'s assay measuring a combined Complex I and Complex III showed no abnormality. Tr. 1212. He argued that if Complex I activity was truly decreased, one would expect a combined figure including Complex I to likewise show a decrease. *Id*. Indeed, Dr. Cohen, pointed out that many laboratories report only the combined Complex I and III results as a proxy for the Complex I results, finding it to be a more "robust assay." *Id*.

Another significant point is that A.K.'s respirometry results – a measure of the functioning of the entire mitochondrial respiratory chain – were equivocal. As with the Combined Complex I and III results, Dr. Wallace argued that if there was a true Complex I defect, its impact should be evident in the broader respirometry results. Tr. 1110-11. The fact that this result is equivocal suggests that the respiratory chain as a whole is functioning normally – or at least not functioning in a demonstrably abnormal way – and that there is therefore an insufficient basis to argue the presence of a defect. *Id*. Doctor Cohen likewise stressed that the equivocal finding indicates that Dr. Shoffner did not find anything supportive of a Complex I defect on respirometry. Tr. 1212-13. In that regard, I note that Dr. Shoffner himself indicated that "high resolution respirometry may more closely reflect the in vivo state of the respiratory chain and oxidative phosphorylation function." Pet. Ex. 32, p. 45.

Doctor Wallace also noted that Dr. Shoffner supported his Complex I finding by citing "correlative protein chemistry changes" shown on a "Western blot" test. Tr. 1113; Pet. Ex. 32, p. 3. He pointed out that, although Dr. Shoffner listed a "possible" decrease in the ND6 subunit within Complex I, the actual numbers generated by the Western blot support a "normal" finding for ND6. Tr. 1077, 1112. Doctor Cohen agreed that the finding for Complex I was normal, and that such a finding is incongruent with the enzymology result. Tr. 1213-14. Doctor Wallace further noted that Dr. Shoffner's interpretation of the ND6 finding as potentially decreased was not supported by subsequent genetic testing which found no mutation to the ND6 gene. Tr. 1113-15.

Doctor Kendall did not delve into the details of Dr. Shoffner's report. Pet. Ex. 65 at 3, 7. She offered no rebuttal to any of these points, aside from simply reciting Dr. Shoffner's findings. In fact, by the time of her testimony, Dr. Kendall indicated that she couldn't even remember if respirometry had been performed. Tr. 314.

Thus, respondent's experts persuasively argued that the best interpretative approach, normalizing over citrate synthase and/or Complex II, indicated that A.K.'s

enzymology testing showed no defect in Complex I. Moreover, even if I accepted the Dr. Shoffner's finding of a Complex I defect at face value, respondent's experts established that, in light of the overall results reported by Dr. Shoffner, the "defect" was better characterized as an incongruent finding, rather than evidence of a respiratory chain defect or dysfunction.

2. Metabolic Indicators.

The Bernier paper did not define what constituted a finding of a metabolic indicator of impaired respiratory chain function, beyond noting that a number of subjects were given such a coding based on a finding of elevated lactic acid in either blood or cerebral spinal fluid. Pet. Ex. 90 at 1409. In her expert report, Dr. Kendall indicated that "persistent, significant elevations in lactate," constitute an indicator of mitochondrial disorders.[135] Pet. Ex. 65 at 5. Doctor Cohen similarly noted that evidence of persistently elevated lactate is necessary for the lactate level to be considered indicative of a mitochondrial disorder. Tr. 1199-1200.

Doctor Cohen explained that a problem with using elevated lactate levels as a metabolic indicator of a mitochondrial disorder is the difficulty in collecting blood under conditions that do not artificially elevate lactate. Another problem is the lack of specificity of elevated lactate, which can be indicative of factors other than mitochondrial defects, including such common occurrences as exercise.[136] Res. Ex. SS, at 11; Tr. 1199-1200. He stressed that the question for mitochondrial patients is whether there is a *chronic* elevation of lactic acid and indicated that one test for lactic acid is never indicative of a mitochondrial disorder. Tr. 1199-1200. Doctor Kendall also acknowledged that lactate tests are subject to collection errors and that lactate findings should be confirmed either through multiple tests showing a persistent elevation or by considering the lactate finding as a ratio to pyruvate.[137] Tr. 357-59. Although she indicated that she would not "completely discount" an otherwise unconfirmed elevation in lactate, Dr. Kendall did agree that it would "raise an indicia of suspicion that the elevated lactate might be a collection artifact." Tr. 358. She seemed to acknowledge

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[135] Doctor Kendall also noted in her expert report that decreased plasma carnitine, increased blood alanine, generalized aminoaciduria, and findings of Kreb cycle intermediates, tiglygylcine, and 2-oxoadipic acid on organic acid analysis are also biochemical markers supportive of a mitochondrial disorder. Pet. Ex. 65 at 7, 12 (table 2). She did not, however, indicate that any such findings were made in A.K.'s case. As part of his evaluation of A.K., Dr. Shoffner did a metabolic work up, including blood, urine and cerebral spinal fluid testing, and found no abnormalities whatsoever. Pet. Ex. 32, p. 1.

[136] For this point, Dr. Cohen cited R. Hass, et al., *The In-depth Evaluation of Suspected Mitochondrial Disease: The Mitochondrial Medicine Society's Committee on Diagnosis*, MOL. GENET. METAB. 94(1): 16-37 (2008) (unedited prepublication manuscript), filed as Res. Ex. SS, Tab 7 [hereinafter "Haas, Res. Ex. SS, Tab 7"]. This paper indicated that "spurious elevation of plasma lactate is indeed the most common cause, resulting from either a patient (usually a child) struggling or the prolonged use of a tourniquet during sample collection." Res. SS, Tab 7 at 3. Another article by Hass, Pet. Ex. 63, Ref. 17, contains a table titled "Causes of Plasma Lactate Elevation," listing a variety of reasons for elevated lactate. *Id.*, Table 2, at 147.

[137] There has been no suggestion in this case that A.K.'s elevated lactate was confirmed via computation of a lactate/pyruvate ratio. For example, when Dr. Shoffner ran his tests in August of 2008, A.K. showed normal lactate and pyruvate. Pet. Ex. 32, pp. 17-21. And on July 1, 2002, when A.K. did test high for lactate, pyruvate does not appear to have been measured. Pet. Ex. 3, p. 375.

that reliance on "one or two lactate levels" as demonstrative of mitochondrial dysfunction would be subject to challenge. Tr. 362.

Doctor Kendall contended that A.K.'s lactate tests evidenced a mitochondrial disorder, because they showed "elevated lactate levels on a number of occasions." Pet. Ex. 65 at 7; Tr. 250. This position was not supported by the facts. Petitioners identified only one instance in which A.K. had elevated lactate (*see* Pet. Ex. 3, p. 375), while respondent pointed to multiple instances of normal or near normal lactate levels[138] Pet. Exs. 3, pp. 303, 333; 32, p. 17. Moreover, in the one instance of elevated lactate, the pyruvate level was not reported. Pet. Ex. 3, p. 375. Even if this instance did not involve a collection artifact or some benign reason for elevation, Dr. Kendall acknowledged that a single instance of elevated lactic acid compared to multiple instances of normal findings would not be indicative of persistent, significant elevation, which is what she opined was necessary for lactate levels to be evidence of a mitochondrial disorder. *Compare* Pet. Ex. 65, p. 5 *with* Tr. 316.

Thus, Dr. Kendall, in an apparent retreat from her claim of multiple instances of elevated lactic acid, ultimately opined that in A.K.'s case his elevated AST/ALT ratio[139] was "more of a biomarker" than his lactate levels, because that elevation was persistent. Tr. 402-03. Doctor Kendall has not, however, substantiated her opinion that elevated AST or an elevated AST/ALT ratio is a biomarker for mitochondrial disorders.

Although she listed elevated AST values as an indicator of mitochondrial disorder in her expert report, Dr. Kendall provided no accompanying citation. Pet. Ex. 65, p. 4. In her testimony, she indicated that "Richard Kelley has published some information about if the ratio is elevated between the two of them [referring to AST and ALT] that can be indicative. It's a biomarker for mitochondrial disease." Tr. 362. Doctor Kendall provided no specific citation, however, nor did I find any article authored by Richard Kelley cited in her report or filed anywhere in the extensive record of this case. Indeed, in discussing Dr. Kendall's assertion in their post-hearing brief, petitioners cited Pet. Ex. 40,[140] rather than any publication by Dr. Kelley. ECF No. 297 at 73. This citation was

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[138] Doctor Cohen, who routinely uses Dr. Shoffner's lab, noted that he believed Dr. Shoffner's measures of both lactate and pyruvate to be very accurate. Tr. 1197-98. Doctor Shoffner found A.K.'s lactate and pyruvate levels to be normal when he conducted his complete metabolic analysis. Pet. Ex. 32, pp. 17-21.

[139] *See* n.43 (defining "AST"). "ALT" stands for "alanine aminotransaminase." ALT is found predominantly in the liver, and ALT elevations are most often caused by liver dysfunction, including hepatitis and cirrhosis. MOSBY'S LABS at 39-40. The ratio between the two tests is used to differentiate viral hepatitis from other liver diseases. *Id*. Diagnosis of mitochondrial disorders is not listed as one of the conditions for which this test has clinical significance. *Id*. at 40.

[140] Petitioners referred to this Brief Communication, published in the JOURNAL OF CHILD NEUROLOGY, as the "Zimmerman mitochondrial regression report." ECF No. 297 at 110. This labeling was disingenuous. Doctor Zimmerman is listed as the senior researcher (the last listed author) on the case report. *See* Pet. Ex. 40, *Developmental Regression and Mitochondrial Dysfunction in a Child With Autism*, J. CHILD NEUROL. 21(2):1-3 (2006). However, the principal author was Jon Poling, and another author was John Shoffner, the clinician who performed the mitochondrial disorder testing on A.K. *Id* .at 2. Most journal articles are cited by the name of the first author or by all authors, rather than by the name of the senior researcher alone. A perusal of Pet. Ex. 40 reveals that the exhibit is the same as the Poling article, Res. Ex. MM, Tab 14, and also filed as Pet. Ex. 63, Ref. 18 and as Pet. Ex. 91 (the clearer of the latter two copies). This, in turn, is the same article criticized by the editor in chief of the journal in which it appeared

misplaced, in that this citation to Dr. Kelley's unpublished research in Pet. Ex. 40 did not involve using the AST/ALT ratio as a marker for mitochondrial dysfunction; rather, Dr. Kelley's unpublished work was cited for use of the alanine to lysine ratio as a surrogate for pyruvate measurements. Pet. Ex. 40 at 1.

Although the authors of Pet Ex. 40 speculated that findings of elevated AST on a retrospective evaluation of laboratory records might be suggestive of abnormal mitochondrial function, that conclusion was not actually supported by the findings. Pet. Ex. 40 at 2. Rather, they reported elevated AST, but not ALT, among subjects with *autism*, not mitochondrial defects, as compared to typically developing controls. *Id*. Moreover, the authors cautioned that even this retrospective evaluation lacked the data necessary to rule out false-positives. *Id*.

Petitioners further cited Weissman, Pet. Ex. 39, a cohort analysis of 25 children with mitochondrial disorder and ASD diagnoses, as evidence that AST/ALT is a marker of mitochondrial disorder. ECF No. 297 at 9. Doctor Cohen was one of this study's authors. The Weismann study provided scant support for this contention. The researchers conducted "a chart review of the biochemical, genetic and histopathological findings in 25 patients with ASD who had unequivocal evidence of a disorder of oxidative phosphorylation," *i.e*., a respiratory chain defect: *Id.* at 1. These were children with an ASD diagnosis "referred for genetic and/or metabolic evaluation of autism, but not specifically for evaluation for mitochondrial disease." *Id.* at 2. Thus, the study was not composed of randomly selected ASD patients; something in their medical history or clinical picture suggested that additional screening for a genetic or metabolic problem was recommended. As a part of that screening the Weismann researchers looked at AST/ALT results, but did not list these results as a part of the biochemical evidence of mitochondrial dysfunction, listing only "increased blood lactate and pyruvate levels, elevated plasma alanine level, and increased urinary levels of Krebs cycle intermediates or 3-methylglutaconate." *Id*. at 2.

Although 52% of subjects showed some abnormality of AST and/or ALT, the authors did not indicate why they considered the AST/ALT ratio at all, much less indicating that it was a marker of mitochondrial disease. Weismann, Pet. Ex. 39 at e3815. To the extent that liver dysfunction can be seen in mitochondrial disease (*see* Bernier, Pet. Ex. 90 at 1407, Table 1, listing the hepatic organ system as one of the possible symptoms in which mitochondrial disorder symptoms might present), perhaps the Weismann researchers were looking for evidence of liver problems.

Doctor Wallace testified that, despite researching the question, he could not find any peer-reviewed literature indicating that either AST or ALT was considered a marker for mitochondrial disease. Tr. 1116-17. Similarly, Dr. Cohen indicated based on his own observations of an ongoing 30-subject clinical trial he is conducting, that there was

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for the failure of the authors to disclose that Dr. Poling was the father of the child whose case was reported. *See* n.216, *infra*. in Section VIII.A.3.a, where I discuss the reasons this article, regardless of name, has little evidentiary value in terms of petitioners' theory of causation.

no correlation between AST or ALT and mitochondrial disorders.[141] Tr. 1203-04. Doctor Cohen also pointed out that there are other simple explanations for elevated AST levels that have nothing to do with mitochondrial disorders. Tr. 1203-04.

Doctor Cohen testified that elevated AST is an indicator of muscle breakdown, which may be seen in active children. Tr. 1203-04. He opined that if A.K.'s elevated AST was the result of a chronic process, rather than the result of activity, elevated creatine kinase ["CK"] would be present as well. Tr. 1202. Both the Weissman paper and the Poling case report (Pet. Exs. 39 and 40, respectively) cited by petitioners reported the AST/ALT levels in conjunction with CK values. Pet. Ex. 39 at 3; Pet. Ex. 40 at 2. Doctor Cohen noted, however, that A.K. did not have elevated CK, which suggested that his AST/ALT ratio results were not significant as an indicator of a mitochondrial problem. Tr. 1202.

Finally, there was also some suggestion by petitioners that elevated ammonia levels could also be considered a marker of mitochondrial disorders. Doctor Kendall never actually opined that elevated ammonia was an indicator of mitochondrial dysfunction, never cited elevated ammonia when discussing the signs of mitochondrial disorder in A.K.'s case, and declined to even opine that the finding of elevated ammonia in A.K.'s case was genuine.[142] Tr. 244-47, 249-51, 317, 400. Respondent's experts also disputed that elevated ammonia is itself an indicator of mitochondrial disease. Tr. 1127-28, 1204-06. In particular, Drs. Cohen and Wallace both noted that ammonia can be elevated for many reasons, including digestion, lack of sleep, illness or other stresses. *Id*. Doctor Cohen indicated that it is a "very nonspecific marker," and both opined that it would not be of any clinical significance to a mitochondrial disorder without a corresponding elevation in glutamine, which A.K. did not have.[143] *Id*.

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[141] I add that I did not give much weight to Dr. Cohen's testimony about his on-going, but unpublished, research but did not discount it entirely, as experts frequently use their own clinical experiences in forming opinions.

[142] Doctor Boris, A.K.'s pediatrician, testified that he believed the elevated ammonia was an indicator of abnormal metabolism. Tr. 172-73. Similarly, in his expert report, Dr. Deth also indicated that elevated ammonia is suggestive of a mitochondrial dysfunction. Pet. Ex. 117 at. 5. Neither of these doctors, however, is qualified to diagnose a mitochondrial disorder. Indeed, as previously indicated, Dr. Deth explicitly deferred to the other experts in this case on that subject. Tr. 796. In their post-hearing brief, however, petitioners juxtaposed Dr. Kendall's above-discussed opinion regarding lactate and AST with the additional fact of A.K.'s elevated ammonia (*see, e.g.,* ECF No. 297, p. 54) before ultimately arguing that "Dr. Deth and Dr. Kendall both testified that all of these findings taken in totality are suggestive of metabolic disorder." ECF No. 297, p. 74. This is a disingenuous attempt to bring their argument regarding the significance of the elevated ammonia under the imprimatur of Dr. Kendall, their only mitochondrial expert in this case. The only time Dr. Kendall ever actually discussed the elevated ammonia findings, she explicitly indicated that it "might not be" of any significance and cautioned that ammonia in particular needs to be handled carefully. She specifically testified that she "can't tell" if the elevation was genuine. Tr. 400. I resolve the conflict between the opinions of Drs. Deth and Boris that the presence of high ammonia is significant to the diagnosis of mitochondrial disorders and the opinion of Dr. Cohen that it is not, in favor of Dr. Cohen's position.

[143] In a prior decision I noted that "In individuals with urea cycle disorders, an illness (or dehydration due to an illness) may produce an excess of ammonia in the body, termed "hyperammonemia," resulting in a metabolic decompensation." *See Holt,* 2015 WL 4381588, *24. Doctor Kendall, however, specifically noted that A.K. does not have a urea cycle disorder. Tr. 359-60.

Thus, contrary to petitioners' argument, none of the testifying mitochondrial experts in this case assigned any significance to the finding or elevated ammonia. Nor have petitioners established that AST, ALT, or the ratio of the two, represents a hallmark of mitochondrial disorder. And although the experts agree that chronic or persistent elevation of lactic acid is an indicator of mitochondrial disorder, the evidence in this case does not establish any such persistent elevation, showing at most only one instance of elevated lactic acid.

3. Clinical Features.

Doctor Kendall identified a number of clinical features of mitochondrial disorders, Pet. Ex. 65 at 11, Table 1 and argued that, among those features, A.K.'s medical history is significant for the following: ASD, developmental delay, hypotonia[144], gastrointestinal problems, fatigue, and temperature instability/autonomic dysfunction.[145] Tr. 249-51, 252. These are the same clinical features included in Dr. Shoffner's brief clinical summary. Pet. Ex. 32, p. 1. Doctor Cohen agreed as a general matter that these symptoms can be present with mitochondrial disorders; however, he characterized them as "nonspecific findings." Tr. 1173-1176; Pet. Ex. FFF at 2-3. Absent confirmation from history, physical examination, or laboratory results, Dr. Cohen did not find these clinical presentations diagnostic of a mitochondrial disorder. Tr. 1186. Rather, citing Haas, Res. Ex. SS, Tab 6,[146] Dr. Cohen argued that A.K. does not have any of the "classic" mitochondrial phenotypes or "red flags." Tr. 1169-73; Res. Ex. SS, Tab 6 at 1327 (Table 1), Red-Flag Findings in Mitochondrial Disease.

Doctor Kendall did not address the distinction between clinical symptoms that would be considered diagnostic "red flags" versus nonspecific findings. Her table of mitochondrial disorder symptoms within her expert report is not so divided and in her testimony she merely states that "clinically, [A.K.] has a number of features that you certainly see in mitochondrial disease." Pet. Ex. 65 at 11; Tr. 249. Her table reflects a kitchen sink list of symptoms, few of which appear on Dr. Haas' "Red Flag" Table 1. Res. Ex. SS, Tab 6, at 1327.

Her argument seems to be that having a sufficient number of relevant clinical symptoms – regardless of which particular symptoms – is a basis for putting a patient "into that basket," *i.e.,* diagnosing a mitochondrial disorder. Tr. 250. This is consistent with her review article on mitochondrial disorder diagnosis, which indicates that the

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[144] The transcript reflects that on direct examination, Dr. Kendall indicated that "hypertonia" was an indication that A.K. had a mitochondrial disorder. In her expert report, however, Dr. Kendall indicated that A.K. was "hypotonic" (Pet. Ex. 65 at 2) and that low muscle tone was a sign of mitochondrial disease (Pet. Ex. 65 at 4.) Moreover, on later questioning, Dr. Kendall referenced "low tone" when reiterating which clinical indicators she believed to be relevant to A.K.'s diagnosis. Tr. 363. Thus, this reference to hypertonia is likely a typographical or transcription error. I can find no other instance where Dr. Kendall sought to link hypertonia to mitochondrial disease.

[145] Doctor Kendall also indicated that regression was another factor in her clinical diagnosis. Tr. 252. For the reasons discussed in Section VII.C, below, however, I have found that A.K. did *not* experience a regression as petitioners alleged.

[146] Doctor Cohen was a co-author of this article, as was Nicole Wolf, one of the co-authors of Court Ex. I, the article establishing the Nijmegen diagnostic criteria.

presence of "widespread, seemingly unrelated multisystem problems" is itself "highly suggestive of mitochondrial disease." Pet. Ex. 172 at 195.

According to the Haas article, "some symptoms and signs truly are more suggestive of a mitochondrial disorder than others." Ex. SS, Tab 6 at 1327. So-called "red flag" findings "warrant the initiation of a baseline diagnostic evaluation for mitochondrial disease" while "nonspecific" symptoms (such as A.K. has) "frequently occur in infants and children with mitochondrial disease but have a broad differential diagnosis, and more often lead to other clear diagnoses." *Id*. Thus, Dr. Cohen noted, that the presence of ASD and developmental delays, which were key clinical findings for Dr. Kendall, also occur in children with other types of neurological conditions. Tr. 1186. A study by Oliviera, et al,[147] found that only a small percentage of children with ASD had evidence of mitochondrial disorder.[148] Tr. 1184-85. Even Dr. Kendall acknowledged, for example, that mitochondrial disorders cannot explain the imbalanced male-female ratio in ASD. Tr. 260. Thus, autism should not be considered a "red flag" for a possible mitochondrial disorder. Even if mitochondrial disease occurs in the ASD population at a higher rate than in the general population, the vast majority of ASD cases do not have the co-morbid mitochondrial diagnosis, much less a causal relationship between the two diagnosis. Perhaps this explains why Dr. Cohen does not believe that a child with A.K.'s presentation, and most notably his ASD, warrants screening for ASD.

Given the lack of evidence of mitochondrial disorder in this case in terms of histology, function, molecular pathogenicity, genetics, enzymology, and metabolic indicators, the lack of any red flag findings in A.K. is highly significant. Although Dr. Cohen could not rule out the possibility that one could have a mitochondrial disorder without any manifestation of the "red flag" findings (Tr. 1170-73), that is an issue different from the one presented here—petitioners' burden to demonstrate that A.K. actually has such a disorder. In that regard, Dr. Cohen opined that, by today's standards, a patient with A.K.'s clinical features (most notably ASD) would not even be screened for a mitochondrial disorder, absent multiple positive findings on blood and urine testing. Tr. 1183. And indeed, Dr. Kendall was unable to opine based on clinical features alone that A.K. in fact had any mitochondrial disorder based on the Bernier

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[147] Pet. Ex. 38, G. Oliveira, et al, *Epidemiology of autism spectrum disorder in Portugal: prevalence, clinical characterization, and medical conditions*, DEVELOP. MED. & CHILD NEUROL. 49: 726-733 (2007) [hereinafter "Oliveira, Pet. Ex. 38"].

[148] Doctor Cohen indicated that the Oliveira study showed that 7% of the studied population had evidence of mitochondrial dysfunction based on electron transport chain testing. Tr. 1185. In fact, the study indicated that approximately 4% of ASD cases had co-morbid mitochondrial disorder diagnoses. Pet. Ex. 38 at 730 (Figure 1). The authors indicated that 102 idiopathic cases of autism were evaluated and of those, five patients were classified as having a definite mitochondrial disorder. *Id*. at 730. Nonetheless, the authors noted that this represented an "unexpectedly high rate" of respiratory chain disorders. *Id*. at 726. Significant to Dr. Cohen's point, however, after screening these subjects for related conditions including mitochondrial disorders, the study found that 80% of cases were still considered idiopathic. *Id*. at 730 (Figure 1).

criteria. At most he would satisfy only one *minor* criteria, which is insufficient for a diagnosis.[149] Pet. Ex. 90 at 1406-07.

Moreover, in reviewing Dr. Kendall's expert report, testimony, and her own review article, I do not see any indication that Dr. Kendall would diagnose a mitochondrial disorder based on clinical features alone. For example, even in regard to a well-defined mitochondrial disease with a clear constellation of symptoms, such as seen in Leigh disease, Dr. Kendall still indicated that a diagnosis must be confirmed by at least "minimal" testing. Pet. Ex. 172 at 196. Where those clinical features, while *consistent* with mitochondrial disorder, are not red flags for or, in Bernier's terms, "essentially pathognomonic" for a respiratory chain disorder, and, in fact, more often lead to *other* diagnoses, a diagnosis based on clinical features alone would be overreaching. Haas, Res. Ex. SS, Tab 6 at 1327; Bernier, Pet. Ex. 90 at 1407 (Table 1).

Additionally, Dr. Cohen challenged certain aspects of Dr. Kendall's clinical summary. For example, he questioned whether A.K. in fact had hypotonia, noting that while Dr. Boris recorded hypotonia in his notes, Dr. Rapin instead identified "loose joints." Doctor Cohen argued that loose joints, an unrelated condition not associated with mitochondrial disorders, is frequently misdiagnosed as hypotonia, noting that he himself has made the error. Tr. 1193-94. He also drew a distinction between alternating constipation and diarrhea such as A.K. had, with pseudo-obstruction, which is a non-physical blockage often requiring hospitalization. Although Dr. Cohen noted that he has seen mitochondrial disorder patients with constipation, he stressed that only a pseudo-obstruction would constitute a classic phenotype for a mitochondrial disorder, and indicated that A.K.'s constipation was more likely to be associated with his ASD, than indicative of a mitochondrial disorder. Tr. 1186-89, 1220-21; Ex. FFF at 3. Doctor Cohen observed that if A.K.'s constipation was related to a mitochondrial disorder, one would expect to see some "red flag" findings, such as "findings in the classic mitochondrial phenotype description." Tr. 1304. Nothing in Dr. Kendall's testimony directly rebutted any of these points.

D. A.K.'s Medical Records Do Not Establish that A.K. has a Mitochondrial Disorder.

In addition to Dr. Kendall's opinion, petitioners also argued that A.K.'s mitochondrial disorder was evidenced by the diagnoses and opinions of several treating physicians. They therefore assert that A.K.'s medical records are sufficient to meet their burden of proof on the question of A.K.'s mitochondrial disorder diagnosis. ECF No. 297 at 17. Indeed, petitioners claim that "the medical evidence, both diagnostic and clinical establishing that A.K. has a mitochondrial disorder, is overwhelming." *Id*. Specifically, petitioners highlight the laboratory findings of Dr. Shoffner, which they argue were "reviewed and affirmed by several other practitioners expert in or familiar

[149] As previously indicated, Dr. Kendall testified that she could not opine that A.K.'s clinical symptoms met the requirements for a major finding under Bernier. Specifically, she conceded that A.K. does not have a clinically complete respiratory chain encephalomyopathy and that she could not identify a "progressive clinical course with episodes of exacerbation" as would be necessary to alternatively conclude that he had a mitochondrial cytopathy. Tr. 309-10. Doctor Kendall testified that she did not see any evidence of any progression or worsening of A.K.'s mitochondrial disorder. Tr. 325.

with mitochondrial disorder." *Id*. at 11. Those practitioners are Drs. Sims, Korson, Hoffman, and Alvarez-Altalef.[150] *Id*. at 11-15.

Although petitioners' argument encompassed both the fact of these treating physicians' diagnoses as affirmation of their claim, as well as the underlying clinical data on which the physicians relied, this section deals exclusively with the significance of the alleged diagnostic statements themselves. In the preceding section, I have already addressed the most pertinent underlying clinical data addressed by Dr. Kendall and found it lacking. None of these treating physicians' reports provide any additional evidence bearing on the validity of—or, more accurately, the significance of the data to a correct and accurate—mitochondrial disorder diagnosis. Moreover, although these records contain extensive clinical histories, the physicians who took the histories largely declined to assign diagnostic significance to the clinical symptoms reported. This is unsurprising, in that these records do not represent the independent diagnoses that petitioners claim they do.

Although contemporaneous records from treating physicians are normally given considerable weight,[151] petitioners dramatically overstated the significance of the record notations made in this case. As an initial matter, the "diagnosis" made by Dr. Shoffner is of dubious provenance, something that would not be apparent to a treating physician simply informed of the diagnosis or even one who read the summarized report. For the reasons described in Section VI.C, above, there are considerable problems with Dr. Shoffner's diagnosis of a Complex I defect, based on both on his own testing and on symptomology reported by petitioners. Even Dr. Kendall acknowledged the problems evident in Dr. Shoffner's diagnosis.

To the extent a mitochondrial diagnosis requires clinical evaluation in addition to laboratory findings, there is no evidence to suggest that Dr. Shoffner had access to A.K.'s complete medical history or conducted any physical examination of A.K to

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[150] Petitioners also cited a consultation report by Dr. Marcel Kinsbourne as further confirmation of A.K.'s diagnosis (Pet. Ex. 48; ECF No. 297 at 16-17). This report was filed as a part of petitioners' efforts to buttress their motion for reconsideration (ECF No. 100) of my decision dismissing their petition for failures to prosecute and comply with court orders (ECF No. 99), a motion I subsequently granted (ECF No. 106). Doctor Kinsbourne's report selectively summarized the medical records and affidavits and concluded that "investigations have substantiated [A.K.]'s diagnosis of mitochondrial disorder." Pet. Ex. 48 at 2. Doctor Kinsbourne was neither a treating physician nor a testifying expert in this case. Moreover, unlike neurologists who testified as experts in this case, there is no evidence in the record to suggest that he has any special competency in diagnosing mitochondrial disorders. In any event, Dr. Kinsbourne's report, which contains a discussion of A.K.'s case that is cursory at best, is effectively a restatement of petitioners' contention that Dr. Shoffner's findings were accepted by other treating physicians. Pet. Ex. 48 at 2. The report does nothing to further substantiate that claim or otherwise elucidate the diagnostic issues presented.

[151] *See, e.g., Cucuras v. HHS*, 993 F.2d 1525 (Fed. Cir. 1993) (noting that "medical records, in general, warrant consideration as trustworthy evidence. The records contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. With proper treatment hanging in the balance, accuracy has an extra premium. These records are also generally contemporaneous to the medical events."); *see also Capizzano*, 440 F.3d at 1326 (noting that "treating physicians are likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'").

substantiate the histories provided to him. I have found that Dr. Shoffner's opinion that A.K. "probably" had mitochondrial encephalomyopathy (Pet. Ex. 32, p. 3) is not reliable, as his test results were not normalized as required by the Bernier diagnostic criteria, and were based on reports of symptoms that did not meet the diagnostic strictures of that criteria.[152] Thus, to the extent Drs. Sims, Korson, Hoffman, and Alvarez-Altalef have based their own diagnoses on Dr. Shoffner's report, and depended on his underlying finding of a Complex I defect, their resulting reports would be of equally dubious evidentiary value.[153]

But in any event, petitioner's argument that each of these doctors "accepted" Dr. Shoffner's finding of probable "mitochondrial encephalomyopathy" begs the question of whether that acceptance was critical or passive.[154] To the extent that any of these reports reflected a diagnosis of mitochondrial disorder, they do not reflect any independent application of the diagnostic standards or any interpretive analysis of Dr. Shoffner's findings.[155]

It is not uncommon for treating physicians to rely on a diagnosis supplied by another specialist, and to simply accept that diagnosis at face value. Doctor Kendall suggested as much, indicating during questioning that she saw patients for symptom

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[152] Doctor Cohen, in particular, argued that Dr. Shoffner overstepped in reaching such a diagnosis. Tr. 1220-22.

[153] The issue of this reliance is distinct from any issue regarding the qualifications of these physicians, a separate point which petitioners have stressed.

[154] I find it significant that petitioners are inconsistent in the phrasing of their argument. At some points they argue that these physicians "concluded" that A.K. had a mitochondrial disorder. *See, e.g.,* ECF No. 297 at 57. At other points in their brief, however, they merely argue that these physicians had "accepted" Dr. Shoffner's findings. *See, e.g.,* ECF No. 297 at 74.

[155] The significant issue here is one of interpretation rather than accuracy. As treating physicians, these doctors each had an incentive to be accurate in their diagnosis and no reason to mold their records to a particular outcome, as is often a concern in litigation. That makes their records "trustworthy." *See Cucuras, supra.* The testifying experts in this case have made it clear, however, that there is disagreement among practitioners in this field regarding the proper interpretation of laboratory results and have submitted their analysis of those results to the scrutiny of the court. In the present context, that detailed analysis simply outweighs any competing, yet unexplained, view of A.K.'s treating physicians. *See, e.g., Snyder v. HHS*, 88 Fed. Cl. 706, 745 n. 67 (2009) (emphasizing that a statement of a treating physician is not "sacrosanct" and can be rebutted). I also note that Dr. Shoffner's testing and diagnosis can be viewed as ones sought primarily for the purposes of this litigation. The testing was requested and performed shortly after the entitlement decision in the Poling case was issued and publicized. *See* Res. Ex. MM, Tab 17, R. Brumback, *The Appalling Poling Saga*, J. CHILD NEUROL., 23(9): 1090-1091 (Sept. 2008) [hereinafter "Brumback, Res. Ex. MM, Tab 17"]. Petitioners explicitly withdrew their case as an OAP test case in order to pursue a new theory of causation at around the same time the Poling case became public knowledge. ECF No. 40 (motion to Withdraw, filed Apr. 10, 2008); ECF No. 45 (status report filed July 1, 2008, reflecting that petitioners were pursing "additional medical evaluation and testing for [A.K.} to determine the extent to which theories of causation in addition to the thimerosal theory are applicable."); ECF No. 54 (status report, filed Mar. 3, 2009 (reflecting that their "new theory" was the impact of vaccinations on a child with mitochondrial DNA defects). They sought testing from one of the authors of the Poling case report. The testing performed, the symptoms recorded and relied upon, and the conclusions reached by Dr. Shoffner (*see* Pet. Ex. 32, filed Jan. 16, 2009).have significant shortcomings, as explained by the testimony and reports of Drs. Cohen, Wallace, and at least some of which were acknowledged by Dr. Kendall. *See* Sections VI.C.1-3, *supra*.

management that she has not herself diagnosed.[156] Tr. 372. Moreover, respondent's expert, Dr. Cohen, likewise indicated that he believes it is not uncommon for physicians in this context to accept a prior doctor's statement as true without necessarily arriving at an independent conclusion. Tr. 1223, 1324-25. In fact, Dr. Cohen and Dr. Kendall both indicated that in their own practices they will guide patients through symptom management on a provisional or presumptive basis even where they do not necessarily believe the patient's testing was positive for a mitochondrial disease.[157] Tr. 249, 1223-25.

Doctor Cohen did not believe that the records in this case showed evidence of any independent conclusion by these treating physicians. Tr. 1223. Similarly, Dr. Kendall acknowledged with regard to Dr. Sims's report, for example, that she could not tell from the report whether Dr. Sims had independently reached a diagnosis or simply reported a prior diagnosis. Tr. 354-55.

Doctor Sims noted in her report[158] that A.K. was "recently diagnosed with a type I mitochondrial disorder" and that "the family presents today to initiate management of his mitochondrial disorder." Pet. Ex. 35, p. 13. There is nothing, however, to indicate that Dr. Sims had separately analyzed, let alone agreed with, that diagnosis. In fact, although Dr. Sims specifically noted Dr. Shoffner's findings, she explicitly characterized his data as "incomplete" and indicated in her treatment plan that "we have asked for more complete records particularly the Shoffner mitochondrial work-up detail." Pet. Ex. 35, pp. 13-14. These notations are directly contrary to petitioners' argument that Dr. Sims and the other treating physicians "affirmed" Dr. Shoffner's findings and raise the question of whether any of the doctors were even provided with Dr. Shoffner's complete findings.

Similarly, with regard to Dr. Alvarez-Altalef, petitioners argued that, "based upon her own examination of A.K., her review of A.K.'s history and record and 'extensive workup,' including A.K.'s laboratory reports and the objective findings therein, and a review of the objective findings of Dr. Shoffner, Dr. Alvarez-Altalef concluded that A.K. had a mitochondrial disorder." ECF No. 297 at 15. There is no statement in Dr.

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[156] Specifically, I asked Dr. Kendall "what are the primary reasons that children with mitochondrial disorders and autism come to you? Is it to have the mitochondrial disorder diagnoses?" She responded that "It can be that. *It depends on where they are in the process of being evaluated*, but it certainly can be for diagnosis, number one, and then the other can be again symptomatic management." Tr. 372 (emphasis added). I note that Dr. Kendall has also appeared frequently as the petitioners' expert in cases alleging vaccines cause "mitochondrial autism," and has provided expert reports in many more cases that have not yet involved hearings.

[157] Doctor Cohen in particular stressed that a patient's clinical problems still need to be treated regardless of whether they are a manifestation of a mitochondrial disorder. He therefore indicated that there is no harm in acting on a "working" or unsubstantiated mitochondrial disorder diagnosis so long as it does not impede investigation of other potential diagnoses. Tr. 1223-25; *see also* R. Frye, et al, *Treatments for mitochondrial dysfunction associated with autism spectrum disorders*, J. PEDIATR. BIOCHEM. 2: 241-249 (2012), filed as Pet. Ex. 186, at 242 (noting that treatment of mitochondrial disorders relies primarily on precautions to prevent decompensation, vitamin supplements, and modification of diet).

[158] The report was actually prepared by a resident, Dr. Robin Ryther, under Dr. Sims's direction. Pet. Ex. 35, p. 14.

Alvarez-Altalef's report, however, that would indicate that she arrived at any independent conclusion regarding A.K.'s mitochondrial disorder diagnosis. All of the language cited by petitioners in support of their argument (*see* ECF No. 297 at 14-15 quoting Pet. Ex. 36, pp. 1, 3) is contained in Dr. Alvarez-Altalef's recitation of A.K.'s prior history, which indicates that he was *previously* diagnosed with mitochondrial disorder (*see* Pet. Ex. 36, pp. 1-4).[159] Moreover, it appeared that Dr. Alvarez-Altalef may have viewed A.K.'s prior mitochondrial diagnosis as being a working or provisional diagnosis only. She stated in her report that A.K.'s work up yielded "at this point" a diagnosis of mitochondrial disorder.[160] Pet. Ex. 36, p. 1.

Doctor Hoffman's report[161] is also ambiguous. Although it is true, as petitioners argued, that the report reflects an evaluation of A.K., it is unclear the extent to which the report was focused on diagnosis as opposed to symptom management. The report reflected that A.K. and his family approached Dr. Hoffman precisely because they already believed A.K. had a mitochondrial disorder. The beginning of the report stated that "[A.K.] and his family came to us today in order to discuss his history and how to move forward in terms of taking care of his mitochondrial disease and optimizing his care." Pet. Ex. 34, p. 1. To the extent that Dr. Hoffman's report indicated in the summary that she believed A.K. to have a mitochondrial disorder, the particular phrasing, stating that A.K. "is felt to have mitochondrial disease," obscured whether she was referring to her own diagnosis or a prior diagnosis. Pet. Ex. 34, p. 5-6.

The very fact of these treating physician reports does provide some support for petitioner's argument of a mitochondrial diagnosis. However, the evidence of mitochondrial disorder diagnosis contained in A.K.'s medical records is far more equivocal than petitioners suggested. Petitioners portrayed the record as reflecting multiple independent diagnoses of mitochondrial disorder, but I do not find these claims of "independence" to be substantiated in the records. Moreover, all of these alleged instances of diagnosis ultimately relied on Dr. Shoffner's initial laboratory assessment and are predicated on Dr. Shoffner's finding of enzyme abnormalities, an interpretation which I have rejected.

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[159] Doctor Kendall indicated during her testimony that she did not believe that Dr. Alvarez-Altalef is known to be among the country's small number of mitochondrial specialists. Tr. 421-22.

[160] Petitioners have emphasized testimony by Dr. Kendall indicating that working diagnoses are common in this field due to the unusual level of uncertainty in mitochondrial disorder diagnosis. ECF No. 297 at 58 (quoting Tr. 426).

[161] Petitioners characterized Dr. Hoffman as an assistant to Dr. Korson and her report as one from a joint evaluation conducted by both Dr. Hoffman and Dr. Korson. ECF No. 297 at 13. Doctor Hoffman was a geneticist at the Floating Hospital for Children at Tufts Medical Center in the Division of Genetics and Metabolism while Dr. Korson was the Chief of Metabolism. Pet. Ex. 34, p. 1. Doctor Hoffman's report to Dr. Zirin, A.K.'s pediatrician, noted the additional involvement of Dr. Korson in the medical treatment of both A.K. and his sister, but is not explicit in describing what, if any, involvement Dr. Korson had in the evaluation discussed. Pet. Ex. 34. Moreover, even if Dr. Korson did participate in the evaluation, there is no statement indicating that he reviewed or approved the report itself. Thus, to the extent petitioners attempted to characterize the report as reflecting the views of Dr. Korson as a mitochondrial expert (*e.g.*, ECF No. 297 at 57), that argument is not supported by the report itself. In that regard, it is also worth noting that while it is undisputed that Dr. Korson is well respected in the field of mitochondrial disorders (Tr. 417-18, 1326-27), his actual qualifications are not a part of this record.

E. Conclusions and Finding of Fact Regarding A.K.'s Mitochondrial Diagnosis.

There are significant issues with Dr. Kendall's interpretation of A.K.'s clinical history. She has relied on non-specific clinical findings to diagnose A.K. with mitochondrial disease. The reliance by A.K.'s treating physicians on Dr. Shoffner's report appears to have shaped their diagnostic impressions and their diagnostic conclusions thus rise or fall based on the reliability of Dr. Shoffner's diagnosis. Treating A.K. for a mitochondrial disorder is not confirmation that he actually has that diagnosis, for such treatment is without significant side effects. Tr. 249, 372, 1223-25.

Mitochondrial disorders are difficult to diagnose—a point on which the experts for both sides agree. A.K.'s clinical symptoms, to the extent they are interpreted as signs of mitochondrial disorder, cannot be matched up to other key findings such as enzymology, metabolic testing, histology, or genetics, for all of the reasons described above. He does not reach the "possible diagnosis" level under Bernier, let alone the probable or definite diagnosis classification posited by Dr. Kendall. Indeed, the Bernier criteria would characterize A.K.'s case as "unlikely." Pet. Ex. 90 at 1406. Doctor Kendall herself stressed that a mitochondrial disorder diagnosis must be made in light of the totality of evidence, including laboratory data, with "enough data points" favoring such a diagnosis. Tr. 249. She argued that in A.K.'s case "when you look at all of it . . . I say to myself, well, that looks like it's probably a mitochondrial disease based on all of the different points of data that come together." Tr. 251.

But, for all of the reasons discussed above, I do not find that most of these data points exist, much less "come together," in the manner Dr. Kendall suggested. Thus, while it have been reasonable for A.K.'s treating physicians to engage in symptom management based on the *suspicion* of a mitochondrial disorder, such a suspicion does not meet petitioners' burden of proof here. That is, considering the record as a whole, I do not find that it is more likely than not that A.K. actually has either a mitochondrial disorder or dysfunction.

VII. The Onset of A.K.'s ASD is Not Temporally Related to his Vaccinations and the Course of A.K.'s ASD is Inconsistent with Petitioners' Theories.

Regardless of the mechanism, petitioners allege that A.K.'s influenza vaccinations ultimately led to his ASD.[162] As indicated above, Dr. Shafrir's and Dr. Kendall's causation opinions rely heavily on the supposition that the onset of A.K.'s ASD, or ASD-like symptoms, is temporally related to A.K.'s two administrations of

[162] Petitioners have been inconsistent in describing the exact nature of A.K.'s injury. They have variously described A.K.'s injury as consisting of "epigenetic changes in his brain, evidenced by autistic symptoms" (ECF No. 297 at 105) or as "a regressive encephalopathy with features of autism spectrum disorder" (2d Am. Pet at ¶ 74). They have also argued more directly that A.K.'s ASD itself is a vaccine-caused injury, noting that "petitioners maintain [the] position that the flu vaccinations caused A.K.'s condition, including autism." ECF No. 297 at 128. Regardless of how they characterize the injury, however, petitioners have been clear in asserting that there is a temporal relationship between the onset of A.K.'s symptoms, inclusive of his ASD symptoms, and his vaccinations, arguing that "A.K.'s medical records and the testimony of his parents and Dr. Boris establish not just an association between the vaccinations and the onset of symptoms, but indeed, challenge re-challenge." ECF No. 297 at 124.

influenza vaccine. Thus, determining the timing of that onset is critical to assessing petitioners' causation claim. Not surprisingly, petitioners expended considerable efforts in an attempt to discredit the primary witness who placed onset of A.K.'s ASD prior to administration of these vaccinations, Dr. Miller.

There is no dispute in this case that the onset of A.K.'s ASD predated his first explicit ASD diagnosis by years. A.K. was first diagnosed with ASD by Dr. Rapin on April 22, 2004, at about four and a half years of age. Pet. Ex. 11, p. 3. At that point, Dr. Rapin indicated that "there is no doubt that [A.K.] is a child on the autistic spectrum." *Id*. An earlier evaluation on July 10, 2002, using the Childhood Autism Rating Scale ["CARS"], had found that A.K. was not autistic. Pet. Ex. 5, p. 3. However, that evaluation showed that, at 32 months of age, he was not functioning at the appropriate age level in cognitive, language, adaptive, and social development skills. Pet. Ex. 5, p. 7.

Petitioners' expert in pediatric neurology, Dr. Shafrir, expressed doubt regarding the earlier CARS evaluation's conclusion. Tr. 526-27. He opined that the substance of that report reflected ASD, even if that ultimate conclusion was not expressed. Tr. 527. And, although respondent's expert in autism, Dr. Miller, did not specifically discuss the accuracy of the July 10, 2002 CARS evaluation, she did note that in 2002, ASD screening techniques were not sophisticated enough to reliably identify ASD before about ages three to four, older than A.K. was at the time of the CARS evaluation. Tr. 1037-38. Doctor Miller also noted that, even today, with more advanced and proactive approaches to ASD diagnosis, it can still take families "years" to get a diagnosis. Tr. 860-61. Thus, the parties agree that A.K.'s 2004 diagnosis in itself does not pinpoint the onset of his ASD.

Unsurprisingly, however, petitioners and respondent have very different perspectives regarding the time by which A.K.'s ASD actually manifested. Petitioners have alleged that "there is no evidence . . . in this record that A.K. was autistic prior to the administration of the influenza vaccinations. There is ample evidence, moreover, that A.K. became autistic in November and December 2001, after the administration of the vaccinations." ECF No. 297 at 131. Petitioners further argue the November/December onset of A.K.'s ASD represented the beginning of a clear regression. *See, e.g*. ECF No. 297 at 102-03.

Respondent disagrees. Respondent argues, primarily through the expert opinion of Dr. Miller, that A.K. showed clear signs of his ASD as early as 14 months of age, well before he received the two doses of influenza vaccination implicated in this claim, and that there is no credible evidence of regression. *See, e.g*. ECF No. 295 at 24-25.

For the reasons described below, I find that respondent has established that A.K.'s ASD became evident prior to his influenza vaccinations and that there is insufficient evidence in the record to suggest that he regressed as petitioners contend.

A. Respondent's Primary Expert on ASD Diagnosis, Dr. Miller, Was Highly Persuasive.

The question of when A.K.'s ASD first manifested was most extensively addressed by Dr. Miller on behalf of respondent and by Dr. Shafrir on behalf of

petitioner.[163] In their post-hearing brief, petitioners raised objections to Dr. Miller's testimony and I have addressed those objections in my prior ruling in which I declined to strike her testimony. *See* Motions Ruling, filed on Sept. 28, 2015 (ECF No. 319), at Section II.F. Here I note that Dr. Miller's presentation regarding the proper screening and diagnosis for ASD is not only acceptable, it was in fact far more extensive, better supported, and far more credible than Dr. Shafrir's testimony on the same topics.[164]

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[163] Petitioners also filed an expert report (Pet. Ex. 107) by Dr. Mary Megson, a developmental pediatrician, primarily to address the significance of the video evidence filed in this case. *Id*. at 2. Although I address Dr. Megson's report below, I note here that she was unable to testify in this case.

[164] I stress that although I have considered all of petitioners' objections to Dr. Miller's testimony, I have not only found that they are without merit; in many instances, they are deliberate misrepresentations of Dr. Miller's testimony. For example, in their response to respondent's post-hearing brief, petitioners argued that Dr. Miller had criticized Dr. Rapin for not following "appropriate medical protocol" in arriving at her diagnosis. ECF No. 302 at 7. Petitioners' counsel engaged in a protracted cross-examination of Dr. Miller on this point, during which Dr. Miller was quite clear in stating that petitioners' counsel was incorrect in summarizing Dr. Miller's testimony as being critical of Dr. Rapin for using insufficient diagnostic criteria in A.K.'s case. Tr. 983-84. Rather, Dr. Miller testified that Dr. Rapin likely relied at least in part on parental reports and that it is not standard medical practice to fact-check parental reports. Tr. 984-85. Petitioners characterize this as "ironic," because Dr. Miller's own diagnostic tools rely on parental reports (ECF No. 302 at 8), but there was nothing ironic in Dr. Miller's testimony. She simply offered what should be an uncontroversial observation – that parental reports can provide important information, but that not all parental reports are equally reliable. In that regard, Dr. Miller explained that parental reports can be assessed for their reliability by "drilling down" with follow up questions that call for concrete examples and by matching up parental claims to what is observed clinically. Tr. 948-950. Contrary to petitioners' argument, Dr. Miller did not testify that this was not done in A.K.'s case, only that it cannot be confirmed and therefore the reliability of those reports is an open question. This issue is addressed in more detail in Section VII.C.3, below.

In another example of overreaching, petitioners argued that Dr. Miller should be discredited on the basis that she indicated that A.K.'s influenza vaccinations were not recorded in his "official" immunization record. Petitioners claim that this statement demonstrated Dr. Miller's lack of familiarity with pediatric practice. ECF No. 297 at 27-28. The point that Dr. Miller made in her report is quite clear: she wrote that she could find no notation of A.K.'s first influenza vaccination in either his "official" vaccine record, referring to the page of A.K.'s medical records constituting his "vaccine administration record" (Res. Ex. OO at 2 (citing Pet. Ex. 2, p. 2.), nor in the progress note for the visit at which he received the vaccine (Res. Ex. OO at 2 (citing Pet Ex. 2, p. 21.) Instead, she pointed out, the influenza vaccine is only noted in a summary of vaccinations. Res. Ex. OO at 2 (citing Pet. Ex. 2, p. 1. and Pet. Ex. 61, p. 4). Unlike the administration record, the vaccine summary lacks parental signatures or an administrator signature and/or initials. Compare Pet. Ex. 2, p. 1 and p. 2. Particularly in light of Dr. Miller's clear citation to the precise record she was characterizing as "official," petitioners' belaboring of Dr. Miller's word choice is not a persuasive argument regarding Dr. Miller's fitness as an expert witness. The extent of the testimonial evidence than no vaccine record can be considered "official" was Dr. Shafrir's general umbrage at the idea that any "official" immunization record could even be thought to exist. Doctor Shafrir was obviously disdainful of Dr. Miller as a non-pediatrician or even a physician, and it was this attitude, rather than any actual misunderstanding of Dr. Miller's reference to the records. Tr. 506-510. And, Dr. Miller was not wrong in contending that there is an "official" vaccination record. *See* § 300aa-25 (requiring that each health care provider who administers a vaccination shall record in a permanent medical record or office log the date of administration, the manufacturer and lot number, the name and address of the health care provider, and other information required by regulation). Even if I thought that Dr. Miller's word choice was a poor one, there is no question as to what her underlying point was and no evidence to suggest that Dr. Miller was confused regarding the nature of the records she reviewed.

Doctor Miller extensively described the ASD diagnostic methods available, explaining that ASD diagnosis is based on observable behaviors listed in the DSM and describing the diagnostic criteria under both the DSM IV and DSM V. Tr. 889-95. She explained in detail the stages of inquiry, beginning with general monitoring, or surveillance, through more specific assessments known as screening, and ultimately leading to diagnosis. Tr. 857-59.

Doctor Miller explained that an ASD diagnosis is based primarily on developmental history and clinical observation. Tr. 861-62. She indicated that the "gold standard" for ASD diagnostics are the Autism Diagnostic Interview, Revised ["ADI-R"] and the ADOS. Tr. 862-64. These are commercially available screening tools, but training is required to establish that the practitioner is statistically reliable. Tr. 863. Doctor Miller has not only completed such training, she is herself responsible for supervising that training. Tr. 863-64. Doctor Miller also addressed the different age-based modules of the ADOS. Tr. 865-69. She explained how the different modules correspond, not only to the DSM autism criteria, but also to CDC recommendations regarding social milestones. Tr. 872-73; Res. Ex. DDD.

Significant to this case, Dr. Miller noted that the ADOS includes a module for one to two year olds that accounts for the fact that children of that age are less verbal. Tr. 866-69; Res Ex. CCC at 9. She explained that in the absence of fully developed speech, practitioners can screen for ASD by evaluating a number of features. These include: joint attention (where the child is aware that both he and another person are looking at the same object); imitation (which involves both re-creating actions and being able to "pretend" an object is something else); eye contact and facial expressions; play (both functional and pretend); responding to name; social interest and reciprocity (*i.e.* when the child gets excited, is the attention fixated on an object or is the affect shared with others); and stereotyped behaviors (unusual movements or fixations). *Id*.

Doctor Miller also explained that the ability to reliably screen toddlers at about 2 years of age is a more recent development. Petitioners were very critical of Dr. Miller's testimony, in part, because she did not accept the clinical observations of Dr. Boris or Dr. Zirin. ECF No. 297 at 31-32. Doctor Miller observed, however, that at the time A.K. experienced the onset of his ASD, screening techniques for one to two year olds were not yet available. Tr. 1047-50. She explained that early screening became possible because of research into nonverbal social communication which has found that certain behaviors "come online" even before a child speaks his first word. Tr. 871-72. The American Academy of Pediatrics released screening recommendations for 18 to 24 months in approximately 2007 or 2008. Tr. 1048. Because the pediatric records at issue in this case were generated in the 2001 to 2002 timeframe, Dr. Miller observed that A.K.'s pediatricians would not have had screening questions available to them that would have led to an earlier ASD diagnosis. Tr. 1037-38. She observed that, at the time that Drs. Boris and Zirin would have been observing A.K.'s development and noting any concerns, children were not routinely referred for ASD evaluations prior to age three or four.[165] Tr. 1048.

[165] Petitioners are quite vociferous in their objections to this aspect of Dr. Miller's testimony. They argue that Dr. Miller "does not know Dr. Boris or his practices" and that "Dr. Miller's opinion that Dr. Boris would

In contrast, Dr. Shafrir offered a polemic decrying the state of autism knowledge generally, and the DSM diagnostic parameters in particular. He argued that knowledge of the cause or causes of autism has not advanced since the 1980's and that in the face of what he calls an "epidemic" of autism, attempts to understand the condition via study of psychology and genetics are failures. Tr. 481-84. He argued that attempts to develop guidelines for the assessment and treatment of autism are self-serving, if not fraudulent, attempts by academics to earn fame and promotion. Tr. 496. He believes that recommendations are being made "without any practical information" and that this is "sad" and "shocking." Tr. 497. And ultimately, he opined that approaching autism diagnosis from a psychiatric perspective based on observable behaviors is a fundamental flaw in thinking on autism. Tr. 522-24. Apparently he believes that because ASD cannot be cured, studying how it presents is useless.

Doctor Miller's testimony thoroughly rebutted Dr. Shafrir's claim that ASD assessment guidelines are being made without basis and without "any practical information." Tr. 496-97. Although Dr. Shafrir was correct in noting that we do not yet know the cause of ASD, Dr. Miller has clearly shown that ASD assessment is based on an understanding of the ways in which the ASD population deviates from expected social development milestones. Indeed, when asked to define ASD himself, Dr. Shafrir offered a description that is utterly consistent with Dr. Miller's explanation of the ADOS module for one to two year olds. He testified that autism is "a child who has impairment in communication, in socialization, and in imagination, which means that they . . . have primitive play without any use of imagination with the play. They can communicate verbally or non-verbally. They [sic] most traumatic one is they don't relate to other people." Tr. 580.

In addition to his testimony that essentially no progress in understanding the causes of autism has been made since the late 1980's (Tr. 495-98), he also opined that there has been little progress in screening and diagnosis as well (Tr. 525-26). However,

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not recognize the early signs of autism is both outrageous and inadmissible." ECF No. 297 at 102. They also contend that "Dr. Miller's entire testimony concerning the observations and diagnoses of A.K.'s physicians was predicated on speculation." ECF No. 302 at 7. Protracted questioning of Dr. Miller on re-cross-examination suggests that petitioners fundamentally misconstrued the nature of Dr. Miller's testimony. Tr. 1045-55. She did not testify that A.K.'s physicians, nor Dr. Boris in particular, made diagnostic errors in A.K.'s case. She testified that their findings must be understood in the context of the state of ASD screening knowledge at the time. That is, to the extent that Dr. Boris's records indicate no developmental concern, a conclusion contrary to the contemporary video evidence in this case, Dr. Miller explained that this fact is less significant than it otherwise would be, because the prevailing practices at the time would tend to suggest that Dr. Boris could not reasonably be expected to have made such an observation. Screening practices simply were not sensitive to many behaviors at that time. This is not the "speculation" petitioners decry. It is much-needed context from an expert in such matters. Indeed, by raising this objection, in effect petitioners argue that Dr. Boris's observations and professional judgments were not merely unassailable, but actually not even constrained by the medical community's understanding of ASD. Although Dr. Boris testified to having some familiarity with ASD, nothing in his testimony indicated that he was unusually positioned to be able to pick up on early autistic behaviors. He did not testify that he actually looked for and ruled out the presence of any of the behaviors Dr. Miller noted as present on the videos. Petitioners' outrage over Dr. Miller's testimony is completely misplaced. That she saw things AK's doctors did not is not an indictment of their expertise or observational skills; it is that she observed AK's behavior with the benefit of advancements in the understanding of ASD and how it may present, as well as hindsight.

Dr. Miller's testimony regarding the increased ability to diagnose ASD, even in toddlers, which has developed within the last ten years, suggests that Dr. Shafrir's assessment of the diagnostic standards is either outdated or overly pessimistic. In that regard, I note that when asked about his specialized training in autism, Dr. Shafrir cited experience ending in 2000, well before the developments Dr. Miller described. Tr. 525. Moreover, as I indicated in Section VIII.B.1, below, I found Dr. Shafrir's attempt to distinguish between autism and autistic regression to be unsupported and damaging to his credibility.[166]

B. The Video Footage Filed In This Case Supports Respondent's Argument that A.K.'s ASD Predated His Vaccinations.

The biggest point of contention between the parties in terms of identifying the onset or first manifestation of A.K.'s ASD stems from a series of videos filed in this case, some of which were presented to the experts during the hearing. Two of respondent's experts, Drs. Miller and Cohen, experts in child psychology and pediatric neurology respectively, opined that the videos collectively show signs of ASD well before A.K.'s second birthday.[167] In contrast, Dr. Shafrir, petitioners' expert in pediatric neurology, contended that the videos show no signs of ASD prior to November 10, 2001, and that the November 10 footage shows a dramatic overnight change compared to footage recorded the day before on November 9, 2001.[168] Drs. Kendall and Megson (a non-testifying expert) similarly, but less forcefully, opined that although A.K. experienced some prior speech delays, the period following his second birthday

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[166] In their response to respondent's post-hearing brief, petitioners state that "petitioners recognize that Dr. Miller is well credentialed in her field of clinical psychology. She is not, however, a medical doctor and should not be given license to substitute her judgments most, if not all of which, are based on conclusory statements and speculation, without any support in the record, for the observations of highly experienced medical doctors." ECF No. 302 at 8-9. I note, however, that Dr. Miller's testimony is being considered solely with regard to the onset of A.K.'s ASD which is, in fact, a matter falling within the practice of clinical psychology. Doctor Shafrir, for example, decried the fact that the diagnosis of ASD under the DSM "has nothing to do with medical practice" because "we let psychiatrists run the show." Tr. 522-24. Thus, Dr. Shafrir himself has separated his medical expertise as a pediatric neurologist from ASD diagnosis and has undercut petitioners argument that Dr. Miller's status as a non-medical doctor has any bearing on her opinion regarding the application of the DSM. *See, e.g. King S*, 2010 WL 892296, at *79 (noting that "autism is considered a neurologic and a psychiatric disorder" and that "psychologists are also often specialists who diagnose autism."); *see also Synder*, 2009 WL 332044, at*32 (noting that "[a]ll of the disorders falling within the autism spectrum are defined by a collection of symptoms or behaviors. With the exception of Rett's disorder, all ASDs are diagnosed by comparing behavioral symptoms exhibited by a child against an established set of broad diagnostic criteria. The diagnosis is made by direct observation, videos of the child, and from parental reports, as there is no biochemical test for ASD.").

[167] In the interest of brevity, Dr. Cohen's testimony regarding the video footage was limited to confirming his agreement with Dr. Miller's testimony and noting that in his opinion the video footage in totality shows a slow evolution of abnormal findings beginning prior to two years of age rather than any abrupt change as petitioners allege. Tr. 1148-49. Doctor Cohen's opinion regarding the videos is otherwise contained in his expert report. *See* Res. Ex. SS.

[168] This marked a change from Dr. Shafrir's report wherein he indicated that A.K.'s loss of speech was the first indication of A.K.'s alleged regression. Pet Ex. 63 at 11-14. However, Dr. Shafrir had not seen the videos when he wrote his expert report. Tr. 458-59. He testified that he still opined there was a loss of speech, but that the behavior change seen in the videos is "much more dramatic." Tr. 530-31. Doctor Shafrir's assertion regarding speech loss is addressed in Section VII.C, below.

presented more pronounced developmental problems. Tr. 283-84; Pet Ex. 107 at 6. For the reasons described below, I find respondent's interpretation of the videos more persuasive.

1. Doctor Shafrir's Interpretation of the November 9 and 10 Videos Was Not Persuasive.

The November 10, 2001[169] video shows A.K. at his second birthday party surrounded by many other children of various ages. Pet. Ex. 236, 64KV. For much of the video, A.K. wandered throughout the large room, which appeared to be an activity room at a community center or similar facility. He does not interact with the other children and does not engage with the adults who attempt to get his attention, nor does he participate in the activities presented for the children. For example, when the other children sat in a circle and used sticks to tap along to a song, A.K. wandered the perimeter of the room and twirled the sticks. *Id*. The experts all agreed that A.K.'s behavior at this party shows clear signs of ASD. *See, e.g.,* Res. Ex. SS at 7-8; Tr. 471, 900-02. Doctor Shafrir, in particular, described the autistic features on display in this video as "absolutely striking." Tr. 471.

In contrast, the November 9 video depicts a family gathering in [A.K.'s * * *] home to celebrate A.K.'s second birthday. The more intimate in-home setting marks a contrast to the larger, louder party of November 10. The clip played during the hearing shows A.K. unwrapping and receiving presents, including an "Elmo" toy and a train set, and having "happy birthday" sung to him. Pet. Ex. 236, 63KV. According to Dr. Shafrir, this clip shows that as a matter of personality A.K. is quiet and less outgoing than his sister, but that he is "more or less normal." Tr. 472-73. Doctor. Shafrir stressed that the video showed that A.K. could engage in interaction and could show enthusiasm.[170] Tr. 473.

According to Dr. Miller, the November 9 video, just as the November 10 video, largely shows A.K. wandering around without paying much attention to the people around him. Tr. 904-07. She indicated that the video showed that it was difficult for

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[169] The videos were originally filed by petitioners on eight CDs marked Pet. Exhibits 109- 116. Petitioners subsequently refiled the footage in reduced "clips" that extracted the footage specifically pertaining to A.K. These reduced clips were filed as Exhibit 236, with individual clips identified by number with the initials "KV." The November 9 video of A.K. was resubmitted for presentation at the hearing as Exhibit 236, 63KV, and the November 10 video as Exhibit 236, 64KV.

[170] The video clearly showed A.K. smiling and responding when his family began singing "Happy Birthday." Importantly, Dr. Miller noted that even though that represented a social response, A.K. did not voluntarily seek out affection. Tr. 904. She acknowledged that the video footage in this case does show occasional "good" moments of appropriate social interaction. Her testimony was that those moments were far, far fewer than would otherwise be expected. Tr. 1041-42. In contrast, Dr. Shafrir rejected the idea that anything less than "striking" features of autism should be considered significant. Tr. 473-74. Doctor Shafrir appeared to opine that the fact that A.K. could be induced to interact or become enthusiastic at all, was an indication that he was not autistic. Tr. 474-75. In this regard, Dr. Shafrir attempted to use the presence of behaviors present in typically developing children to "rule out" ASD, but ASD cannot be ruled out because particular behaviors are "normal" or not diagnostic of ASD. It is the presence of the abnormal behaviors that leads to the ASD diagnosis; but the concurrent presence of other behaviors that are present in typically developing children does not nullify the diagnosis.

people to get A.K.'s attention, noting in particular his lack of interest in his sister's dancing. Tr. 904. She also pointed out that A.K. remained focused on or distracted by his toy train cars. Tr. 905-07.

Doctor Miller explained that, at two years of age, A.K. should have had the cognitive ability to recognize that a wrapped birthday present was for him and that it would contain something intended for him. Tr. 905. However, A.K. did not stay engaged in opening the present, and that when he was participating, he seemed focused on the wrapping paper itself, not what it contained. *Id*. His face did not register any emotional change when the new toy was revealed. *Id.*

Specifically, Dr. Miller pointed out that A.K. initially failed to recognize the Elmo doll as a depiction of the Elmo character, and instead became fixated on the toy doll's eyeball. This is similar to the behavior he exhibited on November 10. When A.K. met the costumed Elmo character, he became fixated on the fur of the costume, rather than interacting with the character. Tr. 902-03.

In addition, Dr. Miller noted that the November 9 video showed A.K. banging the toy train cars together as mere objects rather than playing with them as parts of a toy train. Tr. 905. This behavior appears akin to the manner in which A.K. interacted with the sticks at the larger November 10 party: he was unable or unwilling to use the sticks in accordance with the organized activity.

These behaviors are consistent with the signs and symptoms Dr. Miller discussed from the ADOS module for the appearance of ASD behaviors in children one to two years of age. *See, e.g*., Res. Ex. CCC at 9. Although the setting and the obvious dichotomy between A.K. and other children made A.K.'s behavioral differences more obvious in the November 10 video, the parallel between the two videos in terms of A.K.'s reaction to Elmo is striking, as is A.K.'s propensity in both videos to separately bang or twirl the sticks and train cars without apparent interest in the others in the room. In both videos, A.K. demonstrated a lack of imaginative play (an inability to recognize a "pretend" Elmo) and instead engaged in object-focus regarding Elmo's eyeball on November 9 and fur on November 10. While sitting in his box and banging the train cars on November 9, A.K. failed to respond to his father calling his name three or four times. Pet. Ex. 263, 63KV. He similarly failed to respond to his name in the November 10 video. Tr. 903; Pet Ex. 236, 64KV. A child's failure to respond to his own name is specifically noted as a warning sign in the ADOS. *See, e.g*., Res. Ex. CCC at 9. In fact, Dr. Miller testified that failing to respond to one's name is specific to autism, constituting a "big red flag." Tr. 1007-08. A.K.'s failure to respond to his name in the November 9 video, when in a familiar environment with fewer distractions, may be of more significance than the similar failure on November 10, when in a less familiar environment with more distractions.

Dr. Miller also noted that the November 9 video shows A.K. holding his ear. Tr. 904. This is a behavior that Dr. Miller noted across many of the videos, including the November 10 video, as well as in a subsequent video from March 2003, a time after which it is undisputed that A.K. was symptomatic for ASD. *See, e.g.*, Tr. 897, 901, 904. Significantly, the ear holding could also be seen in videos as early as about 14 months of age. Tr. 916. Doctor Miller opined that A.K.'s ear holding, which is shown

consistently throughout the videos, is a mannerism consistent with ASD. Tr. 932-33. Although A.K.'s medical records do note A.K.'s ear holding as a possible symptom of teething (*e.g.* Pet Ex. 61, p. 56), Dr. Miller noted that A.K. does not appear to be holding his ear out of pain, and that the consistency over time of his habit of ear holding suggests it is not related to teething (Tr. 932-33).

Moreover, in addition to Dr. Miller's competing opinion, Dr. Shafrir's interpretation of the videos is undercut by the fact that petitioners' other experts did not appear to find the same significance in the November 9 and 10 videos. Whereas Dr. Shafrir testified that the November 9 and 10 videos displayed an "amazing change" constituting "the most dramatic appearance of behavior change I've seen in my career" (Tr. 528), neither Dr. Kendall nor Dr. Megson expressed any similar opinions. Although Dr. Kendall indicated that A.K.'s second birthday party represented the time when A.K. began losing his social connectedness, she did not specifically cite the distinction between the November 9 and 10 videos. Tr. 281-84. Indeed, Dr. Kendall did not offer any testimony regarding the November 9 video at all. For her part, Dr. Megson, like Dr. Miller, highlighted the fact that on November 9, A.K. retreated to his blue box to hold his two train cars and did not vocalize much. Pet. Ex. 107 at 5. At no point in her report did Dr. Megson draw any specific contrast between the November 9 and November 10 videos. Instead, Dr. Megson contrasted A.K.'s behavior at the larger birthday party with his behavior in early videos from September of that year.[171] *Id*.

Doctor Shafrir contended that the November 9 video, when contrasted with the November 10 video, showed a dramatic and overnight change. Tr. 470. In my viewing the two videos, both at and after the hearing, it is clear that the November 10 video places A.K.'s behavior in stark and startling contrast to the behavior of the other children. However, in the November 10 video, the focus of the camera is almost exclusively on A.K. in a setting where his behavior is qualitatively and dramatically different from that of the other children present. In contrast, the November 9 video is not so exclusively focused on A.K., and he is not in a place where the presence of other children and activities could be overwhelming. When viewing the two videos at and after the hearing, I found Dr. Miller's description of A.K.'s behavior in the November 9 video as showing features of ASD to be accurate and convincing. I noted what she testified about—that the difference between the two videos does not reflect a distinction in A.K.'s behavior so much as the larger, louder party puts that same behavior in a context which makes it appear more obvious. Tr. 907. I agree with Dr. Miller's interpretation. I find that the November 9 and November 10 videos do not evince the dramatic change in A.K.'s behavior that Dr. Shafrir contends they do. Rather, I find that

[171] Doctor Megson's ultimate conclusion was that A.K.'s developmental problems began to become more pronounced after his second birthday, citing November 9, 2001, as the key date. Pet. Ex. 107 at 6. At first blush, this would appear to directly contradict Dr. Shafrir's contention that A.K.'s behavior on November 9 was "more or less normal." I note, however, that Dr. Megson incorrectly indicated that both of A.K.'s birthday parties occurred on November 9. Pet. Ex. 107 at 5. Although this error makes her precise meaning unclear, the resulting ambiguity underscores the fact that, unlike Dr. Shafrir, she did not describe any clear contrast between the two videos and did not seek to distinguish between the two. Indeed, Dr. Megson's opinion was that the critical period of regression occurred in December 2001. *Id*.

both the November 9 and November 10 videos show behaviors consistent with A.K's later ASD diagnosis.[172]

2. Earlier Videos and Medical Records Also Demonstrate Behaviors Consistent with ASD Much Earlier than A.K.'s Influenza Vaccinations.

In addition to noting the presence of ASD features in the November 9, 2001 video, Dr. Miller also opined that videos dating as far back as January 2001, when A.K. was approximately 14 months old, also show A.K. exhibiting behavior indicative of ASD, at a time long before he received the influenza vaccines at issue in this case. Doctor Miller also pointed out notations in A.K.'s pediatric records that point to an earlier onset of ASD than petitioners claim.

In a video dated August 26, 2001, A.K. was at a restaurant with his grandmother. Pet. Ex. 236, 58KV. According to Dr. Miller, this video shows A.K. failing to respond to his name several times, and only responding to his grandmother's prompts once she is extremely close, close enough to be felt. Tr. 907. Failing to respond to one's name is "a big red flag" in terms of ASD screening. Res. Ex. CCC at 9; Tr. 1007-08. Doctor Miller also suggested a lack of appropriate social interaction in this video segment. Although Dr. Megson's characterized A.K. as "extremely responsive" to his grandmother in this video (Pet. Ex. 107 at 4), Dr. Miller noted that A.K. did not maintain the interaction and instead appeared to simply watch the movement of his grandmother's mouth. Tr. 908-09, 1008-10. She did agree, however, that he smiled. *Id.* According to Dr. Miller, even accounting for his language delay, A.K should have been reflexively mimicking his grandmother's motions. Tr. 909. Absent that type of response, Dr. Miller opined that this is not actually a social interaction.[173] Tr. 909.

In a video from June 2001, when A.K. was about 19 months old, A.K. was shown at home with his family, spending much of his time in the video playing with a bat. Pet. Ex. 236, 53KV. In this video, A.K. did not appear to demonstrate age-appropriate, purposeful play with the bat, according to Dr. Miller. Tr. 910. Rather, he appeared to simply flip it around while pacing or wandering. *Id*. This behavior with the bat was quite similar to his behavior at the birthday party depicted on the November 10 video, where he was twirling the sticks while wandering. I note the similarity in these behaviors in

[172] To the extent that Dr. Shafrir has contended that A.K. was "more or less normal" appearing during the November 9 video (Tr. 472-73) and would attribute the different interpretations to his assertion that "you cannot make comments about thing[s] that you expect to see but don't see" in videos" (Tr. 470), I stress that upon my viewing of these videos I find the ASD-like behaviors described by Dr. Miller to be readily observable. I add that video evidence is frequent filed in contested cases alleging vaccine causation of ASD, and I have viewed video evidence in at least 30 cases, including the OAP test cases.

[173] During the hearing, Dr. Shafrir was shown this August 2001 video in conjunction with the November 9, 2001 video. Tr. 472. It is obvious from his overall testimony that he believed that, like the November 9 video, it showed A.K. as being "more or less normal," but he did not offer any testimony specific to this video. Tr. 471-75. Doctor Kendall testified that this clip showed A.K. making eye contact and being interactive. Tr. 282-83. Doctor Miller noted that it was difficult to tell if there was any eye contact because A.K.'s grandmother was wearing sunglasses. Tr. 1008. I agree with Dr. Miller's impression that A.K.'s gaze appeared to be on his grandmother's mouth and not as far up as her eyes, perhaps because A.K.'s grandmother was exaggerating her pronunciation and facial movements while repeating the words "ball" and "pencil."

light of Dr. Shafrir's testimony that A.K. displayed a classic ASD presentation on the November 10 video. The flipping and twirling of the bat and sticks represents circumscribed interests, a DSM symptom of ASD, according to Dr. Miller. Res. Ex. CCC at 18.

Moreover, as in the other videos, at 19 months of age, A.K. showed a lack of appropriate social interaction. Tr. 910-12. Doctor Miller testified that he mostly kept a neutral facial expression, wandered back and forth in a repetitive manner, and failed to keep interactions going. *Id*. For example, during an attempt at playing peek-a-boo with a blanket, A.K. did not look at his mother and instead simply hit the blanket with his bat. Tr. 910. A.K. enjoyed a sensory activity, being tickled, but did not keep the interaction going. Tr. 911. Once again, he failed to respond to his name after multiple prompts. Tr. 910. These types of behaviors reflect a lack of nonverbal communication, a lack of social sharing, and a lack of emotional reciprocity, all indications of ASD under the DSM. Res. Ex. CCC at 18.

In another clip from June 2001, Dr. Miller noted that A.K. was being prompted by the phrase "diggly do." Tr. 912-14; Res. Ex. 114, file 1. Doctor Miller opined that "diggly do" is representative of "jargon."[174] Tr. 912-14. She noted that jargoning is distinct from babbling and jargon is common among children with ASD. *Id*. She explained that specialists refer to "jargon" as a technical diagnostic term distinct from "babbling." Tr. 927-28, 1038-40. Babbling constitutes the beginning of speech and will ultimately lead to proper speech, but jargon has none of the inflection of babbling. It does not lead to proper speech, but is rather a form of self-stimulating behavior symptomatic of ASD. Tr. 1038-40. Once again, Dr. Miller asserted that A.K.'s use of stereotyped language is a symptom of ASD appearing in the DSM. Res. Ex. CCC at 18. She also noted that this video showed that A.K. was not engaging in a functional way with the objects he encountered and that he did not initiate any interaction with anyone, and that a child of his age would be expected to display those behaviors. Tr. 912-14.

According to Dr. Miller, a video from February 22, 2001, when A.K. was about 15 months old, shows a good moment where A.K. responded to his name (though not on the first try) and smiled. Res. Ex. 113, file 1; Tr. 914-16. She noted, however, that that interaction did not persist and that for the remainder of the video there was no more social interaction. *Id*. At that age, there should be "hundreds" of such moments of interaction. *Id*. Similarly, a video from about a month earlier, on January 15, 2001, showed some good signs, such as the potential beginning of pretend play as A.K. lifted a phone to his ear. Pet. Ex. 236, 22KV; Tr. 916-17. Nonetheless, there were numerous indicators of ASD in the same clip. For example, Dr. Miller indicated that A.K. failed to respond to his name.[175] Tr. 916. He appeared to be exploring his toys in a non-

[174] Although this clip only shows A.K.'s parents using the term "diggly do" and not A.K. himself, Dr. Miller testified that based on the parents' use of the phrase, she believed it was fair to infer that A.K. used it as well. Tr. 1042-43. She also testified that she did recall A.K. using the phrase himself on another video, though she did not specify what video. *Id*. Tr. 1042-43. But in any event, A.K.'s use of jargon is not in dispute. Petitioners' expert Dr. Megson indicated in her expert report that A.K. could be heard jargoning in videos as early as 15 months of age and as late as three and a half years of age. Pet Ex. 107, at 3.

[175] She observed that an alternate explanation of A.K.'s lack of response in both the 14 month and 15 month videos was that A.K. may have been distracted by the television. Tr. 915-16.

functional way, failed to maintain interaction, engaged in hand flapping and repetitive behavior, and paced in the same manner as in other videos. Tr. 917-18. According to Dr. Miller, the whole "the lack of responding when other people are trying to get his attention and the lack of other functional play all comes together to indicate that this [behavior].is not typical"[176] Tr. 919.

Although Dr. Megson's report indicated that A.K.'s developmental "slow-down" increased "markedly" following his vaccinations, she nonetheless noted that "from 16-24 months of age, he seems to plateau in his level of alertness, and processing language." Pet. Ex. 107 at 6. Thus, in some degree, one of petitioners' own experts confirms Dr. Miller's opinion that A.K. showed signs of difficulty prior to his vaccinations, albeit while disagreeing as to the ultimate significance of those observations. Doctor Megson opined that "the video shows repeated instances of excellent social engagement and normal interaction" prior to age 24 months, but also noted instances of behavior seemingly consistent with Dr. Miller's observations. For example, Dr. Megson observed that A.K. appeared "somewhat self-absorbed" in videos from about age 19-20 months and "a little less aware of his environment" just a couple of months prior to his vaccinations. Pet. Ex. 107 at 3-4. She also noted several points at which A.K. was jargoning. *Id.*

On the whole, however, I attach less weight to Dr. Megson's report than I do to Dr. Miller's testimony because Dr. Megson's characterizations of the videos run counter to what I observed while viewing them. For example, while Dr. Miller clearly demonstrated at the hearing that A.K. was hand-flapping, playing with his ears and failing to respond to his name as early as 14 months of age, behaviors I was able to observe first-hand while the videos played, Dr. Megson intimated that these behaviors first appeared after his influenza vaccinations. Pet. Ex. 107 at 5. Based on Dr. Miller's testimony, as well as my own observation of the videos, I find that Dr. Megson's assertions are simply incorrect. Similarly, Dr. Megson described the above-discussed August 26, 2001 video of A.K. with his grandmother as showing A.K. was "extremely responsive" and specifically noted that he "turns in immediate response to her." Pet. Ex. 107 at 4. Having viewed these videos myself, I do not find these characterizations accurate. While there is clearly some room for disagreement regarding the level of interaction between A.K. and his grandmother, it is very clear that Dr. Megson's description of A.K. turning "in immediate response" is a mischaracterization. In fact, as

[176] On cross-examination, Dr. Miller was also shown video clips from October and May 2001. Tr. 1008-22; Pet Ex. 236, 60KV, 40KV. The October 2001 video, in particular, was one that Dr. Kendall described as showing purposeful play and engagement with A.K.'s sister. Tr. 283. However, Dr. Miller disputed that the video showed A.K. playing with his sister. Rather, she noted that he was focused on his toy and that the two were just playing "near" each other, known as "parallel play," a type of play significant for its lack of interaction. Tr. 1010-11. She felt that the October 2001 video – showing A.K. and his mother with a bat and ball – showed a lack of social interaction, although it did show that A.K. was capable of establishing some level of routine. Tr. 1014-17. Counsel questioned Dr. Miller extensively regarding moments of the film that may have shown A.K. making eye contact with his mother, but she felt the video was inconclusive about eye contact, in that A.K.'s mother was out of view. Tr. 1017-22. She also commented on how A.K. viewed the ball, asserting that it was unusual in that A.K. had been playing with it for some time, but suddenly focused his gaze on it. Tr. 1022.

noted above, A.K. failed to respond to his grandmother calling his name twice before he turned to look at her.

Moreover, despite having noted at least some delay or plateau in both A.K.'s language and alertness prior to age two, Dr. Megson's report seems to strain to minimize the significance of A.K.'s pre-vaccination behavior. That is, she noted similar behaviors occurring both pre and post-vaccination, but sought to characterize only those behaviors relative to the post-vaccination footage as symptomatic of ASD. For example, she noted that A.K. was seen "wandering about" in videos at both 15 months of age and also at about age four and a half, but only ascribed a lack of social interest to that wandering in connection with the later, post-vaccination, video. Pet. Ex. 107 at 3-4. Having viewed these videos, I find no basis for the failure to treat similar behavior as symptomatic of ASD.[177]

I also note that Dr. Miller's opinion was fully corroborated by Dr. Cohen's report. Res. Ex. SS. Although Dr. Cohen did not testify in detail about the videos, he was present in the hearing room during her testimony, and expressed his complete agreement with that testimony. Tr. 1148-49. His report included his conclusions based on the video footage, conclusions that are substantially similar to Dr. Miller's observations. Res. Ex. SS at 5-8. Like Dr. Miller, he opined that "the video recordings of A.K. demonstrate a child who began showing signs of atypical developmental behavior sometime between January and March 2001. By March 2001, there was marked impairment of social skills and by June 2001, A.K. was evidencing problems with expressive language skills . . . the video recordings made during and after June 2001, and up through October 31, 2001, before his first influenza vaccine, clearly demonstrate a child who showed behavior as seen in autism." Res. Ex. SS at 8.

In contrast, Dr. Shafrir did not offer any opinion or testimony specific to any of these videos. His only response to Dr. Miller's opinion regarding these early videos was to generally assert that it is error to attempt to identify what he considers to be "subtle" early signs of autism. Tr. 473-74. However, Dr. Shafrir never substantiated his opinion that all features of ASD must necessarily be striking or dramatic. Doctor Shafrir testified that "autism is not a subtle condition" and that "everybody can make a diagnosis of autism." Tr. 483. But these statements completely beg the question of any distinction between actual onset and perceived onset, early symptoms and those that manifest at a point when "everybody" can agree that an autism diagnosis is appropriate. They reveal Dr. Shafrir's lack of understanding regarding the screening techniques Dr. Miller

[177] Although she did not specifically identify these videos as she did with other examples, Dr. Megson appears to have been comparing a video from either February or March 2001 in which A.K. is at home during a birthday party for his sister (she noted he was wandering around with a piece of bread) to a video from A.K.'s fourth birthday party. Pet. Ex. 113, files 1 and 2. Although there is a moment in the earlier video where A.K. accepted a cup of juice from his mother, at no point did he seek out any interaction with anyone. In fact, at one point during the video A.K. appeared completely oblivious to his sister, who was poking him. I do note that there are moments in the earlier video where A.K. appeared to be laughing or smiling, although not at or with anyone. For example, at one point he laughed when shown a party favor. This does contrast with the later video in which A.K.'s expression appeared more disinterested. Overall, however, both videos appear consistent with the type of wandering and lack of interest that Dr. Miller noted during her testimony.

explained in detail. They may also reflect Dr. Shafrir's own experience in that his patients are referred to him for ASD diagnosis — a point when other have recognized already that a child may be autistic.

In effect, Dr. Shafrir contended that autism is not autism until its appearance is so obvious that even a lay person can recognize it. As Dr. Miller explained, the appearance that ASD is worsening stems from the fact that when a child with ASD plateaus in development, the absence of skills becomes more pronounced over time because the gap between the condition of the child with ASD and the expected development curve for a typically developing child becomes wider as more milestones are missed. Tr. 998-99. As Dr. Shafrir would have it, however, early indications of developmental problems should not be viewed prospectively as indicators of autism unless or until the condition is obvious. Tr. 483. At no point, did Dr. Shafrir address the question of whether such developmental problems, when viewed in hindsight, can be linked to autism once a stable ASD diagnosis has been confirmed. Doctor Miller did address this question in detail, and her testimony regarding the early video footage is very persuasive.

Doctor Miller linked her analysis of the video footage to A.K.'s medical records. Although the experts on both sides expressed the view that A.K.'s earlier pediatric records were of limited use in determining the true nature of his development (Tr. 461, 921-22), Dr. Miller pointed out that some of these records include notations that reflect "red flags" (Tr. 921-22). For example, Dr. Miller pointed out that on April 4, 2001, when A.K. was approximately 17 months old, a health care provider characterized him as a "fearless Wildman." Tr. 928-29; Pet. Ex. 61, p. 68. She noted that it is an unusual notation for a pediatric record. Tr. 929. Doctor. Miller acknowledged that this phrase in isolation is subject to multiple interpretations, but stressed that particularly in light of the videos, it may well be an indication that A.K. lacked social or safety awareness. *Id*. That is, it may indicate that he was susceptible to wandering without "checking in" with his parents. *Id*.

Doctor Miller also noted that at two years of age, A.K.'s pediatric record described him as "self-sufficient." Tr. 933-35; Pet. Ex. 61, p. 55. A record from December 17, 2001, described him as "very focused." Pet. Ex. 61, p. 54. Doctor Miller opined that these notes were unusual and not age-appropriate. Tr. 933-37. In her opinion, they were indicative of A.K.'s general propensity in the videos to wander and not respond, *i.e*. to "be in his own world." *Id*. Again, this evidences a lack of social sharing or emotional reciprocity. Res. Ex. CCC at 18. In addition, as noted above, Dr. Miller explained that the references in A.K.'s pediatric records to ear rubbing, though attributed to teething at the time, likely show evidence of a mannerism or stereotyped behavior related to his ASD. Tr. 932-33; Res. Ex. CCC at 18; Pet. Ex. 61, p. 56.

3. Petitioners' Arguments against Consideration of the Video Footage Are Without Merit.

Finally, the most basic issue raised by petitioners with regard to the videos is whether it respondent should be permitted to rely on the video footage at all. In raising this point, petitioners seek to use the video footage both as a shield and a sword. On the one hand, they affirmatively rely on the videos, arguing repeatedly that their own

testimony, as well as the opinions of both Drs. Shafrir and Kendall, is corroborated by the videos. ECF No. 297 at 18, 21, 40, 48, 56. Yet, to the extent respondent's experts noted that the video evinced behaviors contrary to petitioners' description of onset, they then assert that "the video record provides mere intermittent snippets of A.K. The video is not a clear chronology fully depicting A.K.'s life. The video record is an insufficient evidence source from which to draw diagnostic conclusions." ECF No. 297 at 86. In particular, Dr. Shafrir testified that it is "profoundly wrong" to review video footage for signs of autism. Tr. 467. He testified that "I don't think anybody can make a diagnosis of autism based on a few minutes of videotape. . . . You can see behaviors and identify behaviors that you see in autistic children, but can you say that you can make the diagnosis of autism using videotapes, it's just ludicrous." Tr. 467.

In making this argument, both petitioners and Dr. Shafrir mischaracterized the nature of Dr. Miller's testimony and evinced a misunderstanding of the scientific bases for the utility of videos in the diagnosis of ASD. At no point did Dr. Miller indicate that she was "diagnosing" A.K. based on the video footage alone. Rather, Dr. Miller testified that her opinion that A.K. has ASD was based on the complete medical record, including contemporaneous evaluations, "supplemented" by the videos. Tr. 896; Res. Ex. OO at 3-5. Due to the state of screening techniques available at the time A.K.'s ASD manifested, the medical records did not address enough behaviors to support a diagnosis on their own. It was significant for her testimony that the videos and the records together "point[ed] toward the same direction." Tr. 921-22. She indicated that she could see "a lot more behaviors in the videos than are in the record before the age of two" but noted that the medical records did raise "some pretty significant red flags." *Id*.

Thus, petitioners' criticism is misplaced. As noted above, Dr. Shafrir himself acknowledged that on video "you can see behaviors and identify behaviors that make you worried, you can see behaviors that you see in autistic children." Tr. 467. That is exactly what Dr. Miller did. As noted in the prior section, there is a difference between engaging in diagnosis and recognizing with the benefit of hindsight that certain signs or symptoms are indicative of a subsequently diagnosed condition. Indeed, Dr. Miller testified that stable diagnosis of ASD is possible only at about two years of age. Tr. 870-71. Thus, the question is not whether the videos are diagnostic of A.K.'s ASD in themselves, but whether A.K.'s behavior in the videos is consistent with or contrary to petitioners' description of the timeline of onset.

Moreover, Dr. Miller was convincing when she explained as a general matter that videotapes are useful diagnostic tools. Tr. 919-21. She noted that, beginning about 10-15 years ago, studies were conducted to see whether home videos could be used to provide diagnostic consistency in the face of inconsistent or unreliable parental reports.[178] Tr. 920-21. She indicated that those studies found that additional social

[178] Some of these studies were filed as exhibits in this case. See*, e.g.*, Res Ex. C, A. Mars, et al, *Symptoms of pervasive developmental disorders as observed in prediagnostic home videos of infants and toddlers*, PEDIATR., 132(3): 500-04 (1998) (finding that children later diagnosed with PPD could be differentiated from typically developing peers on the basis of specific anomalies, such as a lack of joint attention, observed in home video footage); Res. Ex. D, E. Werner, et al, *Brief Report: Recognition of Autism Spectrum Disorder Before One Year of Age: A Retrospective Study Based on Home Videos*, J.

behaviors indicative of ASD, that otherwise would have been missed, were present on the videos. Tr. 920. For example, a journal article filed with Dr. Miller's expert report found that parental reports are particularly unreliable with regard to non-language behaviors, and that such parental reports benefit from confirmation by supplemental sources such as videos. *See* Res. Ex. OO, Tab 1, W. Goldberg, et al, *Use of Home Videotapes to Confirm Parental Reports of Regression in Autism*, J. AUTISM DEV. DISORD., 38: 1136-1146 (2008). Another study filed with Dr. Miller's report found that "there is low agreement between parent report and home video" and suggested that "later aberrant patterns of development likely stand out to parents because of their alarming nature, proximity in time to the interview, and consistent with their child's current presentation." Res. Ex. OO, Tab 4, S. Ozonoff, et al, *Onset Patterns in Autism: Correspondence Between Home Video and Parent Report*, J. AM. ACADEMY CHILD & ADOLES.T PSYCHIATRY, 50(8): 796-806 (2011) [hereinafter "Ozonoff, Res. Ex. OO, Tab 4"]. Doctor Miller also pointed out that home videos are especially useful in that they depict a child in a familiar environment, allowing the clinician to account for behaviors that should be attributed to the clinical setting. Tr. 920-21. She further noted that home videos remain a diagnostic tool in current use by practitioners, particularly with regard to the emergence of early behaviors that cannot be fully observed during clinical observation. Tr. 921.

By contrast, Dr. Shafrir failed to provide any substantial basis for his rejection of videotapes as an aid screening for ASD. With hyperbole typical of his testimonial criticism of mainstream medical approaches to ASD, he characterized the use of videotapes in autism diagnosis as "one of the blackest chapters of pediatrics." He then focused the brunt of this criticism on the moral implications of using videotapes to screen foreign adoptees for signs of autism. Tr. 467-69. While such a practice may be troubling, Dr. Shafrir's testimony on that practice was a non sequitur. The use of videos in the instant case does not have any of the moral implications Dr. Shafrir decried. Moreover, nothing in Dr. Shafrir's testimony indicated any basis for claiming that use of videos as part of ASD screening would be inaccurate or ineffectual. In fact, Dr. Shafrir indicated that he was unaware of any of the studies regarding the use of videotapes to aid in diagnosing autism. Tr. 570-71. While Dr. Shafrir cautioned with regard to video footage that, "I really feel that you cannot make comments about thing[s] that you expect to see but don't see," he also conceded that "you can identify autistic behaviors or behavior that are frequently found in autistic children in a videotape." Tr. 470. Thus, Dr. Shafrir's harangues aside, he did not actually opine that the use of video would lead to inaccurate diagnosis or wrong conclusions.[179]

AUTISM & DEV. DISORD., 30(2): 157-62 (2000) (a study finding that early onset ASD can be detected on video as early as 8-10 months of age and noting that failing to response to one's name is a particularly evident feature of early onset ASD) Res. Ex. E, E. Werner, et al, *Validation of the Phenomenon of Autistic Regression Using Home Videotapes*, ARCH. GEN. PSYCHIATRY, 62(8): 889-895 (2005) (study concluding that parental reports of regression on the ADI-R can be validated using home video footage.)

[179] In fact, when viewed in the full context of his testimony, Dr. Shafrir's attempt to distinguish between affirmative signs of autism observable on video and "things you expect to see but don't" appears to be more of a semantic distinction than anything. Despite attempting to discredit Dr. Miller's opinion on that basis, Dr. Shafrir's opinion regarding the contrast between the November 9 and November 10 videos was entirely predicted on the fact that in the November 10 videos A.K. was not relating to or being social with

Petitioners advanced that particular argument themselves, contending that "the testimony and evidence interpreting the tapes is fraught with inconsistency, as is demonstrated by the inconsistent and at times polar opinions of the various experts who testified concerning their respective interpretations of segments of the tapes." ECF No. 297 at 86. That experts disagree is no basis for rejecting expert testimony. Petitioners' concern does not implicate the usefulness of the videos themselves, which constitute objective evidence, so much as the quality of the expert testimony in this case. The qualifications of respondent's witnesses to diagnosis ASD were far superior to those of the experts upon whom petitioners relied. Inconsistencies among the experts' opinions actually make the videos all the more valuable as evidence, because it provides a benchmark against which to assess the reliability and credibility of these experts. As described above, I found Dr. Miller's descriptions of the videos to be highly persuasive in no small part because her observations tracked most closely to my own impression of the videos whereas Dr. Shafrir's description of a dramatic overnight change was inconsistent with what I saw while watching the video footage.

Petitioners are also unconvincing in arguing that the videos are of little value because they constitute only "intermittent snippets" of A.K.'s life. ECF No. 297 at 86. Even accounting for the fact that the footage of A.K. himself is far less than the whole of what was initially filed, multiple hours of video showing A.K.'s behavior were filed in this case.[180] In that regard, Dr. Miller was clear in explaining that in her opinion the available video footage was in itself, without extrapolation, sufficient to demonstrate a clear deficit in A.K.'s social development. Tr. 1041-42. That is, Dr. Miller acknowledged that there are instances in the videos which show A.K. engaging in developmentally appropriate interaction, such as making eye contact (Tr. 1026-28), but stressed that "based on the totality, he has extremely few moments that look good, and at his age and across the number of hours of video we have, we should see hundreds of examples of that kind of moment that we saw maybe two or three of." Tr. 1042.

In any event, even if these videos were mere "snippets," petitioners have conspicuously stopped short of arguing that the clips are aberrations from A.K.'s overall behavior. To the contrary, to the extent they assert that the footage corroborates their own testimony and their experts' opinions that A.K. was developmentally normal prior to receiving his vaccinations, petitioners implicitly argued that these videos actually are representative of A.K.'s overall behavior. ECF No. 297 at 18, 21, 40, 48, 56. And even if there were times when A.K.'s behavior was substantially different (an unsubstantiated

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others in the room or being incited to happiness. Tr. 476. Doctor Shafrir characterized this as dramatic self-directed behavior, but one could easily characterize it as a lack of expected social interactions. Indeed, Dr. Shafrir specifically cited A.K.'s failure to laugh, smile or clap his hands as distinguishing features of the November 10 video. Tr. 478. Moreover, Dr. Shafrir testified that a September 2002 video of A.K. showed "a traumatic severe classic autism" despite also testifying that in the same video "you don't see any positive autistic symptoms." Tr. 476-77 (citing Pet. Ex. 236, 74KV). Thus, it is not really clear in what way Dr. Shafrir's approach to analyzing these videos actually differs in practice from Dr. Miller's, other than that Dr. Miller's conclusions differed from his..

[180] For her part, Dr. Miller estimated that there were approximately three to four hours of video of A.K. prior to two years of age. Tr. 1043-44. Petitioners similarly estimated that 20-30% of the 12 hours of footage originally filed is of A.K., which would amount to about three hours. ECF No. 297 at 86.

supposition[181]), Dr. Miller and Dr. Shafrir both made the point that ASD symptoms do not have to exist at all points in time to be consistent with an ASD diagnosis. Tr. 478, 1005-08. The fact would still remain that the videos clearly show A.K. demonstrating ASD-like behaviors at an age when petitioners contend that he was not.

In any child diagnosed with ASD, there was a point in time at which parents or caregivers became concerned about the child's behavior. They may have chosen to acknowledge their misgivings and seek help or advice from physicians, therapists, or friends. They may have chosen to engage in watchful waiting. They may simply have put aside their concerns until they were confronted with something that they could not ignore. The point at which their awareness that their child's behavior differed substantially from that of other children crystalized does not necessarily include a regression or mark the first instance of abnormal behavior. It simply marks the point at which excuses could no longer be made or that they finally became aware that something was truly wrong. This does not mean that symptoms of ASD were not present at earlier points in time.

C. Neither the Video Footage nor the Contemporaneous Medical Records Support Petitioners' Claim of a Speech Regression.

Notwithstanding the compelling evidence that A.K.'s ASD manifested far earlier than A.K.'s second birthday, petitioners contend that A.K. experienced an autistic regression that was most clearly evidenced by a loss of speech. Petitioners acknowledged that prior to receiving his influenza vaccinations, A.K. may have demonstrated "subtle" developmental delay that consisted of a slowing in A.K.'s speech progress, but they argued that his loss of words following vaccination was distinct. ECF No. 297 at 130. Doctor Shafrir initially relied very heavily on the idea that the onset of A.K.'s condition was most clearly evidenced by his loss of speech. Pet. Ex. 63 at 11. And although, he later opined that there was a more dramatic change in behavior visible in the video footage discussed above, he still maintained that A.K.'s condition was evidenced by a loss of speech following his November 2001 vaccination. Tr. 530-31.

Specifically, Dr. Shafrir indicated in his expert report that "the most crucial dramatic and clearly defined component [of A.K.'s autistic regression] was the fact that he stopped talking. This is a highly specific and unusual phenomenon in children, which always imply [sic] brain injury, either permanent or transient." Pet. Ex. 63 at 11. In terms of timing, Dr. Shafrir testified that there was excellent documentation of A.K.'s loss of language following his first dose of the influenza vaccine which worsened after his second dose. Pet. Ex. 63 at 12. Specifically, Dr. Shafrir cited a December 17, 2001 notation indicating that A.K. had "no spontaneous speech" as indicating that A.K. experienced a critical event that stopped all of his speech. Pet. Ex. 63 at 14. Doctor Shafrir contended that record "is decisive and does not leave room for alternate interpretation." *Id*.

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[181] For example, petitioners' own expert made a point of stressing that it is reasonable to view the videos as representative of A.K.'s overall behavior. With regard to the behavior he observed during the November 10 footage, which he pegged as the beginning of A.K.'s "dramatic" autistic behavior, Dr. Shafrir colorfully quipped that somebody could tell him that A.K. "recited the Declaration of Independence" between video clips, but that absent such information, the videos are what we have to go on. Tr. 478.

I do not find his interpretation of the record dispositive or credible. Doctor Shafrir's opinion is belied by the fact that A.K. began to show signs of speech difficulty as early as 18 months of age. The record as a whole does not support the claim that A.K. experienced a sudden loss of speech. Rather, as respondent's experts suggested, it appears more likely than not that A.K. experienced a speech impairment beginning at about 18 months of age that became more concerning as A.K. fell further behind developmental milestones and his ASD became more pronounced.[182]

1. The Onset of A.K.'s Speech Delay Was at about 18 Months of Age.

In their expert reports, both Drs. Kendall and Shafrir characterized A.K.'s 18 month well visit as reflecting normal language development. Doctor Kendall stressed that A.K. was noted as having "short phrases," while Dr. Shafrir indicated that A.K. was reported as having a vocabulary of "about 20 words." Pet. Ex. 65 at 2; Pet. Ex. 63 at 3. Neither of these characterizations, however, is accurate. There is not much detail in the 18-month well visit record regarding A.K.'s development, but it does indicate that A.K. was able to say "oh, look." Pet. Ex. 61, p. 65. It also appears to indicate that A.K. was using the words "yes," "no," and "more," could point for needs, and was using "jargon."[183] *Id*. There is nothing in that record, however, to indicate a broader

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[182] Petitioners argued in their post-hearing brief that A.K.'s onset of speech delay at 18 months is irrelevant, because speech delay was removed from the DSM-V criteria for ASD. ECF No. 297 at 127-28. Petitioners are partially correct, but effectively wrong. The DSM-IV-TR diagnostic criteria for autistic disorder had three categories of behavior (social interaction, communication, and restricted repetitive and stereotyped behavior), with diagnosis requiring qualitative impairments in each of the three categories. Speech delay was a specific criterion in DSM IV-TR, under the category of communication. DSM -IV-TR at 70-71, 75. The DSM V merged the communication and social interaction categories to create a category called social communication and social interaction but there are no specific symptoms that must exist, simply a non-exhaustive list of examples. Although speech delay is no longer listed as one of the examples in the new DSM (DSM-V at 50), it remains a symptom of ASD. In a section of DSM-V's chapter on ASD, under the heading "Diagnostic Features," the following explanation appears:

> Verbal and nonverbal deficits in social communication have varying manifestations, depending on the individual's age, intellectual level, and language ability, as well as other factors such as treatment history and current support. Many individuals have language deficits, ranging from complete lack of speech through language delays, poor comprehension of speech, echoed speech, or stilted and overly literal language.

DSM-V at 53. *See also* Tr. 890-91 (Dr. Miller explaining that while "the essence of everything that was in DSM-IV is still in DSM-V," language delay was removed as a listed diagnostic criterion in DSM-V because it is not specific to autism.)

The explanation quoted above, along with Dr. Miller's testimony, establishes that speech delay or loss of speech remain symptoms of ASD, although they are less specific in pointing toward a diagnosis than the repetitive mannerisms or restricted patterns of interest that A.K. also displayed. More importantly, petitioner's argument misses the point. The onset of A.K.'s speech delay is not significant merely because it indicates that A.K. might have autism. It is significant because it speaks to the question of A.K.'s overall language development. That is, it is evidence supporting respondent's contention that A.K. struggled to develop language skills in the first instance, rather than experiencing the type of sudden loss of previously acquired skills that petitioners suggest. Regardless of whether it is a symptom of ASD, petitioners have specifically argued that the pattern of A.K.'s speech development is evidence that their experts' theories of causation are correct. ECF No. 302 at 18-19.

[183] As noted above, Dr. Miller indicated that specialists refer to "jargon" as a technical diagnostic term distinct from "babbling," in that it does not have intonation or lead to speech. Tr. 927-28, 1038-40. She

vocabulary beyond the three to four words explicitly mentioned, nor is there any indication of additional phrases beyond "oh, look." Indeed, Dr. Kendall acknowledged this latter point when I questioned her about it. Tr. 345. Prior pediatric records do indicate additional words A.K. had used. For example, at his 15-month visit, A.K. was noted to say "good," "dada," and "ah." Pet. Ex. 61, p. 69. But even taking these prior records into account, I still do not see evidence in the pediatric records that A.K. had a 20 word vocabulary as Dr. Shafrir contended.[184]

Doctor Miller opined that although the 18-month record does not note any concerns, the data recorded actually reflects language development that is "minimal for this age." Res. Ex. OO at 3. She did not necessarily believe the record reflected a state of development likely to generate a high level of concern, as there was "some" development. Tr. 930-31. Nonetheless, she felt the record showed language skills that are "not great." Tr. 931. Specifically, she noted that the record is insufficient to indicate that A.K. had any of this vocabulary in any permanent sense. Rather, she interpreted it as reflecting that the parents had reported that he said each word "at least once." Tr. 930. She also cautioned that the reference to the phrase "oh, look" should not actually be assumed to be the use of a phrase. Tr. 930-31. To be considered a phrase or simple sentence, there would need to be evidence that A.K. was additionally using the words "oh" and "look" separately. *Id*. There is nothing in the records to indicate that he was doing so.

In contrast to Dr. Miller's close reading of the record, both Dr. Kendall and Dr. Shafrir seem to base their interpretation of the record as reflecting normal development on expansive inferences drawn from these sparse notations. For example, Dr. Kendall indicated that she reported A.K. as having multiple simple phrases on the assumption that the notation of a single short phrase was intended as an example of the fact that A.K. was generally capable of forming phrases. Tr. 345. More broadly, Dr. Shafrir relied on the lack of any specific indication of a developmental concern as evidence that no developmental problem was present. Tr. 493. When asked about his opinion regarding A.K.'s speech development, however, Dr. Shafrir indicated that it was difficult to develop such an opinion, because "the pediatric records are pretty sketchy." Tr. 461. He repeated later the point that because the pediatrician was "very, very brief in his [sic] writing" it was "very difficult" to use the medical records to determine A.K.'s language development. Tr. 530. This acknowledgement, coupled with Dr. Kendall's and Dr. Shafrir's overstatements regarding the contents of the 18 month record, suggest that these experts are straining to interpret A.K.'s earlier records, not as merely silent or inconclusive, but as affirmatively reflecting normal speech development.

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did not feel there was a basis, however, to conclude that A.K.'s pediatrician was making that distinction, suggesting that references in A.K.'s medical records to jargon are likely more accurately interpreted as babbling. Tr. 927-32. That interpretation would seem to be consistent with [A.K.'s mother's] testimony as well. [A.K.'s mother] described both babbling and jargon as steps leading to speech. Tr. 28-29.

[184] Years later, in 2004, Dr. Rapin took a history wherein A.K. was reported by his parents as having 20 words at two years of age. Ex. 11, p. 1. Nonetheless, she still characterized A.K. as having delayed speech at two years of age. *Id*.

Moreover, petitioner's own experts conceded that the video footage filed in this case supported Dr. Miller's interpretation that A.K. was experiencing speech delay by 18 months of age. That is, Dr. Kendall conceded that A.K. demonstrated speech delay in the videos at 18 months of age, notwithstanding what the medical records reflected. Tr. 272-74, 283-84. Specifically, she acknowledged that, contrary to her initial report which indicated A.K. was developmentally normal until November 2001, the videos taken when A.K. was 18-19 months of age showed a lack of spontaneous or expressive speech that was indicative of a speech delay.[185] Tr. 290-92. Doctor Kendall declined to identify a cause of A.K.'s early speech delay, but she conceded that it could be caused by ASD.[186] Tr. 292. Doctor Megson, a non-testifying petitioners' expert in child development, likewise indicated her report the videos of A.K. show "a very subtle language delay emerge at 15 to 16 months, when [A.K.]'s vocabulary fails to increase and two-word phrases are heard only sporadically." Pet. Ex. 107 at 6. Although he disputed its significance, Dr. Shafrir also acknowledged that the videos showed "very little language." Tr. 462.

Ultimately, Dr. Shafrir indicated that he believed the parental reports to be more reliable in this case than either the video or the medical records. Tr. 529-32. In that regard, it is significant that both [of A.K.'s parents], despite attributing a vocabulary to A.K. of between 20 to 30 words,[187] testified that they were concerned about A.K.'s speech by the time of this 18 month visit. [A.K.'s mother] repeatedly testified that she first had concerns regarding A.K.'s speech when he was between 15 to 18 months old.[188] Tr. 33-34, 81. [A.K.'s father] similarly testified that he became concerned regarding A.K.'s speech at about 18 months. Tr. 99. Consistent with Dr. Miller's interpretation of A.K.'s medical record, [A.K.'s father] testified that they were not "especially concerned" about A.K.'s speech delay at that point, but that it was noticed.[189] Tr. 100. Consistent with Dr.

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[185] During the hearing, Dr. Kendall viewed and discussed a video from March 2001 marked as Ex. 236, clip 29KV. Tr. 260-63. She testified regarding clip 58 from August 26, 2001, clip 60 from October 2001, and clips 64 and 66, from A.K.'s second birthday on November 10, 2001. Tr. 270, 275-76, 282-83. She indicated, however, that her opinion reflected her impression of all 88 videos filed in this case. Tr. 283-84.

[186] In subsequent testimony Dr. Kendall did backtrack a bit insofar as she expressed doubt about the significance of what she observed on the 18-19 month video when contrasted with the record of A.K.'s 18 month well visit. Tr. 411. However, she maintained her contention that the video showed a lack of spontaneous speech. *Id*.

[187] [A.K.'s mother] testified that A.K. had over 30 words. Tr. 63-64. [A.K.'s father] testified that A.K. never had more than 20 words. Tr. 112.

[188] I note that this timing tracked with the allegations in this case when it was still an OAP test case. At the time the petition was filed, the influenza vaccine which is now alleged to be causal was not a vaccine covered by the Program. Influenza vaccine was not added to the Vaccine Injury Table until 2005, about three years after the original petition was filed.

[189] In their second amended complaint, petitioners argued that their early speech development concerns were "unfounded," because the concern was based, incorrectly, on the idea that A.K. should have developed speech on a similar pace as his older sister. 2nd Am. Pet. at ¶ 30. I note, however, that neither of [A.K.'s parents] attempted to disclaim those concerns during their hearing testimony, beyond noting that they were reassured by doctors that it was normal for boys to develop speech slower than girls. Tr. 32-34, 99-100. But in any event, [A.K.'s parents'] recollections are significant for the fact of what they observed, not the significance they ascribed to those events. Neither of [A.K.'s parents] have any

Miller's interpretation of the medical record, [A.K.'s mother] testified that she raised her concern about A.K.'s speech during that time period, but was told it was not a significant concern.[190] Tr. 33-34.

A.K.'s speech delay was first explicitly noted in his medical records at his 2 year well child visit on November 21, 2001, approximately three weeks following his first dose of influenza vaccine.[191] Pet. Ex. 61, p. 55. His medical record described him as jargoning and having the "beginnings or ends of words." *Id*. At that point his pediatrician recommended observation only. *Id*. To the extent [A.K.'s parents]described that A.K. was speaking less, a concern which they raised at that visit with Dr. Zirin, [A.K.'s father] testified that the diminution was "not dramatic." Tr. 103. [A.K.'s] mother] confirmed in her testimony that Dr. Zirin "did not seem at all concerned" about the speech delay. Tr. 39. In fact, although [A.K.'s mother] testified that A.K. had stopped speaking a few days after his first influenza vaccination (Tr. 64), there was no mention of speech concerns when she called Dr. Zirin's office on November 16, 2001 (Pet. Ex. 2, p. 21). Rather, [A.K.'s mother] testified that, as of November 16, A.K. had other physical symptoms related to nasal congestion and teething which she considered more worrying. Tr. 65-67. In any event, [A.K.'s mother] described the loss of speech she was concerned about as a lack of response or that he "wasn't speaking spontaneously." Tr. 64. In other words, it appears to be precisely the type of concern the experts in this case observed when watching the videos dating back to 18 months of age.[192]

2. A.K.'s Subsequent Course is Consistent with a Continuation or Progression of His Earlier Speech Delay.

Subsequently, on or about December 3, 2001, [A.K.'s] family visited Dr. Boris's office for administration of influenza vaccines – the second dose for A.K. Tr. 40, 156-57. [A.K.'s mother] described A.K.'s speech as being "plateaued" at this point, neither worsening nor improving in terms of his ongoing speech delay and lack of spontaneous speech. Tr. 72. Doctor Boris testified that he recalled A.K. as appearing to be "a normally functioning child" and indicated that he observed nothing "abnormal." Tr. 158. On cross-examination, however, Dr. Boris indicated that he could not recall any of the

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special competency in child development, but their observation that A.K.'s speech appeared delayed to them is consistent with the considered opinions of experts on both sides of this case.

[190] I note that A.K.'s pediatrician, Dr. Zirin, signed a declaration indicating that "prior to November 21, 2001, I made no observation of [A.K.] or notations in the medical record showing that he had any developmental problem whatsoever." Pet. Ex. 108 at ¶ 8. [A.K.'s mother] testified that another partner in the pediatric practice, Dr. Weindorf, discussed A.K.'s speech delay with her. Tr. 34.

[191] To the extent that Dr. Shafrir relies at least in part on this notation as proof that A.K. lost speech after his first dose of influenza vaccine (Tr. 531-33), I note that Dr. Shafrir indicated that he believes that speech "delay" is a misnomer and a hedge for what he believes is more accurately termed speech "impairment." (Tr. 462-64.) Doctor Shafrir indicated that he believed pediatricians routinely hesitate to document developmental delays and stressed that a notation of speech delay does not indicate when the condition started or how severe it is. *Id*. Thus, Dr. Shafrir criticized his own reliance on that record.

[192] [A.K.'s mother] asserted that A.K. lost vocabulary at that time, but was unable to give specifics beyond noting that she believed he was "reduced to his basic beginning words," and stressed that her concern related to frequency. Tr. 64-65. She indicated that "I don't remember the variety, but the frequency diminished greatly." Tr. 65.

details of his interactions with any of the four family members present for vaccinations. Tr. 191-95. Moreover, in a prior declaration, Dr. Boris indicated that he did not conduct a speech evaluation of A.K. despite being told by [A.K.'s mother] that the family had concerns regarding A.K.'s speech. Pet. Ex. 47 at ¶ 11. At best, I take Dr. Boris' testimony as an indication that he did not recall anything grossly abnormal about A.K. (or anyone else in the family) at that visit. The record of this vaccination appears in [A.K.'s mother's] medical records, and it simply records that the vaccinations were administered. Pet Ex. 118, p. 1; Tr. 190-91.

Approximately a week later, at a social function on December 9, 2001, Dr. and Mrs. Boris had an opportunity to observe A.K. for an extended period. Tr. 198-200. Mrs. Boris observed A.K. was playing, but was not nonresponsive to what was happening around him, and brought the issue to Dr. Boris's attention. That prompted Dr. Boris to observe A.K. for the remainder of the afternoon. Tr. 199-200. Although Dr. Boris indicated he believed there was a "marked" change in A.K. based on his prior limited observations, he seemed to indicate that it was no cause for alarm, testifying that he recommended that A.K. go for a hearing test, a normal first step, rather than believing the situation warranted an emergency necessitating a hospital visit. [193] Tr. 199-201.

As Dr. Boris had recommended, A.K. had his hearing tested on December 12, 2001. Pet. Ex. 31, pp. 2-6. His hearing was within normal limits. *Id*.

At a pediatric visit on December 17, 2001, Dr. Zirin noted for the first time that A.K. had "no spontaneous speech." Pet. Ex. 61, p. 54. This is the record that Dr. Shafrir characterizes as decisive evidence of a dramatic event that implies brain injury. Pet. Ex. 63 at 11, 14. Contrary to Dr. Shafrir's contention, however, the above timeline suggests that the notation of "no spontaneous speech" on December 17 is simply the culmination of an evolving understanding of A.K.'s lack of speech development.

Both of [A.K.s' parents] testified that they were aware of delayed speech as early as 18 months and had reported the same on multiple occasions and as recently as two to three weeks prior to this alleged dramatic event. Moreover, [A.K.'s mother] specifically indicated that her concerns regarding A.K.'s speech encompassed, by no later than November 21, the issue of a lack of spontaneous speech. And indeed, the videos filed in this case, as interpreted by the experts, confirmed a prior lack of spontaneous speech. In particular, petitioners' own expert, Dr. Kendall, specifically

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[193] Although Dr. Boris was A.K.'s pediatrician for the first year of life, Dr. Boris left the Woodbury pediatric practice after that first year, and Dr. Zirin became A.K.'s pediatrician during the period when A.K.'s speech delay began at about 18 months of age. Tr. 37. Although Dr. Boris indicated that he continued to see A.K. at social functions in the year following his departure from Woodbury pediatrics (Tr. 155-56), he was not able to provide any specifics and could not recall the details of any interaction with A.K. (Tr. 178-83). And, to the extent he had the opportunity to observe A.K. on December 3, he acknowledged that he did not do any developmental or speech evaluation of A.K. at that office visit. But in any event, it is also worth noting that it was not Dr. Boris, but Mrs. Boris, who noticed A.K.'s lack of responsiveness. I do not draw from this testimony that A.K. was therefore markedly different from how he behaved previously. Since Dr. Boris only noticed A.K's behavior in this one instance when prompted, there is no reason to assume he would have noted A.K.'s developmental condition on prior occasions. The fact is that Dr. Boris never independently recognized A.K.'s developmental delay regardless of the timing of onset.

indicated that the videos showed a lack of spontaneous speech dating back to 18 months. In light of this history, none of the notations in A.K.'s contemporary medical records actually indicated any worsening, much less a dramatic or sudden one, of A.K.'s speech. Thus, Dr. Zirin's notations of "speech delay" on November 21 and her subsequent note of "no spontaneous speech" on December 17, are both consistent with the previously noted concerns.[194]

There is also good reason to doubt Dr. Shafrir's interpretation from a medical perspective. Respondent's expert in pediatric neurology, Dr. Cohen, opined that, when viewed together, the medical records and video footage in this case show a slow evolution of abnormal findings and no evidence of the type of dramatic change Dr. Shafrir described. Tr. 1149; Res. Ex. SS at 7-9. Doctor Cohen testified that if A.K. experienced the type of sudden loss of speech Dr. Shafrir alleged – a loss of speech that would implicate a brain injury – then there should be evidence in the contemporaneous records of urgent concern among A.K's physicians about a neurologic emergency. Res. Ex. SS at 10. Doctor Cohen stressed that A.K.'s subsequent medical records showed no such concern. In particular, he noted that medical records from A.K.'s December 12 hearing test, the December 17 visit with Dr. Zirin, and his December 31 sick-child visit, do not note any regression or major developmental change. Nor do they express any urgent concerns. Tr. 1157-59; Pet. Ex. 3, pp. 2-6; Pet. Ex. 61, pp. 52-54. Doctor Boris testified that, although he felt he was observing an acute change, he did not believe A.K. was in any immediate danger which belies a concern about any brain injury. Tr. 229-30.

On direct examination, Dr. Shafrir took issue with Dr. Cohen's contention that his descriptions of the December event constituted an emergency situation. Tr. 464-67, 504-05. He maintained that the complete loss of speech in a two year old does not indicate an acute neurological event, such as stroke, as it would in an older individual and stressed that children with regressive autism are not routinely sent to the emergency room. Tr. 466-67. Doctor Cohen explained, however, that a sudden regression or loss of speech occurring over a period of weeks, or especially over a period of days as alleged here, would be a medical emergency in the sense that the proper standard of care would require testing, to include an MRI.[195] EEG,[196] and

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[194] Doctor Shafrir's interpretation of Dr. Zirin's notations as reflecting a loss of speech between November and December, *i.e.*, a progression from mere "speech delay" on November 21 to a more serious "no spontaneous speech" on December 17, is further contradicted by Dr. Zirin's subsequent records. As described below, Dr. Zirin reverted to referring to A.K.'s condition as "speech delay" in June 2002. Pet. Ex. 61, p. 42. If Dr. Zirin had intended for her notation of "no spontaneous speech" to supplant her prior notation of "speech delay" as indication of a distinctly worsened condition inclusive of a loss of speech, one would not expect her to continue referring to A.K.'s condition merely as "speech delay" in later records. Moreover, even taking those differing notations at face value, respondent's expert, Dr. Cohen, still disagreed with Dr. Shafrir's interpretation, opining that "in the context of the variability and ups and downs in a child's life, I don't know that to be a significant change." Tr. 1372-73.

[195] A magnetic resonance imaging (MRI) is "a method of visualizing soft tissues of the body by applying an external magnetic field that makes it possible to distinguish between hydrogen atoms in different environments." DORLAND'S at 916.

[196] An electroencephalogram (EEG) is "a recording of the potentials on the skull generated by the currents emanating spontaneously from nerve cells in the brain. . . . [f]luctuations in potential are seen in the form

possibly a spinal tap (lumbar puncture), over the succeeding weeks in order to rule out serious conditions that can cause loss of speech in a child, including seizure disorders or epileptic conditions such as Landau-Kleffner syndrome. Tr. 1154-56.

And indeed, his incredulity in testimony notwithstanding, Dr. Shafrir's own report conveyed a sense of medical emergency. He stated that "the fact that [A.K.] stopped talking, is dramatic and well documented. It is seen only with acute macroscopic structural brain injury such as stroke, certain rare epilepsies such as Landau-Kleffner Syndrome or autistic regression." Pet. Ex. 63 at 12. Despite raising these conditions as potential causes in his expert report, Dr. Shafrir offered no explanation for why there would be no need to rule them out in A.K.'s case. Thus, Dr. Shafrir ultimately acknowledged on subsequent questioning that a sudden and severe regression would be a neurological emergency. Tr. 577.

The medical records subsequent to Dr. Boris's December 9 observation evince an investigation of the type of ongoing speech concern that had already been recognized, rather than any urgent concern reflective of an emergent neurological condition. Although Dr. Shafrir's expert report identified potential causes of speech loss that constituted serious medical conditions, Dr. Shafrir's acknowledgment that a routine hearing test was the appropriate next step (Tr. 465) belied his characterization of the comments of Dr. Boris and Dr. Zirin as indicative of a dramatic neurologic event. It suggests that this characterization may have been yet one more example of the hyperboles Dr. Shafrir frequently employed.

Concerns about A.K.'s speech were not mentioned in his pediatric records again until April 29, 2002, (Pet. Ex. 61, p. 46) and he did not see a speech specialist until July 2002, after Dr. Kovacs, a pediatrician from whom [A.K.'s family] sought a second opinion, made the referral in June 2002 (Pet. Exs. 26, p. 2; 21, pp. 4 (speech therapy intake in June), 14 (summary sheet reflect first speech therapy session on July 24, 2002). At that point – consistent with Dr. Miller's opinion that A.K. never developed true speech – Dr. Kovacs characterized the chief complaint for A.K.'s visit as "child [the word "still' lined through] not talking yet." Pet. Ex. 26, p. 2. Around that same time, on June 24, 2002, Dr. Zirin completed a health status report for the early intervention program which, once again, characterized A.K.'s issue as "speech delay." Pet. Ex. 61, p. 42. None of these records mentioned speech regression or loss of speech.

3. Noncontemporaneous Parental Reports of Regression Are Not Persuasive.

The subsequent evolution of the parental reports of regression is evident in the records. On June 17, 2002, A.K.'s intake form for early intervention indicates that [A.K.'s parents] reported that "child has few words" and that he "used to have some words that he doesn't use unless prompted now. (ex – will say dog only when sees one now)." Pet. Ex. 21, p. 1. That same record characterized [A.K.'s mother's] concern as being "speech delay" possibly caused by the fact that A.K.'s nanny was Spanish- speaking. *Id*. During a July 10, 2002, speech and language evaluation, [A.K.'s mother] characterized A.K.'s as having "very limited spontaneous language." Pet. Ex. 21, p. 32.

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of waves, which correlate well with different neurologic conditions and so are used as diagnostic criteria." DORLAND'S at 600.

She indicated that as he developed, A.K. had steady progress in vocalization, but that his verbal abilities were "very inconsistent." *Id*. A.K.'s evaluation showed that his verbal abilities were "not progressing on an age appropriate level" and that his vocabulary contained "a very limited repertoire of true words." Pet. Ex. 21, p. 33.

In August 2002, Dr. Boris reflected the extent of A.K.'s speech ability with less precision, noted that he "had some words" and that they were lost "after developing them." Pet. Ex. 3, p. 144. A month later, in September 2002, Dr. Boris recorded that A.K.'s parents were reporting "normal development until 16-18 months, including speech," that A.K. had about 10 words, and that A.K.'s parent noted a loss of speech and eye contact at about 22-24 months. Pet. Ex. 3, p. 141. A.K. was 22 months of age in September 2001 and 24 months of age in November 2001.

By the time A.K. was evaluated by Dr. Rapin in April 2004, about a year after the original petition was filed in this case, A.K.'s parents were explicitly reporting that A.K. had experienced a "language regression." Pet. Ex. 11, p. 1. The history recorded by Dr. Rapin reflected that A.K.'s language "was delayed in that he had had only about 20 words at age 2 years when parents became aware that he had in fact regressed, that he mostly did not speak at all and had lost his sociability." Pet. Ex. 11, p. 1.

Doctor Rapin appeared to accept that a regression had occurred (Pet. Ex. 11, pp. 2-3), however, the contrast between this report and the contemporaneous records is striking. None of A.K.'s records from the first report of speech delay in November 2001 to his early intervention evaluation in July 2002 contain any reference to any regression. To the extent there are references to a "loss" of some words, it is to the extent of noting a lack of spontaneous speech, something which [A.K.'s mother] characterized as late as July 2002 as limited and inconsistent throughout A.K.'s speech development. All of these records characterized A.K.'s issue as speech "delay" and Dr. Kovacs' record explicitly indicated that the chief complaint at that visit was a lack of any language development in the first instance. Moreover, as late as August 2002, A.K.'s parents were still reporting that A.K.'s language had always been very limited. At that time, they estimated he had 10 words before they became concerned. By 2004, they were reporting to Dr. Rapin that A.K. had, at some unspecified point, developed 20 words. At the fact hearing in this case, [A.K.'s mother] inflated A.K.'s prior vocabulary further, testifying that prior to his influenza vaccines A.K. had over 30 words. Tr. 63-64.

Thus, the record clearly reflects that as time passed, [A.K.'s parents'] recollection of these events deviated ever more significantly from the medical records themselves.[197] Their testimony and their later parental reports regarding regression do not have sufficient indicia of reliability to be credited over the contemporaneous medical records and their own earlier statements, which do not show speech regression. *See, e.g., Reusser v. Sec'y, HHS.,* 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

[197] As I note, *infra*, with regard to the Shoffner study's (Res. Ex. MM, Tab 16) reliance on parental reports of regression, in the OAP test cases considerable doubt about the validity of later-reported regressions was noted, particularly in view of the widespread information about the purported link between MMR vaccines and onset of autistic symptoms or loss of skills. *Dwyer*, 2010 WL 892250, at *36, n.163, *169; *Snyder, 2009 WL 332044,* at *44, *137.

reliable than the recollection of a party to a lawsuit many years later."); *Vergara v. HHS*, 08-882V, 2014 WL 2795491,*4 (Fed. Cl. Spec. Mstr May 15, 2014) ("Special Masters frequently accord more weight to contemporaneously-recorded medical symptoms than those recorded in later medical histories, affidavits, or trial testimony.") *See also Cucuras,* 993 F.2d at 1528 (noting that "the Supreme Court counsels that oral testimony in conflict with contemporaneous documentary evidence deserves little weight.").)[198]

In sum, the totality of the record, including A.K.'s contemporaneous medical records, videos, and parental testimony, suggests that A.K. showed signs of language difficulty as early as 18 months and that this language difficulty became more pronounced as he aged. The record does reflect, however, any sudden or severe loss of language. Subsequent claims by A.K.'s parents of a clear regression are not supported by the contemporaneous records or videos.

D. Conclusion and Findings of Fact: A.K. Did Not Experience an Autistic Regression or a Challenge-Rechallenge Reaction Following His Vaccinations.

Although the expert testimony regarding a possible regression focused primarily on the question of whether A.K. lost speech (*see, e.g*. Tr. 498-500, 993, 1154), Dr. Shafrir did testify about other signs of autism – including lack of social interaction – as part of what he characterized as A.K.'s autistic regression. Tr. 479-80. Based on the history provided by A.K.'s parents, Dr. Rapin similarly noted that A.K.'s alleged regression at about age two included a loss of sociability. Pet. Ex. 11, p. 1. Petitioners' claim that the onset of his ASD was sudden and included a loss of previously achieved milestones, including but not limited to speech. Indeed, Dr. Shafrir opined that the videos showed that the change occurred "overnight."

As noted in the preceding sections, however, I have found that A.K.'s ASD manifested much earlier than petitioners' contend. I also noted that the signs of ASD found on the video footage include a clear lack of social development, including, most glaringly, the repeated failure to respond when called by name. These symptoms were visible in videos dating as far back as January 2001 when A.K. was approximately 14 months of age.[199]

I find that what A.K. experienced was a gradual manifestation of ASD which could be observed long before he was administered either of the two doses of influenza

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[198] To be sure, "it must [also] 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, however, the contemporaneous medical records do not simply fail to report regression, they are inconsistent with regression. Moreover, a loss of language would be highly significant and not likely to go unreported for so long if actually present.

[199] To the extent Dr. Shafrir also cited symptoms such as malaise, weakness or hypotonia occurring after vaccination, he acknowledged that, like the alleged regression in speech, these symptoms were reflected only in much later parental reports and not in the contemporaneous medical records. Tr. 534-37. But in any event, he did not establish that these were symptoms of ASD or autistic regression.

vaccine in the fall and winter of 2001.[200] Had there been a dramatic change on November 10, I find the parental inaction to such a change, and their failure to mention it at subsequent visits, inexplicable. As indicated above, Dr. Miller explained that often the appearance that ASD is worsening stems from the fact that a child with ASD falls further from the typical development curve as he ages. Tr. 998-99. To the extent that petitioners' experts have opined that there was a marked increase in A.K.'s ASD-like behavior following his vaccinations, each of these opinions was predicated on that expert's related opinion that A.K. appeared, in the words of Dr. Shafrir, "more or less normal" prior to vaccination. That is, the opinion that A.K. was markedly worse was expressed relative to apparently normal behavior prior to the vaccinations. Since I have declined to accept those observations, finding them to be inaccurate, then the correlative statement that he was therefore "worse" in the later videos necessarily fails as well.

This also eliminates, as a factual matter, the possibility that A.K. experienced a challenge-rechallenge reaction.[201] As noted in Section VIII.B.3.b, below, challenge-rechallenge is not even a relevant concept in this case. Indeed, [A.K.'s mother] testified that A.K. has had his speech disappear and reappear several times over the years without any suggestion that it was associated with vaccination. Tr. 52. Nonetheless, I note that the record as a whole does not support the contention that A.K. experienced two distinct reactions to his vaccinations.

Contrary to petitioners' claim, the above analysis shows that the onset of A.K.'s ASD predated his first vaccination. Although the first notation of speech delay in the medical record was recorded during the period between his two vaccinations, I find it more likely than not that this notation was reflective of an ongoing concern that was first noted by A.K.'s parents at about 18 months of age. Moreover, there is no credible evidence to suggest that A.K.'s condition actually worsened following the first vaccination. To the extent A.K.'s parents testified that there was a worsening in A.K.'s spontaneous speech, they themselves acknowledged that it was "not dramatic," and that concern itself is consistent with what was observed in the video footage prior to his

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[200] I do not reach the question of whether A.K.'s onset of ASD at 14 months would itself constitute a regression, because even if it did occur, it obviously would not be temporally related to his vaccinations.

[201] The "challenge-rechallenge" concept has been addressed in numerous cases within the Vaccine Program. Most notably, the Federal Circuit succinctly summarized the theory by explaining that "a rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine." *Capizzano*, 440 F.3d at 1322. More specifically, the Institute of Medicine defines a rechallenge case as one in which "an adverse event occurred after more than one administration of a particular vaccine in the same individual. Each rechallenge, however, must meet the same attributes of reasonable latency, documentation of vaccination receipt, and clinician diagnosis of the health outcome." Pet. Ex. 223, K. Stratton, et al, Adverse Effects of Vaccines: Evidence and Causality, Institute of Medicine of the National Academies (2011), p. 46 [hereinafter 2011 IOM Report, Pet. Ex. 223]; *see also* Tr. 1419-20 (Dr. McCusker describing rechallenge as a function of adaptive immune response). Thus, to successfully establish a challenge-rechallenge theory, a petitioner must show a temporal relationship between the occurrence of petitioner's symptoms and multiple vaccine administrations. *See, e.g. Doe v. HHS*, 95 Fed. Cl. 598, 609 (Fed. Cl. 2010)(affirming the decision of the special master and noting that "the special master found that petitioner had not established causation by a preponderance of the evidence because neither of his expert's proposed 'challenge events' had the necessary temporal connection to the first or second dose of the vaccine.")

vaccination. In addition, for the reasons described above, I have declined to accept Dr. Shafrir's characterization that the two birthday videos document a dramatic overnight change from November 9 to November 10.

Nor is there any credible evidence in the record to support the idea that A.K.'s condition worsened again following the second influenza vaccine. This claim is based on Dr. Boris's observations and upon Dr. Zirin's notation of "no spontaneous speech" in late December of that year. Doctor Zirin's notation is fully consistent with the ongoing concern present before the vaccinations. Moreover, Dr. Boris's testimony about a change between December 3 and December 9 is simply not persuasive. He acknowledged that he did not look for speech or development concerns on December 3 and that he could not remember any details of that encounter. I also note that none of A.K.'s medical records, even those later records in which A.K.'s parents eventually reported a prior regression, indicated that A.K. experienced that regression in two distinct phases. The testimony of A.K.'s parents] appears to be colored by the passage of time. Their testimony portrays more development prior to A.K.'s vaccines than is supported by the actual medical records (*e.g*., they contemporaneously reported that A.K. had only 10 words, but testified that he had 20-30 word).

Thus, I find that the onset of A.K.'s ASD was not temporally associated with A.K.'s influenza vaccinations. Nor is there any evidence to suggest that the subsequent course of A.K.'s ASD was in any way aggravated by his vaccinations or, indeed, in any way consistent with petitioners' theories of causation.

VIII. The Causation Theories of Dr. Kendall and Dr. Shafrir Lack Sufficient Indicia of Reliability and are Unpersuasive.

Assuming, *arguendo*, that A.K. has a mitochondrial disorder or dysfunction, the divergent theories advanced by Drs. Kendall and Shafrir must be considered and evaluated. Petitioners summarized their theory as contending that "oxidative stress, exacerbated by inflammation from the influenza vaccination, in A.K., who suffered from a mitochondrial malfunction further impairing his aerobic system, increasing oxidative stress, caused epigenetic changes in his brain, evidenced by autistic symptoms." ECF No. 297 at 105. Put more simply elsewhere in their brief, they argue that "A.K. has been diagnosed with a mitochondrial defect that renders him particularly susceptible to oxidative stress, which was activated by the two doses of trivalent influenza vaccine, thereby causing his decompensation and severe developmental regression." ECF No. 297 at 4. For the reasons described in Section VI, above, I have concluded that A.K. likely does not have any mitochondrial disease or defect. Moreover, for the reasons discussed in Section VII, I have concluded that A.K.'s ASD is not temporally related to his vaccinations. Nonetheless, even assuming, *arguendo,* that he did have a mitochondrial disease or defect and further assuming that the onset of his ASD was consistent with vaccine causation, I would still find that petitioners' theory lacks sufficient indicia of reliability to meet the *Althen* requirement for preponderant evidence of a reliable medical theory.

With the testimony of Dr. Kendall and Dr. Shafrir in this case, petitioners take two distinct approaches to explaining how the influenza vaccines caused A.K.'s condition.

Doctor Kendall proposed a direct causal link between vaccines and developmental regression manifesting as ASD in mitochondrial disorder patients. Doctor Shafrir's approach was much more convoluted. He posited that A.K. had a mélange of factors, including mitochondrial disease, MTHFR polymorphisms, and an abnormal immune system that, combined with his influenza vaccinations during a vulnerable period in A.K.'s development, caused a brain injury resulting in his current condition.

These theories, conjoined only by the necessary presence of a mitochondrial disorder, were further supported by Dr. Deth's presentation regarding the epigenetic consequences of inflammation and oxidative stress. Doctor Deth' s testimony purported to explain in further detail how A.K.'s mitochondrial and other alleged vulnerabilities could result in the type of injury petitioners alleged. Petitioners have stressed, however, that Dr. Deth's presentation goes to the question of what biological mechanism is at work. They therefore argue, since they are not obligated to prove any biological mechanism, that they can meet their burden even without Dr. Deth's testimony. Tr. 597. I first address Dr. Kendall's and Dr. Shafrir's opinions before separately addressing Dr. Deth's presentation in a later section of this decision. For the reasons described below, however, I do not find either Dr. Kendall's or Dr. Shafrir's theory persuasive, with or without Dr. Deth's presentation.

A. Doctor Kendall's Theory.

In her report, Dr. Kendall contended that "recent studies have documented the association of developmental regression and autism in patients with mitochondrial disease following exposure to immunizations." Pet. Ex. 65 at 7. Building on this association, she asserted 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." *Id*. at 7-8. Thus, in light of her assumptions that A.K. had a mitochondrial disorder and that he experienced a developmental regression with onset temporally related to his influenza vaccines, Dr. Kendall opined that A.K.'s two doses of influenza vaccine aggravated his underlying mitochondrial disease "with subsequent onset of clinical symptoms and regression." Pet. Ex. 65 at 8. Doctor Kendall argued that the type of regression A.K. experienced was documented in two articles which noted "a precedent for this association," referring to the Poling and Shoffner articles discussed in more detail below. *Id*.

Doctor Kendall's theory is based on the understanding that mitochondrial disorder patients may experience periods of decompensation or deterioration that can, at least sometimes, be linked to particular stresses. This understanding is not contested. But, in arguing that *vaccines* have been demonstrated to be a stressor that can trigger decompensation, she went beyond that general understanding. The evidence that mitochondrial deterioration can be linked to generally to vaccines is largely anecdotal, and the evidence that mitochondrial decompensation looks like ASD is nearly non-existent. While mitochondrial disease and ASD diagnoses can be co-morbid, the former is generally a progressive and degenerative condition and the latter

condition is not. Although those with ASD may experience plateaus and occasional deteriorations in development and behavior, those with ASD typically continue learning and improving, albeit not at the same trajectory as their typically developing peers. *See* DSM V at 56; *See also* Res. Ex. RML 123, DSM IV at 73. *See also* Pet. Ex. 172, F. Kendall, et al, at 193 (mitochondrial disorders "are often progressive and degenerative in nature."); Res. Ex. SS, Tab 6, Haas, et al ("mitochondrial diseases are usually progressive and multisystemic.").

1. The Context for Dr. Kendall's Theory.

Doctor Kendall's theory builds on an observed characteristic of mitochondrial disorders that is not particularly controversial, even if it has not been well studied or documented. That is, the condition of individuals with mitochondrial disorders often worsens over time. This may occur gradually, or there may be abrupt regressions or decompensations that result in illness and/or the inability to perform motor or cognitive tasks once mastered. Tr. 253-55, 257-58, 1167-69, 1373-75.

These regressions may occur without any apparent cause or may be temporally related to events such as viral or febrile illness, dehydration, or surgery. Tr. 253-55, 327, 444, 1168-69, 1304-06, 1373-75. Some of those who experience decompensation or regression return to baseline, some plateau, and in many, the loss of skills signals a downward spiral in the progression of mitochondrial disease. Tr. 253, 1373-75.

A correlation has been drawn between metabolic stressors, such as illnesses and surgery, and periods of regression in those with mitochondrial disease, based on the temporal relationship between such stressors and a regression or decline in health. No one knows, however, exactly how or why this occurs. Doctor Kendall indicated that the amount of stress necessary to cause this damage is unknown and likely dependent on a "constellation of factors." Tr. 257-58. Fever, in particular, has been recognized as a stressor that can possibly aggravate a mitochondrial disorder though how and why it does so is not well understood. Tr. 1304-05.

The lack of both specificity and strength in the association between illness and decompensation or regression has contributed to the uncertainty about the causal mechanism—that is, what is it about a fever or illness that causes the loss of skills? Not all individuals with mitochondrial disorders experience periods of decompensation with such stresses, and many experience such periods of decompensation even in the absence of metabolic stress. In the face of this already uncertain understanding of mitochondrial regression, petitioner's theory that a vaccine can aggravate a mitochondrial disorder leading to an ASD-like developmental regression significantly extends what is generally accepted about mitochondrial disorders. That is, Dr. Kendall's claim that a *vaccine*, not just an illness, can exacerbate, aggravate, or trigger regression or deterioration goes well beyond the above-described foundation, which is, itself, not well understood. Moreover, she asserted that a mitochondrial decompensation can result in ASD. Her opinions on these matters are based almost exclusively on a wildly overreaching interpretation of two papers discussed below.

2. Doctor Kendall Drastically Overstated the Support Provided by the Shoffner and Poling Papers.

The two articles Dr. Kendall cited in support of her opinion that vaccines themselves can cause developmental regression and autism in mitochondrial disease patient are Poling, Res. Ex. MM, Tab 14 and Shoffner, Res. Ex. MM, Tab 16. In her expert report, Dr. Kendall claimed that these two papers "have documented the association of developmental regression and autism in patients with mitochondrial disease following exposure to immunizations."[202] Pet. Ex. 65 at 7. An examination of the two articles demonstrates that they do not establish the association that Dr. Kendall claimed they did.

a. The Shoffner Study.

The Shoffner study looked retrospectively at 28 patients with co-morbid diagnoses of autism and mitochondrial disease, via a "chart review," ostensibly to examine whether a relationship between autistic regression and fever existed. Shoffner, Res. Ex. MM, Tab 16, at 429-30. The article was vague concerning whether the diagnosis of ASD or the mitochondrial disease diagnosis came first; it contains data about the age of the patients "at the time of evaluation of mitochondrial disease," which ranged from 1.5 to 19.3 years of age, but no data about the age at which ASD was diagnosed. *Id*. at 430.

About 61% (17 of 28) of the children studied were said to have experienced an "autistic regression" ("defined as the loss of developmental skills that included speech, receptive skills, eye contact, and social interests in individuals")—a higher percentage of regression than commonly reported in those with ASD, which the authors estimated at 25%.[203] Shoffner, Res. Ex. MM, Tab 16, at 430-31. Significantly, the Shoffner study does not explain how the authors determined that a regression occurred; whether it was contemporaneously reported or appeared in later histories; or what standard was used to evaluate the presence of regression at the time it was reported. As I noted in *Snyder*:

> Documentation of the nature and extent of skill loss in children with autistic disorder or PDD-NOS is complicated by the retrospective nature of case ascertainment in most studies, concerns about possible reporting bias in

[202] Although she did not specifically reference these studies during her direct examination, Dr. Kendall also testified that she believed vaccines were among the various stressors generally "known" to be capable of causing a deterioration or regression in a mitochondrial disease patient. Tr. 254, 285-86.

[203] The article cites two articles (references 22 and 23) for the percentage of those with ASD who experience a regression or loss of skills. The article at reference 22 was filed in this case. *See* Pet. Ex. F, S. Rogers, *Developmental Regression in Autism Spectrum Disorders*, MENT. RETARDATION & DEV. DISAB. RES. REV., 10(2): 139-43 (2004). Rogers reported that about one-third to one-half of the children with autism show some regression and loss of skills, a number higher than the 25% rate for which this article was cited. *Id*. at 140. The Taylor study (reference 23) was not filed in this case, but was discussed in the Rogers literature review (Res. Ex. F at 142) and in the OAP test case decisions (s*ee, e.g*., *Dwyer*, 2010 WL 892250 at *39), where it was cited in connection with estimates of the prevalence of regression in autism. The prevalence rates in all studies discussed in *Dwyer* ranged from 15%-50%. Estimates of regression in the Theory 1 test cases (*see Snyder*, 2009 WL 332044 at * 42, and n.115) ranged from 5%-50%. Thus, the 61% with regression reported by Shoffner is higher than the upper levels reported in the studies examined in the test cases. Given the small number of children in the Shoffner study, the difference between the rates of regression reported there and those in other studies is not as significant as it might appear from the 25% rate of regression reported by the Shoffner researchers.

> parental observations, and the lack of a standard measurement for regression. There is general agreement that some children with autistic disorders experience a loss of previously acquired skills, usually at 15-24 months of age. Loss of language skills is most frequently observed, but skill loss may also occur in nonverbal areas of development. . . . The range of estimates may be affected by recall bias, as parental interviews, conducted months or years after the onset of symptoms, were often the only method available to investigators to classify children as having experienced regression.

Snyder, 2009 WL 332044 at *42 (internal citations omitted). Thus, the omission of information concerning how regression was assessed and whether the reports were contemporaneous or made years after the event, the nature of the skills lost, or indeed, any details at all about the regression reported, in a study intended to determine a relationship between autistic regression and fever, are significant omissions. Significantly more detail concerning the mitochondrial disorder manifestations and testing appear in this article than discussions of the nature of the regression.

The authors also reported that 12 of the 17 children experienced an autistic regression within two weeks of a febrile episode. Shoffner, Res. Ex. MM, Tab 16, at 431. Vaccination, without any associated fever, was not associated with regression. *Id*. The authors of the Shoffner article explicitly stated that: "No individual [studied] showed regression with vaccination unless a febrile response was present." *Id*. The authors concluded that "[i]n our patients with mitochondrial disease and autistic spectrum disorders, the vaccines did not appear related to the neurologic regression." *Id*. at 432. I note that the two siblings in this case, who regressed frequently with idiopathic fevers, did not regress after vaccination.[204] *Id.*

Thus, at best, Shoffner, Res. Ex. MM, Tab 16, supported the temporal relationship between a febrile episode and some loss of skills, a phenomenon known to exist in some mitochondrial disorders in some patients some of the time.[205]

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[204] The study contained two siblings, both of whom were reported to have experienced:

> multiple episodes of neurologic regression, all with febrile episodes. Fever was typically idiopathic, with no infectious source identified. The length of time required for recovery lengthened with each febrile event. Regression in these siblings could last for weeks or even several months before they would begin regaining skills. Both brothers received a complete vaccination schedule without incident.

Shoffner, Res. Ex. MM, Tab 16 at 431.

[205] Although Dr. Kendall indicated that A.K. had experienced post-vaccination fevers in her recitation of A.K.'s medical history (Pet. Ex. 65 at 2), there is no contemporaneous or reliable evidence of fever after the influenza vaccinations. Indeed, Dr. Kendall acknowledged on cross-examination that she could not cite to any medical record in support of that assertion. Tr. 294, 342. Although respondent conceded that A.K. received his first influenza vaccine on November 2, 2001, there is no contemporaneous record of its administration. The vaccination is listed in his immunization summary. Pet. Ex. 61, p. 4. In her declaration, [A.K.'s mother] indicated that for about 10 days prior to his November 2 vaccination, A.K. had been experiencing symptoms of an upper respiratory problem, including a runny nose, but that he did not at that time have any fever. Pet. Ex. 46 ¶ 10. [A.K.'s] mother indicated she had concerns about giving A.K. a vaccination while he was still symptomatic. *Id*. In her declaration, [A.K.'s mother] indicated that A.K. ran a "low grade" fever in the days following his vaccination. Pet. Ex. 46 ¶ 11. At the hearing, however, her

Significantly, the authors did not specify whether this regression marked the first manifestation of ASD or whether symptoms of ASD were already extant in the children studies.

b. The Poling Case Report and Study.

The Poling paper contains both a study and a single case report. The case report involved a child who regressed after receiving vaccines at 19 months of age and who was subsequently diagnosed with both ASD and a mitochondrial disorder. Res. Ex. MM, Tab 14, at 171-72. It also included a retrospective analysis of159 children with autism compared to 94 patients with neurological disorders other than ASD. The

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testimony regarding A.K.'s condition following that vaccination did not include fever. Tr. 38. She listed symptoms such as irritability and listlessness. *Id*. She did not mention any fever until prompted by her declaration on cross-examination. Tr. 62. She characterized the fever as "slight." *Id*. I note that this declaration was written in October 2010, almost nine years after the events in question.

A.K.'s medical records in the weeks following his vaccination reflect that on November 16, 2001, A.K. had two nights of waking with nasal congestion. Pet. Ex. 61, p. 56. A.K. was seen for his 2 year check-up less than a week later on November 21, 2001. Pet. Ex. 61 at 55. The notes for that visit indicate that A.K. had rhinitis and [A.K.'s mother] testified that A.K.'s pediatrician felt he likely had a virus. Pet. Ex. 61, p. 55; Tr. 39, 65. In addition, A.K. had elevated lymphocytes as of November 21. Pet. Ex. 61 at 54. None of the records during this period contain any mention of a fever. Pet. Ex. 61, pp. 55-56.

A.K. received his second influenza vaccine on December 3, 2001. Pet. Ex. 118. [A.K.'s mother] testified that after that vaccination A.K. was again listless and had stomach difficulties. Tr. 40-43. She described a dramatic change and indicated that she called the doctor and was told A.K. probably had a virus. *Id*. There is no record of that call in any medical record. [A.K.'s mother] initially described A.K. as slightly warm at that point, but later indicated that he had not been feverish until December 9, 2001. Tr. 42, 74. [A.K.'s mother] indicated that December 9 he was "warm and sweaty, not burning hot." Tr. 74. She reported that he otherwise had no symptoms of illness. *Id*. For his part, [A.K.'s father] testified that he had no independent recollection, but that [A.K.'s mother] may have mentioned that A.K. felt warm. Tr. 109, 133.

The next notation in A.K.'s pediatric record is from about a week later on December 17, 2001. Pet. Ex. 61, p. 54. It indicated that A.K. had cold symptoms. *Id*. Subsequently, on December 31, 2001, A.K. was diagnosed with a "protracted" upper respiratory infection. Pet. Ex. 61, p. 52.

When considering a medical history "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. Sec'y, HHS*, 23 Cl. Ct. 726, 733 (Fed. Cl. 1991), ***aff'd*** 968 F.2d 1226 (Fed. Cir. 1992). However, medical records do "warrant consideration as trustworthy evidence." *Cucuras,* 993 F.2d at 1528. Accordingly where subsequent testimony conflicts with contemporaneous medical records, special masters frequently accord more weight to the medical records. *See, e.g., Reusser,* 28 Fed. Cl. at 523 ("[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.").

Here, there is no documentation of any fever temporally related to A.K.'s vaccinations despite the fact that [A.K.'s mother] was in contact with A.K.'s doctor following both vaccinations due to general concerns regarding illness. This casts doubt on the report of fever. Moreover, even if I did accept that the fevers had occurred, A.K.'s complete medical history reveals other possible, if not more likely, explanations for the alleged fevers. Significantly, [A.K.'s mother] herself indicated that in both instances A.K.'s treating physicians attributed the symptoms to a viral illness and there was no reference to any vaccine as a contributor to the symptoms. Therefore, petitioners have not established, more likely than not, that A.K. experienced any fevers attributable to the two half doses of influenza vaccine implicated by this claim.

specific types of the "other disorders: were not mentioned. The study compared results for some of the same tests performed on the Poling child, finding elevated levels of AST were elevated in the ASD group as compared to the children with other neurological disorders, and a suggestion that the creatine kinase levels were also elevated in those with ASD, although there were too few results available from the "other neurological disorders" group to allow for comparison. The specific numbers of children with AST results available in each group were not reported. *Id*. at 171-72. The authors suggested that, in view of the AST and creatine kinase levels, some of the children with ASD might possibly have a mitochondrial disorder as well. *Id*. at 172. However, in terms of documenting developmental regression with subsequent development of enough behavioral symptoms to qualify as ASD and diagnosis of a mitochondrial disorder, the Poling article presents only a single case report. Moreover, as the Poling child also experienced a fever following her immunizations (*id*. at 171) this case report falls squarely within the parameters of the Shoffner study findings, which implicated fever as a trigger for mitochondrial decompensation, not simply vaccination.[206]

A close examination of the symptoms reported for the Poling child in the case report do not reflect the loss of language or social skills within days or even two weeks of the vaccination. The symptoms reported within 48 hours of the immunizations included a fever, "inconsolable crying, irritability, and lethargy and [a refusal] to walk." Res. Ex. MM, Tab 14 at 171. Four days after the vaccinations, she was "waking up multiple times in the night, having episodes of opisthotonus,[207] and could no longer normally climb stairs." *Id*. She developed a rash 10 days after immunization, and was apparently seen by her pediatrician, who thought the rash was due to her varicella vaccination. *Id*. The precise timing of later symptoms is difficult to discern; the report indicates that: "For 3 months [the start time is not identified, but is presumably the vaccination], the patient was irritable and increasingly less responsive verbally, after which the patient's family noted clear autistic behaviors, such as spinning, gaze avoidance, disrupted sleep/wake cycle, and perseveration on specific television programs." *Id*. at 171. The report does not identify when the language loss began, reporting only that the child lost "[a]ll expressive language" by 22 months of age. *Id.* However, she began speaking again about a month later, before any mitochondrial treatments were administered. *Id.*

Thus, it appears that the Poling child lost motor skills within a short period after the vaccination, but any loss of language or social skills was gradual and did not occur within days or a few weeks of the vaccination. This gradual loss of language may properly be termed an autistic regression, but the behavioral manifestations the study described are quite consistent with the way ASD appears.

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[206] It is also noteworthy that Dr. Shoffner is listed as an author on both papers. C*ompare* Res. Ex. MM, Tab 14 and Res. Ex. MM, Tab 16. Doctor Kendall thus stretched the facts when she claimed that "several groups" have documented this alleged association. *See* Pet. Ex. 65 at 8. Although Dr. Shoffner was one of multiple authors of each paper, the fact that the two papers share a common author suggests that these reports were not independent research, as Dr. Kendall seemed to imply in her report.

[207] Opisthotonus is a "form of spasm consisting of extreme hyperextension of the body; the head and the heels are bent backward and the body bowed forward." DORLAND'S at 1330.

3. Analysis of Dr. Kendall's Claims Regarding Vaccination as a Trigger.

When cross-examined, Dr. Kendall conceded both that Poling paper is not really a study but a single case report (albeit one augmented by attempts to find similar test results in other autism patients), and that the Shoffner study did not find that a vaccination was temporally associated with autistic regression in the absence of fever. Tr. 331-32.

When I expressed my concern to Dr. Kendall that she may have exaggerated the nature of the findings in the Shoffner paper and that her report misrepresented the Poling and Shoffner articles as implicating vaccines as causal, she backtracked on her claim that these papers claimed any association between regression and vaccination. She confirmed that her intent in citing these papers was only to show that "other factors" could impact children with mitochondrial disorders generally, and not to claim that A.K. fit the pattern presented by either the Shoffner or Poling papers. Tr. 368-71. That is, Dr. Kendall contended that she cited the Poling and Shoffner papers merely for the proposition that metabolic stressors generally could cause a regression and not for the more specific contention they claimed that vaccines can act as such a stressor. Tr. 331-32. That distinction is critical, because it is only the latter and not the former point that is disputed in this case.[208]

As described above, Dr. Cohen likewise acknowledged that fever or other illness appears to be capable of triggering a regression in a mitochondrial disorder patient. He stressed, however, that although the mitochondrial community has generally accepted the idea that fevers can be temporally associated with mitochondrial deterioration in some but not all cases – that is they "appear" to be capable of triggering such regression – no one yet knows why. Tr. 1343-46. Doctor Cohen indicated that most instances of regression actually take place with no identifiable stressor. Tr. 1305.

Doctor Cohen further explained that even in cases of viral illnesses, which have been associated with mitochondrial regression and do tend to include fever, it is still is not understood what, if any, impact the fever itself has on that process. *Id*. Other factors associated with viral illness such as anorexia and dehydration may, in fact, have a closer temporal association to subsequent deterioration than does the fever. *Id*.

Indeed, as Dr. Cohen testified, there is no evidence that a fever causes a person to be in a state of oxidative stress. Tr. 1346. Doctor Deth opined similarly that fever

[208] In that regard it is also significant that Dr. Kendall acknowledged that under her theory she cannot rule out A.K.'s contemporaneous respiratory illness (*see e.g.*, n. 205, above) as a contributing stressor. Tr. 286-87. Indeed, Dr. Kendall testified that "sometimes it's hard to determine what's going to be the appropriate combination that's going to lead to problems in a given individual. But certainly, multiple impacts or multiple problems at a given time could have a cumulative effect on them." Tr. 287. She indicated that it is difficult to know the impact of the illness, because she does not know how significant it was or whether A.K. was "back to his baseline" at the time of his vaccination. Tr. 286. Although Dr. Kendall is clearly of the opinion that the vaccination contributed to A.K.'s condition, it is significant that Dr. Kendall did not describe any basis to exclude A.K.'s illness as the sole cause of his condition. Although she felt it was significant that A.K. tolerated prior instances of vaccination or illness (Tr. 328-29), she also testified that intercurrent illnesses cause oxidative stress with or without an associated fever. Tr. 382.

itself does not cause oxidative stress, but rather should be considered a symptom of other conditions, such as inflammation, that may cause oxidative stress.[209] Tr. 808.

Thus, absent an understanding of how or why fever can cause a mitochondrial deterioration, the conclusions one can draw from the temporal association suggested by the Shoffner article are severely limited, a point that goes to the heart of Dr. Kendall's reliance on the Poling and Shoffner articles. That is, to the extent that Dr. Kendall posited that vaccines aggravate mitochondrial disorders by causing oxidative stress, neither the Poling nor Shoffner papers in themselves actually established that any of the subjects who experienced a fever were in a state of oxidative stress. Thus, Dr. Kendall's assertion that the association between fever and deterioration illustrated by Shoffner and Poling offers a "precedent" for her suggestion that vaccines, by virtue of being a source of oxidative stress, can do the same, is actually unsupported speculation.[210]

a. The Shoffner and Poling Papers Are Weak Evidence.

Even evaluating these two papers for the point which they actually make – that a fever, vaccine-induced or otherwise, may trigger a decompensation or regression – I note that they still provide scant evidence that the regression will be an autistic regression or otherwise constitute the first symptom of ASD. The Shoffner study relied upon a very small sample, making it difficult to assign it much weight. Indeed, the Shoffner authors themselves stressed that their data "emphasize the need for larger studies investigating the role of fever, plus coexisting metabolic abnormalities."[211] Res. Ex. MM, Tab 16 at 432.

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[209] Doctor Cohen, in turn, testified that, based on the antigen load involved, that a post-vaccine inflammatory response would be far less than inflammation caused by a viral illness. Tr. 1311.

[210] Doctor Kendall's causation opinion did not directly implicate oxidative stress as a causal mechanism for regression, nor did she directly assert that vaccines create oxidative stress. That aspect of the theory was addressed by Dr. Deth's presentation. Doctor Deth attempted to explain the presence of oxidative stress more broadly in terms of various sources of inflammation. These points are addressed in later sections of this decision. The point here is that the Shoffner and Poling papers do not establish the scientific "precedent" that Dr. Kendall claims.

[211] In recent Vaccine Act cases, Federal Circuit judges have expressed concern about special masters' reliance on small studies involving rare events, perhaps because the studies may not be sufficiently powered to detect the events being studied. *Paluck v. Sec'y, HHS*, 786 F.3d 1373, 1384-86 (Fed. Cir. 2015) (finding that the special master erred in determining a period of onset for symptoms of neurodegeneration using only articles and a case study containing very few participants); *Koehn v. Sec'y, HHS*, 773 F.3d 1239, 1243 (Fed. Cir. 2014) (questioning the special master's reliance on a study insufficiently powered "to produce statistically significant results"). The "power" of a study to detect events is one factor in determining how much weight to give such studies. Reference Manual on Scientific Evidence, Federal Judicial Center, 2011(3d ed.) at 218-19. The concern about small studies expressed by the Circuit judges is one shared by special masters. However, in the traditional toxic tort case, plaintiffs rarely prevail without epidemiological evidence showing a relative risk (odds ratio) of 2 or greater, both to establish general causation (the "can it cause?" query) and that the toxic substance is more likely than not the responsible agent in the case at bar (the did it cause?" query) by preponderant evidence. *Id.* at 217 n.14 (citing *McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1244 (11th Cir. 2005) (additional internal citations omitted)). Toxic tort cases are very similar to Vaccine Act cases in the scientific subject matter, the lack of definitive proof of a substance's effects on the human body, and in the application of the preponderant evidence standard. Unlike toxic tort litigation, a study involving an

Additionally, the lack of explanation of the methodology used makes reliance on the Shoffner study problematic. The Shoffner paper did not clearly indicate when mitochondrial disease was diagnosed in the patients; thus, it is impossible to determine if the autistic regression occurred prior to or after the onset of the mitochondrial disorder symptoms or diagnosis. Nor did the Shoffner study indicate whether the regression was reported contemporaneously, was pulled from later histories in the participants' medical records, or was elicited from interviews of the study participants' parents.[212] It appears

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odds ratio of 2 or greater is rarely, if ever, seen in contested Vaccine Act causation in fact cases. Respondent routinely concedes causation or settles at close to full value in cases where the epidemiology is far less definitive. For example, cases involving influenza vaccine and Guillain Barré syndrome do not have epidemiology showing a relative risk greater than 2, but the vast majority of such cases are settled. *See, e.g.*, *Jones v. Sec'y, HHS,* No. 14-1007V, 2015 WL 2359064, at *1 (Fed. Cl. Spec. Mstr. Apr. 23, 2013) (typical of settlements routinely seen in influenza-Guillain Barré cases). Respondent has agreed to settle cases where the available proof of vaccine causation is even lower. *See, e.g., Tompkins v. Sec'y, HHS*, No. 10-261V, 2013 WL 3498652, at *2 (Fed. Cl. Spec. Mstr. June 21, 2013), *motion for rev. denied*, 117 Fed. Cl. 713 (2014) (recounting the procedural history of the execution of a settlement agreement in the case (rendered void by the death of the vaccinee from unrelated causes)). *Tompkins* later proceeded to hearing on petitioner's causation in fact claim, and in the subsequent decision, I ruled that petitioner had failed to produce preponderant evidence, based in part on the epidemiological evidence regarding both influenza and tetanus vaccines and the lack of a causal association of the tetanus vaccine with Guillain Barré syndrome.

In a Program where *Daubert* is not used to exclude evidence or experts, causation of rare conditions is often alleged and there is little evidence on general and specific causation, other than opinions. Special masters often discuss the evidence filed and relied upon by a party as a part of their statutory mandate to consider the record as a whole. They may accept less definitive epidemiology as some support for a causation opinion, but rarely does a special master rely upon epidemiology alone. Evidence from small studies may be the only evidence available to support or undercut an opinion on causation. When there is no support for a causation theory other than the expert's own *ipse dixit*, a judge in another court may refuse to admit the testimony (*Joiner*, 522 U.S. at 146) (citing *Daubert*, 509 U.S. at 589), but a special master is not similarly constrained by the rules of evidence. In the OAP test cases, the special masters heard evidence from the petitioners on theories that other state and federal courts refused to admit, based on *Daubert* and *Frye v. United States*, 293 F. 1013 (D.C. Cir. 1923). *See Blackwell v. Wyeth*, 971 A.2d. 235 (2009); *Doe v. Ortho-Clinical Diagnostics, Inc*. 440 F. Supp. 2d. 465 (M.D. N.C. 2006); *Redfoot v. B.F. Ascher & Co*., No. C 05-2045 PJH, 2007 WL 1593239 (N.D. Cal. June 1, 2007).

I emphasize that I am not *requiring* either party to produce epidemiological evidence in this (or any other) case, but I must consider the epidemiological evidence the parties filed as part of the statutory requirement to consider the evidence as a whole. When two well-qualified experts testify contradictory to one another on vaccine causation, support (or lack thereof) in the scientific literature is one factor identified in *Daubert* itself as a matter to consider in deciding if the expert testimony is reliable. *Daubert*, 509 U.S. at 596.

[212] In the OAP test cases, considerable doubt about the validity of later-reported regressions was noted, particularly in view of the widespread information about the purported link between MMR vaccines and onset of autistic symptoms or loss of skills. *Dwyer*, 2010 WL 892250, at *36, n.163, *169; *Snyder, 2009 WL 332044,* at *44, *137. In this case, several medical journal articles were filed that discussed discrepancies in parental reporting as compared to contemporaneous evidence such as videos. *See, e.g.*, Ozonoff, Res. Ex. OO, Tab 4, at 802-03 (finding parental recall of behavior patterns and onset conflicted with video evidence from the same periods, and noting that this was seen even when parents were interviewed as little as a year or two after the events recalled).

In my own experience as a special master, with close to 1700 autism cases on my docket in 2007, I have read medical records of many children who reportedly experienced an autistic regression at a particular time, usually proximate to a vaccination, as reported in a later history, the petition, or affidavits.

from comments about the group with fever that either a records review or some form of interview was conducted.[213] Res. Ex. MM, Tab 16 at 431. Perhaps even more significantly, the study made no claim that the regression caused the ASD diagnosis.[214]

The authors of the Shoffner study acknowledged some limitations themselves. As previously indicated, they "did not investigate changes that could be important in the induction of regression such as dehydration, hypoglycemia, decreases in substrate ability to oxidative phosphorylation, and other metabolic abnormalities such as fatty acid oxidation dysfunction." Res. Ex. MM, Tab 16, at 432. Moreover, the authors also commented: "In our patients with mitochondrial disease and autism spectrum disorders, the vaccines did not appear related to the neurological regression." *Id*. Indeed, the two siblings in the study, both of whom had frequent regressions in response to metabolic

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When the contemporaneous medical records and histories more proximate to the events in question were examined, the regression, if any, did not occur as reported in the vast majority of cases. *See Hodges v. Sec'y, HHS*, 9 F. 3d 958, 961 (Fed. Cir. 1993) (noting that Congress contemplated the special masters would use their accumulated expertise in the field of vaccine injuries to judge the merits of individual claims). Conflation of events to place their occurrence close in time to a possible cause has been quite common in the OAP cases, although, with rare exceptions, it does not appear that the conflation was deliberate. Using parental recall to establish that a regression occurred instead of contemporaneous medical records reporting such a regression casts doubt upon the validity of the reports of regression, as well as the temporal connection. Based on the information provided in the Shoffner paper, it is impossible to determine what the authors relied on to determine that a regression had occurred in close temporal proximity to a febrile episode.

[213] The reference to the degree of fever included the qualifier "as reported by parents," which could mean interviews as a part of the study, a review of contemporaneous records, or a review of later histories in the medical records. However, the authors also commented that the "precise fever duration was difficult to ascertain because patients were usually managed in the home." Shoffner, Res. Ex. MM, Tab 16, at 431. This comment suggests that the presence or absence of fever around the time of regression was based on parental recall.

[214] Regression is not required for an autism diagnosis. Loss of skills is not listed as a diagnostic criterion in the DSM V. *See* DSM V at 50-51 (listing diagnostic criteria); 53-55 (diagnostic features discussion). Regression or loss of skills is mentioned only in the section titled "Development and Course." *Id*. at 55-56. Comments pertaining to regression include:

> The pattern of onset description might include information about early developmental delays or any losses of social or language skills. In cases where skills have been lost, parents or caregivers may give a history of gradual or relatively rapid deterioration in social behaviors or language skills. Typically, this would occur between 12 and 24 months of age and is distinguished from the rare instances of developmental regression occurring after at least 2 years of normal development (previously described as childhood disintegrative disorder). . . .Some children with autism spectrum disorder experience developmental plateaus or regression, with a gradual or relatively rapid deterioration in social behaviors or use of language, often during the first 2 years of life. Such losses are rare in other disorders and may be a useful 'red flag' for autism spectrum disorder. Much more unusual and warranting more extensive medical investigation are losses of skills beyond social communication (*e.g.*, loss of self-care, toileting, motor skills) or those occurring after the second birthday.

Id. at 55. Thus, even if a fever or other inciting event triggered a loss of skills in a child with an underlying mitochondrial disorder, the regression would not necessarily constitute the triggering of an ASD or be causal of that condition. And, in a child who already exhibited ASD symptoms, a regression or loss of skills in social behavior or language would appear to be consistent with the natural course of ASD.

stressors, did not report any problems after vaccinations. Thus, this article is a thin reed upon which to hang Dr. Kendall's opinion that vaccines, with or without fever, can trigger onset or aggravate a mitochondrial disorder.

The Poling case report is also weak support.[215] The Poling case study is merely a single instance consistent with the conclusion stated in the Shoffner study. A single case study in isolation is not significant proof of an association because what happened could easily be entirely due to chance. That is, a single instance of something occurring is by definition *not* evidence of a pattern.

Although case reports are not completely without evidentiary value, in this case such an isolated report is especially weak in that Dr. Kendall herself indicated that metabolic disorder patients live in a fragile state where "anything can just cause them to tip over fairly quickly." Tr. 255. She indicated that "lots of different things" can cause them to decompensate, including dehydration, not eating well, surgery, infections or other illnesses. Tr. 255, 327. Indeed, she noted that a mitochondrial disorder patient can experience a deterioration even in the absence of any stressor. Tr. 253-54, 444.

Nevertheless, I have considered this case report, but decline to place much reliance upon it. *See Paluck v. Sec'y, HHS,* 104 Fed. Cl. 457, 475 (2012) (noting that although "case reports 'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value'…. 'the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" (quoting *Campbell v. Sec'y, HHS*, 97 Fed. Cl. 650, 668 (2011)); *Bast,* 2012 WL 6858040, at *24, *28 (discussing the limited value of case reports); The *Reference Manual on Scientific Evidence*, Federal Judicial Center, 2011(3d ed.) at 724 (noting that in determining medical causation, case reports "are at the bottom of the evidence hierarchy," largely because they lack controls and thus do not provide the level of information or detail found in epidemiologic studies; nevertheless, they "may be the first signals of adverse events or associations that are later confirmed with larger or controlled epidemiological studies"). *Id.* "[S]ome courts have suggested that attempts to infer causation from anecdotal reports are inadmissible as unsound methodology under *Daubert*." *Id*. at 217 n.14 (citing *McClain v. Metabolife Int'l, Inc.*, 401 F.3d at 1244) (additional internal citations omitted).

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[215] I am aware of the recent Federal Circuit decision in *Paluck,* 786 F.3d at 1384-86, 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 the fact that, despite describing a young girl experiencing an apparent regression following vaccination, the report does not purport to establish any definitive time frame for the onset of a neurological regression. Any discussion of the significance of the Poling report in terms of petitioner's theory of causation was preempted because respondent conceded the plausibility of the petitioner's causation theory in that case. Indeed, the Federal Circuit's decision in *Paluck* does not address the validity of the petitioners' theory, but rather whether the special master had properly construed that theory for purposes of determining whether the Paluck's child, K.P., had a medical history consistent with the expected time frame stated by the theory. In this case, unlike *Paluck*, respondent is contesting petitioner's theory that a vaccine can cause a regression (as well as petitioners' assertions that the *Poling case settlement* constituted a concession that vaccines could cause a regression (*see* Motions Ruling, filed on Sept. 28, 2015 (ECF No. 319), at Section II.B.3.d)). In the motions ruling in this case, I already addressed why respondent is not constrained by her prior concession in the *Poling* case or, indeed, any case.

If Poling was the first signal that vaccines, accompanied by fever, might serve as the trigger for a Table encephalopathy or even actual causation of "mitochondrial autism," the only followup study filed, the Weissman study (discussed in more detail below), failed to find any incidences of vaccinations alone triggering autistic-type regression in children with mitochondrial disorders.

There are other reasons to give this case report scant weight. Doctor Poling, the lead author, wrote the report about the experience of his infant daughter.[216] The child experienced a developmental regression within 48 hours of a DTaP vaccination and within five to 15 days of a measles vaccination administered at 19 months of age. Res. Ex. MM, Tab 14 at 171 (factual presentation). The onset of neurological symptoms was within the periods for a DTaP Table encephalopathy (72 hours) and a measles Table encephalopathy (five to 15 days). *See* 42 C.F.R. § 100.3(a)(II)(B) and (a)(III)(B)(2011) (Vaccine Injury Table identifying encephalopathy as an associated injury for DTaP and measles vaccines and setting forth the time periods required). The child was eventually diagnosed with both autism and a mitochondrial disorder. Res. Ex. MM, Tab 14, at 171-72; *see also Poling v. Sec'y, HHS,* No. 02–1466V, 2011 WL 678559, at *1 (Fed. Cl. Spec. Mstr. Jan. 28, 2011) (fees and costs decision, noting that the case was compensated as a Table injury).

It is noteworthy then that the Poling child's condition arose after she received multiple vaccinations including diphtheria, tetanus and pertussis and measles mumps rubella (Res. Ex. MM, Tab 14, at 171), two vaccines that carry a presumption of causing

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[216] The familial relationship was not disclosed by Dr. Poling in the case report. *See* Brumback, Res. Ex. MM, Tab 17. In this short commentary, Dr. Brumback, the editor in chief of the JOURNAL OF CHILD NEUROLOGY (the journal in which the Poling article was published) noted that the authors of the Poling article disclosed no conflict of interest at the time the article was submitted for publication or in the 12 months that passed prior to actual publication, in spite of a pending claim filed by Dr. Poling on behalf of his daughter in the Vaccine Injury Program. He commented:

> To any journal editor, this is an appallingly troubling issue. Openness and transparency related to any and all potential conflicts of interest is critical to maintaining the integrity of science in general and of journal quality in particular. Whether the manuscript would have been accepted for publication if the authors had disclosed earlier the conflict of interest is not a moot point, but this does not excuse the behavior of the authors in not disclosing the conflict of interest at the time, despite their current [apologies]. . . .[M]edia linkage of the published article to the legal outcome implies scientific support from [the Journal of Child Neurology] for this legal opinion (referring to the special master's opinion awarding compensation).

Id. at 1090. Doctor Brumback noted that this event provoked a change in policy; all authors' statements regarding potential conflicts of interest would be published. He also observed that "no written statement can substitute for honesty, good faith, and integrity on the part of authors. *Id*. at 1091.

As Dr. Brumback also observed, disclosure of possible conflicts of interest is expected when submitting a medical journal article for publication. Conflicts of interest are a matter to be considered when applying *Daubert.* In its opinion on remand in *Daubert*, the Ninth Circuit considered whether the matters an expert proposed to testify about flowed from research conducted independently of involvement in the litigation in question, noting that this factor provides objective proof that the research was conducted for scientific purposes. *Daubert v.Merrell Dow Pharmaceuticals*, 43 F.3d 1311, 1317 (9th Cir. 1995); *see also Exxon Shipping Co. v. Baker*, 128 S. Ct. 2605, 2626 n.17 (2008) (declining to consider research funded in part by a party to the litigation).

that condition in this program under the Vaccine Injury Table. The same cannot be said of the influenza vaccines at issue in this case. *See also* the discussion of the *Poling* vaccine injury case in the ruling on motions in this case (Motions Ruling, filed on Sept. 28, 2015 (ECF No. 319), at Section II.B.1-2).

b. The Weissman Article Does Not Support Petitioners' Theory.

Although Dr. Kendall did not specifically rely on it in her report or direct testimony, on redirect examination, petitioners' counsel questioned Dr. Kendall about the Weissman article, Pet. Ex. 39. Tr. 375-82. The study is not about vaccinations; however, it does contain one short passage that addresses the subject of vaccine causation. Weissman, Pet. Ex. 39 at 4. Specifically, petitioners' counsel drew Dr. Kendall's attention in particular to a statement wherein the authors indicate that there "might" be no difference between vaccinations and childhood diseases in terms of inflammatory or catabolic stress. *Id.*; Tr. 378. Doctor Kendall indicated that the statement was consistent with her clinical experience. Tr. 378.

Even in isolation, with its use of the word "might," the statement is far from a strong statement regarding vaccine causation and is, at best, equivocal on the issue. Moreover, quoting the relevant passage in full reveals a much different picture, one that indicated that the Weissman authors would not be likely to agree with Dr. Kendall's theory. They stated that:

> Recently, there has been increased concern regarding a possible causative role of vaccinations in autistic children with an underlying mitochondrial cytopathy. For one of our 25 patients, the child's autism/neurodevelopmental deterioration appeared to follow vaccination. Although there may have been a temporal relationship of the events in this case, such timing does not prove causation. That said, there might be no difference between the inflammatory or catabolic stress of vaccinations and that of common childhood diseases, which are known precipitants of mitochondrial regression. Large, population-based studies will be needed to identify a possible relationship of vaccination with autistic regression in persons with mitochondrial cytopathies.

Pet. Ex. 39 at 4 (internal citations omitted).

Based on this passage, the Weissman authors clearly do not believe that a 1- in-25 occurrence of deterioration following vaccination is sufficient to conclude that vaccines can cause autism or neurodevelopmental deterioration. Doctor Cohen, one of the participating authors, testified that the passage was intended by the authors to stress that the temporal relationship present in that one case is not proof of causation. Tr. 1228-29. In other words, despite the statement cherry-picked by petitioners, the passage as a whole is intended to convey that no causal association between vaccinations and decompensation was recognized.

Moreover, the one child in Weissman who experienced a deterioration following vaccination was the Poling child, the subject of the above-discussed Poling case study. This was confirmed not only by the citation to the Poling case report, but also by Dr.

Cohen's testimony. Pet. Ex. 39 at 4 (citing to reference 12, which is the Poling case study); Tr. 1227-29. Thus, not only does the Weissman article not actually bring any additional evidence to bear, it also casts further doubt on the value of the Poling case study.

Like the Shoffner study, the Wiessman study is, of course, very small. In fact, petitioners' counsel noted during his redirect that, assuming there is no overlap[217], the population between the two studies was a mere 53 subjects (28 in Shoffner and 25 in Weissman). Tr. 378-79. Moreover, Dr. Cohen cautioned that the Weissman study was not case-controlled, and therefore not capable of determining statistical significance. Tr. 1227-29. Nonetheless the study does add some broader context to the Poling case study tending to suggest that the Poling report is less significant than petitioners claim.

That is, although the Weissman study does not identify how many patients were screened to arrive at the 25 test subjects, Dr. Cohen did indicate that such a screening process occurred. Tr. 1378. In addition, the article itself states that the subjects were drawn from investigators at major institutions across the country such as the Cleveland Clinic, Massachusetts General Hospital and Kennedy Krieger Institute, suggesting a relatively broad scope. Pet. Ex. 39 at 2. Moreover, the above-quoted passage indicates that the authors considered the potential temporal association between vaccination and deterioration among the subjects. Yet, despite this, the Poling case still remains an isolated case study. While very far from conclusive given the size of the study population and the unknowns regarding the screening process, this does bear to some degree on the weight to be accorded the Poling report as it increases the likelihood that the temporal relationship in Poling was actually a chance occurrence.[218]

4. The Lack of Substantiation.

Doctor Kendall testified that she was not aware of any reports regarding the specific question of whether vaccines act as stressors among metabolic patients.[219] Tr. 365-66. Similarly, she also testified that she was not aware of any evidence that the influenza vaccine in particular can cause regression or significantly aggravate a mitochondrial disorder. Tr. 332. Rather, she confirmed during my questioning that the only evidence she had to support her claim of an association between vaccination and mitochondrial regression were the Poling and Shoffner papers discussed above. Tr. 367-68. Absent her initial reliance on those studies, Dr. Kendall ultimately testified that she was unaware of any medical literature supporting an association between

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[217] This may not be a safe assumption given that both studies sought out patients who had already been diagnosed with both mitochondrial disorders and ASD, a small population, and did so within two years of each other.

[218] I stress again that the Weissman study is very small and was not intended as a study of vaccines or vaccine reactions. As such I am not indicating that it negates the Poling case report. *See* n.211, *supra*, regarding reliance on studies insufficiently powered to detect rare events. Nonetheless, it shows that the Poling case remains the only specifically identified case of a temporal relationship between a vaccination (accompanied by fever) and a regression.

[219] I note that Dr. Shafrir separately cited some additional articles regarding mitochondrial disorders and autism that are discussed in Section VIII.B.2.a, below. None of those articles, however, provide any further support for Dr. Kendall's theory.

vaccination and regression.[220] Tr. 371. Nonetheless she indicated, without further elaboration, that she was taught as a general matter during fellowship training that immunizations can act as stressors for children with inborn errors of metabolism. Tr. 365-66.

Doctor Kendall testified that some of her own patients had some problems subsequent to vaccination. Tr. 255. She agreed, however, that metabolic disorder patients live in a fragile state where "anything can just cause them to tip over fairly quickly." Tr. 255. She indicated that "lots of different things" can cause them to decompensate, including dehydration, not eating well, surgery, infections or other illnesses. Tr. 255, 327. Indeed, she noted that a mitochondrial disorder patient can experience a deterioration even in the absence of any stressor. Tr. 253-54, 444. She offered no specifics regarding these anecdotal instances from her own practice of vaccination aggravating a mitochondrial disorder and did not indicate if any other potential stressors were also present in these patients. In his competing experience, Dr. Cohen testified that he had never seen a vaccination aggravate a mitochondrial disorder. Tr. 1306-07.

B. Doctor Shafrir's Theories.

Although Dr. Shafrir identified A.K.'s alleged mitochondrial disorder as a relevant factor in his analysis, there was otherwise no discernable overlap between his theories and Dr. Kendall's. Doctor Shafrir argued more broadly that A.K. had a "highly specific and extremely rare constellation of independent, genetically determined factors . . . combining in a vulnerable time in his development, to produce an unusual brain dysfunction, which was clearly triggered by the vaccine." Pet. Ex. 63 at 12. He contended that A.K. had a mitochondrial disorder, a MTHFR polymorphism, and a genetically-determined abnormal immune system, all of which, when combined with his influenza vaccination, caused an autoimmune brain injury (encephalopathy) which manifested as an autistic regression. Pet. Ex. 63 at 14-18. Doctor Shafrir relied on the so called "triple hit" hypothesis to explain how these factors would come together. Pet. Ex. 63 at 18; Tr. 549-54.

The "triple hit" hypothesis that Dr. Shafrir referenced was raised in an article by Dr. Manuel Casanova, written as a part of a symposium on the neurobiology of autism.[221] *See* Casanova, Pet. Ex. 63, Ref. 22, at 422-23. According to Dr. Casonova,

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[220] I do note that a great deal of literature was filed in this case, and some of it does address the broader context from which Dr. Kendall's theory derives, namely the possible link between autism, mitochondrial disorders and oxidative stress. Doctor Kendall was clear, however, in explaining that only the Shoffner and Poling papers supported her proposed extension of that understanding to include vaccinations as a trigger for decompensation in a child with a mitochondrial disorder.

[221] Doctor Shafrir's reference 22 was an article by M. Casanova, *The Neuropathology of Autism*, BRAIN PATHOL. 17:422-33 (2007) [hereinafter "Casanova, Pet. Ex. 63, Ref. 22"]. Doctor Casanova's earlier work on minicolumnar pathology of the brain in ASD was cited with approval in *Snyder*, 2009 WL 332044 at n.142 ("Doctor Rust's testimony about minicolumn differences in autistic brains is supported by the research of Dr. M. Casanova"). His expert report was filed in that case, but he was not called to testify by respondent. *Dwyer*, 2010 WL 892250 at n.186. He reiterated his earlier work on minicolumnar pathology in Pet. Ex. 63, Ref. 22, at 426-27.

the triple hit hypothesis suggests that autism is caused by a combination of "(i) a critical period of brain development, (ii) an underlying vulnerability, and (iii) exogenous stressor(s)." Pet. Ex. 63; Ref. 22, at 423 (setting forth the triple hit factors); Pet. Ex. 63 at 18 (Dr. Shafrir asserting the applicability of the triple hit hypothesis to A.K.'s case).

For the reasons described below, however, Dr. Shafrir has failed to establish any of these three factors are either present in A.K. or contributed to his ASD. To the extent that he relied on either an autoimmune encephalopathy or challenge-rechallenge to establish that the influenza vaccine could cause A.K.'s condition, his reliance was misplaced. There is no evidence, other than Dr. Shafrir's opinion, that ASD is caused by an autoimmune reaction or that there was a challenge-rechallenge scenario under the facts of this case.

1. A Critical Period in Brain Development.

Although Dr. Shafrir disavowed that "regressive autism" could be caused by genetics (see Pet. Ex. 63 at 13),[222] Dr. Casanova wrote that while autism is not monogenetic in nature, "current clinical consensus regards autism as a multifactorial trait as opposed to an oligogenic or polygenic disorder. Studies suggest the presence of multiple susceptibility and protective genes that modify the risk of developing the condition." Casanova, Pet. Ex. 63, Ref. 22 at 432. Casanova also noted that "epidemiological studies, including twin studies done in separate or conserved environments, strongly support the presence of heritable factors. Autism in monozygotic twins is stated to be 12 times higher than in the normal population" and that the rate for dizygotic (fraternal) twins is four times higher than in the general population. *Id*. at 422.

Unlike Dr. Shafrir, Dr. Casanova acknowledged that genetics plays a significant role in the etiology of autism. While Dr. Casanova's triple hit hypothesis posited the three factors Dr. Shafrir argued were present in A.K.'s case (a critical period in brain development, an underlying vulnerability, and exogenous stress or stressors), Dr. Shafrir simply ignored the portions of Dr. Casanova's work that indicated that the critical period in brain development was prenatal, not postnatal. Pet. Ex. 63, Ref. 22 at 423-28.

Doctor Shafrir contended that this period of vulnerability extended into childhood and that A.K. was in a state of vulnerability at the time he received his influenza vaccines at around two years of age, because the brain is still developing in infancy and

[222] Indeed, Dr. Shafrir also stated that "[t]he notion that autism is a genetic disease is not supported by evidence." Pet. Ex. 63 at 13. He argued that the increasing prevalence of autism belies a genetic cause. *Id.* He noted that "worldwide genetic studies have failed to identify an 'autism gene' and yielded only a very small number of patients with genetic defects," and claimed that most children with ASD-associated abnormal genes do not experience regression. *Id*. (internal citations omitted). He claimed that the "current view of the genetic component in autism is that it represents an inherited vulnerability to environmental factors," but did not cite any supporting medical literature for this proposition. *Id*. It is thus not clear whether he contends that regressive autism is not genetically caused or whether all autism is not genetically caused. He does clearly assert that autistic regression is somehow etiologically different from early onset autism, claiming that regression "is seen only with acute macroscopic structural brain injury such as stroke, certain rare epilepsies such as Landau-Kleffner Syndrome or autistic regression. It cannot be explained by anything else, but a pathological process affecting the brain." *Id.* at 12.

childhood. Pet. Ex. 63 at 18. During cross-examination, respondent's counsel asked Dr. Shafrir a series of questions relating to specific examples listed in the Casanova article. Tr. 549-54. Doctor Shafrir acknowledged that all of the examples supporting a period of vulnerability related to prenatal events, but nonetheless maintained that the theory could be applied to environmental or exogenous stressors occurring either prenatally or postnatally. *Id*.

The Casanova article reflects that mostly likely vulnerable period is confined to the first trimester of gestation. Specifically, the article concludes by noting that "several studies suggest that birth complications in autism are the result of preexisting prenatal abnormalities. The literature indicates that underlying brain alterations in autism occur well before symptom expression. Most evidence favors the first trimester of gestation as providing a time window of susceptibility." Pet. Ex. 63, Ref. 22, at 9-10.[223]

This conclusion is consistent with and further supported by another much more recent study filed by petitioners.[224] That study looked at the small number of identical twins who are discordant for ASD (only one of the twin pair having an ASD diagnosis). Although identical twins share identical DNA, about 10% of such twin pairs are discordant. The fact that monozygotic twins are not 100% concordant has been used as an argument that ASD is not caused by genetics alone—that "something else" must play a role. The Wong study examined whether epigenetics might be that "something else" to account for the discordance. Epigenetics involves the process by which genes are "turned on" or "turned off" through the methylation of DNA. Pet. Ex. 240 at 1.

Although the study was small, with just 32 twin pairs, the authors stressed that "the use of disease-discordant MZ [i.e.,monozygotic (identical)] twins represents a powerful strategy in epigenetic epidemiology because identical twins are matched for genotype, age, sex, maternal environment, population cohort effects and exposure to many shared environmental factors." Pet. Ex. 240 at 1, 8.

Respondent's expert on genetics, Dr. Raymond, argued that the Wong study was significant because it showed that the epigenetic changes occur very early in embryonic development. Tr. 1470-74. Although Dr. Raymond did not dispute petitioners' evidence

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[223] Two other expert reports, filed while A.K.'s case was still identified as a Theory 2 test case, also provide support for the prenatal origins of ASD. *See* Res. Exs. U (expert report of Dr. Thomas Kemper) and EE (expert report of Dr. Patricia Rodier). Their work was referenced in Casanova, Pet. Ex. 63, Ref. 22, at 431-33 (internal references 10, 65, and 107). Doctor Kemper did some of the early work demonstrating specific differences between the brains of typically developing individuals and those with ASD through autopsy studies, and concluded that most of the differences occurred at early stages of brain development in utero, with the only postnatal change being an arguable increase in head circumference beginning shortly after birth. *See generally,* Res. Ex. U. Doctor Rodier, a teratologist who has studied the toxic effects of mercury, as well as the stages of brain development when autism is thought to arise, opined that autism arises early in gestation, based on known environmental risk factors, histological studies of brains of those with autism, and from the co-occurring craniofacial abnormalities in some children with autism. *See* Res. Ex. EE at 2-8.

[224] *See* Wong, Pet. Ex. 240. Although the article was filed by petitioners during the course of the hearing, I excused the late filing because the study represented newly discovered evidence. Because the article was filed after Dr. Shafrir testified, he did not address it. I note that Dr. Shafrir did not testify in rebuttal, although Dr. Deth did.

that epigenetic changes continue to occur postnatally, he argued that petitioners overlooked a critical distinction between pre and postnatal epigenetics. Tr. 1459. He testified that only prenatal epigenetic changes, occurring while fetal cells are still dividing to create different types of tissues, can carry forward errors in a system-wide manner. Tr. 1461-68.

Doctor Raymond noted that the Wong study drew its epigenetic profile from blood samples as a proxy for each subject's brain profile. Tr. 1470-74. In order for the epigenetic changes to be discordant among the twins and yet observable in the blood sample, Dr. Raymond observed that the epigenetic change at issue must have occurred sometime after the twins "split," but before the developing fetus had differentiated blood and brain tissues. *Id*. He pointed out that this would place the change "at a very, very early stage" of fetal development. Tr. 1472. More generally, and consistent with the Casanova paper, Pet. Ex. 63, Ref. 22, Dr. Raymond also noted that the most critical period of development epigenetically is from conception through the second trimester. Tr. 1458.

Although the earlier Casanova paper indicated that "the exact mechanisms of interaction remain unknown," it indicated that the suggested "window of vulnerability in autism" is supported by, *inter alia*, a "strong association to neuro-embryological dysfunction" among those exposed *in utero* to thalidomide. Pet. Ex. 63, Ref. 22, at 423 (citing to work by Dr. Rodier). Doctor Casanova indicated that those subjects developed certain ear abnormalities in addition to autism. He therefore indicated that "timing of these 'minor' malformations and the supposition that autism may have arisen during the same stage of development suggests a time window of vulnerability early in gestation (20-24 days)." *Id*. He further noted that "the first trimester is the time of development for multiple congenital anomalies that include autism as one of their manifestations." *Id*.

Doctor Raymond's interpretation of the Wong study is therefore particularly compelling. It appears that the Wong study extended and corroborated Dr. Casanova's opinion that a vulnerable period exists during the first trimester of pregnancy, and particularly very early (20-24 days) within that period. Although Dr. Casanova did not posit an exact mechanism, Wong suggested that very early prenatal epigenetics may explain the interplay between genetics and *in utero* "environmental" factors in the development of autism. The relevant vulnerable period that Dr. Shafrir posited is postnatal and that timing is not supported by the literature in this case. His reliance on the "triple hit" mechanism posited by Casanova to explain how A.K.'s ASD emerged after the allegedly causal influenza vaccines at around two year of age is therefore misplaced.[225]

[225] On cross-examination, petitioners' counsel posed the question to Dr. Raymond of whether the prenatal epigenetic changes suggested by the Wong study could create a latent susceptibility to later postnatal environmental insults. Doctor Raymond said he could not completely rule out that possibility, but noted that it is highly unlikely. He again noted that the Wong article shows that the epigenetic changes are happening across all tissues, and so there is no basis to speculate that these changes would cause a vulnerability that would impact the brain and only the brain. Tr. 1514-19.

In his expert report, Dr. Shafrir contended (as did petitioners in the OAP Theory 1 and Theory 2 test cases)[226] that children who experience an autistic regression constitute a distinct phenotype with an etiology distinct from others with ASD. He asserted that autistic regression "cannot be explained by anything else, but a pathological process affecting the brain." Pet. Ex. 63 at 12. But, like his unsupported extension of the Casanova triple hit theory into the postnatal period, this claim is likewise without apparent basis.

A.K. was diagnosed as having ASD by his treating neurologist, Dr. Rapin, in April of 2004. Pet. Ex. 11, pp. 1-4. In addition, Dr. Miller, a child psychologist with significant qualifications and background in the diagnosis of ASD, offered extensive and compelling testimony explaining how A.K. fit into the standard diagnostic criteria for ASD. Indeed, she testified that A.K. met 11 of the 12 DSM-IV criteria for diagnosing ASD.[227] Tr. 937-38. Doctor Shafrir did not appear to dispute these points.

Doctor Shafrir testified that he had no reason to disagree with A.K.'s ASD diagnosis by Dr. Rapin, who he described as "the most famous person in autism until recently." Tr. 526-27. And indeed, he appeared to express doubt about an earlier evaluation that failed to result in an ASD diagnosis. *Id*. Moreover, he testified extensively about A.K.'s evident autism, at one point noting that a particular video clip of A.K. showed "a traumatic severe classic autism." Tr. 476, 526-27. Nonetheless, Dr. Shafrir argued extensively in his expert report that what A.K. experienced was an autistic regression, which, he contended, is distinct from autism itself and remains unexplained. Pet. Ex. 63 at 12-13.

This, of course, was an issue that was addressed at length as part of the OAP. As part of the Theory 1 test cases in the OAP (the MMR or MMR plus thimerosal theory) all three OAP special masters addressed the question of whether regressive autism – children with an ASD diagnosis who experience a loss of previously acquired skills – represented a distinct phenotype with a distinct cause. *Synder,* 2009 WL 332044, *39; *see also Cedillo,* 2009 WL 331968; *Hazlehurst,* 2009 WL 332306. This issue was again further explored in the Theory 2 test cases, which involved the thimerosal causation theory also raised in this case by Dr. Deth. *Dwyer,* 2010 WL 892250; *King,* 2010 WL 892296; *Mead,* 2010 WL 892248.

Significantly, the reason regressive autism was discussed in the OAP was because the petitioners sought to argue that symptoms appearing later in development, contemporaneous to vaccination, could be explained by an external environmental trigger rather than being genetically predetermined. *See, e.g. Synder*, 2009 WL 332044 at *40 (noting that petitioners' MMR theory contended the temporal relationship between

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[226] *See Snyder*, 2009 WL 332044, at *40; *Dwyer*, 2010 WL 892250, at *29, 36-40.

[227] According to Dr. Miller, A.K.'s symptoms included: limited eye contact, lack of facial expressions or gestures to communicate, failure to initiate or share social interaction, appearing as if "in his own world," not responding to or having emotional reciprocity, delayed language, lack of conversational approximation, having repetitive sounds, lack of pretending or imitating, circumscribed interest, mannerisms such as ear holding or hand flapping, and preoccupation with objects or parts of objects. Tr. 937-38. Doctor Miller did not observe any rigid routines, which is the one DSM-IV criteria she noted was absent. Tr. 938.

the vaccine and regression was evidence of causation). This is exactly the argument that Dr. Shafrir advanced in this case, arguing that what he characterizes as autistic regression "cannot be explained by anything else, but a pathological process affecting the brain." Pet. Ex. 63 at 12.

The conclusions in the OAP test cases, however, were exactly opposite to what Dr. Shafrir argued in his expert report. Although a subset of children with ASD experience regression of skills, the evidence was insufficient to conclude that these children have a distinct phenotype or have a distinct etiology with a separate cause or "trigger." Specifically, I noted in *Synder* that "neuropathologic findings, coupled with the association of autism with certain prenatal exposures, strongly indicate that autism has a prenatal onset. The evidence for autism's genetic basis and prenatal origin renders petitioners' MMR theory of causation improbable, as a vaccination in the second year of life is unlikely to generate the brain structure changes seen in ASD. Petitioners have not demonstrated that their postulated regressive autism phenotype is etiologically distinct from other forms of ASD." *Synder*, 2009 WL 332044 at *52. These conclusions were also expressed in the Kemper and Rodier expert reports. See Res. Exs. U and EE.

Doctor Shafrir simply offered no support, other than his opinion that it must be so, for regressive autism constituting a separate phenotype. Although he argued as a general matter that his theory was supported by medical literature, he provided no citation to support his assertion that autistic regression is distinct from autism.[228] Pet.

[228] Doctor Shafrir has cited several studies which suggest that "mitochondrial autism," *i.e.,* a dual diagnosis of autism and mitochondrial disease, may come to be known as a separate phenotype of ASD which in turn can be associated with neurologic or mitochondrial regression. *See, e.g*., Weissman, Pet. Ex. 63, Ref. 16;Pet. Ex. 63, Ref. 17, Haas, Pet. Ex. 63, Ref. 17. I stress, however, that this constitutes speculation, not a reliable theory that "mitochondrial autism" is different from other forms of autism with or without regression. In the seven years since the Weismann study suggested that mitochondrial autism might be a separate diagnostic entity, the evidence that those with both a mitochondrial disorder and an ASD diagnosis might constitute an etiologically, clinically, or genetically distinct group remains lacking. ASD has many co-morbid conditions—seizure disorders, tuberous sclerosis, intellectual disability, anxiety disorders, and psychiatric disorders, only a few of which may be related to the ASD diagnostic symptoms. *See* DSM V at 58-59; Casanova, Pet. Ex.63, Ref. 22, at 422. A number of parallels can be drawn between co-morbidity in ASD and mitochondrial disorders and comorbidity between ASD and tuberous sclerosis, a genetic disorder in which tubers in the body, and in particular in the brain, can cause mental retardation and seizures (*see* DORLAND'S at 397). Casanova noted that a substantial percentage of patients with tuberous sclerosis (estimates ranging from 17%-68%) also have an ASD diagnosis. but only a small percentage of ASD patients also have tuberous sclerosis. *Id.* at 423. In the case of ASD and mitochondrial disorders, the presence of ASD-associated developmental delays and/or regression are clinical symptoms used in the mitochondrial disorder diagnosis as well. For example, pertinent to the instant discussion, Casanova suggested that the presence of comorbidities such as mitochondrial disorder should not be exclusionary from an ASD diagnosis. The co-morbidity underscores the heterogeneity of ASD generally, and supports "the possibility that autism originates early in the first trimester of gestation." Pet. Ex. 63, Ref. 22, at 422. In any event, whether mitochondrial autism is a distinct phenotype is a separate question from whether regressive autism is itself a distinct phenotype caused by a distinct trigger. And ultimately that is a question that leads back to Dr. Kendall's above-discussed theory which in turn fails to link vaccination to mitochondrial regression. In that regard, I note that while the Shoffner study examined a possible link between fever and autistic regression, they specifically noted that "autistic regression occurs prior to 3 years of age in approximately 25% of children with autism, in whom developmental abnormalities were previously unrecognized. The etiology of this

Ex. 63 at 12-13; Tr. 520. This is, of course, a striking contrast to the extensive exploration of the issue during the OAP. Nor did he suggest that the scientific community's understanding of autism has changed in the six years since the first OAP test cases were decided. Indeed, Dr. Shafrir actually argued that our understanding of the causes of autism has been stalled since the 1980's. Tr. 495-98. When specifically asked during cross-examination about the distinction he drew in his report between autism and autistic regression, Dr. Shafrir admitted that there are no published medical criteria defining autistic regression. Tr. 524. He also stated that what he considers autistic regression overlaps with autism in about 95% of cases. Tr. 521.

Despite this, Dr. Shafrir speciously maintains that autistic regression and autism are separate entities, based on what he characterized as short-comings of the "official" definition of autism contained in the DSM, a definition he viewed as overly broad. Tr. 520-24 (Dr. Shafrir's general, unsupported critique of the DSM is discussed in Section VII.A, above). Doctor Shafrir essentially argued that regressive autism is too "major" of an entity to ignore.[229] But such an argument does not actually address the question of whether autistic regression has a distinct etiology. In that regard, it is particularly noteworthy that Dr. Shafrir contended that the cause of autistic regression is completely unknown. Pet. Ex. 63 at 13. Thus, even taking Dr. Shafrir's criticism of the DSM at face value, it is still not actually an argument that necessarily separates autism from autism with regression.

Despite his strong (and laudable) desire to find a cause for ASD, Dr. Shafrir acknowledged that no clear cause has been identified. Tr. 580. His frustration notwithstanding, Dr. Shafrir has not articulated how, in the absence of a clear etiology, autism should be diagnosed other than by observable behaviors. Indeed, when asked to define autism himself, Dr. Shafrir characterized it entirely in terms of observable features, testifying that autism is "a child who has impairment in communication, in socialization, and in imagination, which means that they . . . have primitive play without any use of imagination with the play. They can communicate verbally or non-verbally. The most traumatic one is they don't relate to other people." Tr. 580. Moreover, several of the studies cited by Dr. Shafrir screened their subjects for ASD using the DSM-IV criteria and the screening tools described by Dr. Miller, and did so without noting any criticisms similar to those raised by Dr. Shafrir.[230]

It is understandable that Dr. Shafrir, a neurologist who sees many children with ASD as patients, would be eager to discover a clear neurological cause of autism and I

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regression is unknown." Res. Ex. MM, Tab 16, at 429-30. *See* n.203 *supra,* reflecting that the actual number of children with ASD who experience a loss of skills is higher than 25%. And in any event, even if mitochondrial autism is a separate phenotype, that still cannot explain A.K.'s ASD since I have concluded he did not have mitochondrial disease and therefore he would not fall within that very hypothetical phenotype.

[229] I note that Dr. Kinsbourne made precisely the same argument in the Theory 1 test cases. *Snyder*, 2009 WL 332044 at *41.

[230] *See, e.g.*, Shoffner Res. Ex. MM, Tab 16; Weissman, Pet. Ex. 39; Haas Pet. Ex. 63, Ref. 17; Poling, Res. Ex. MM, Tab 14.

am sure his intensity derives from a sincere desire to help his patients, but his attacks are leveled without apparent support and are therefore very damaging to his credibility in this case. Faced with a clear ASD diagnosis which he does not dispute, Dr. Shafrir unconvincingly strained to discredit the generally-accepted ASD diagnostic approach in favor of an understanding of autistic regression derived from his own *ipse dixit*. He redefined autism to require a "trigger" that fit his theory. He sought, without apparent basis, to extend the so called "triple hit" theory beyond the prenatal development despite the above-cited contradictory evidence in the record of this case. Thus, regardless of whether the alleged vulnerabilities Dr. Shafrir cites actually have the significance he claims, the fact remains that Dr. Shafrir's entire theory stems from an unsupported and likely false premise, namely that an environmental insult at two years of age could cause the type of fundamental changes within the brain evidenced in autism.

2. A.K.'s Alleged Genetic Vulnerabilities Either Do Not Exist or Do Not Have the Significance Dr. Shafrir Claims.

Assuming, *arguendo,* that Dr. Shafrir has established that A.K.'s autism results from a brain injury caused at about two years of age, I address Dr. Shafrir's claims that the injury occurred because separate genetic conditions made him vulnerable to adverse effects of the influenza vaccine: mitochondrial disease, a genetic polymorphism (the MTHFR polymorphism) and an abnormal immune system which may be genetically based. These conditions represent the second prong of the triple hit hypothesis. Although the core of Dr. Shafrir's theory is that A.K. experienced an autoimmune reaction, he argued that these genetic vulnerabilities "enhanced" the insult to A.K.'s brain. Pet. Ex. 63 at 18. And, although Dr. Shafrir does not explain in any detail how such an enhancement might occur – instead deferring to Dr. Deth in that regard – it is quite clear that Dr. Shafrir alleges that these conditions are "risk factors" associated with ASD. Thus, the second critical issue raised by Dr. Shafrir's theory is whether the vulnerabilities he cites actually exist in A.K., and if so, whether they have the significance to autism causation that he claims.

For the reasons described in Section VI above, I have found that A.K. does not have any mitochondrial disease or defect. Doctor Shafrir's reliance on that alleged vulnerability is therefore misplaced. Nonetheless, I note that his reliance on that condition to explain A.K.'s alleged injury suffers the same shortcomings as Dr. Kendall's opinion. And, although it is undisputed that A.K. does have MTHFR polymorphisms, contrary to Dr. Shafrir's contention, I do not find a significant association between MTHFR polymorphisms and autism. The evidence that he has an abnormal immune system is scant, and largely conclusory in nature.

a. Mitochondrial Disorder.

In claiming that A.K.'s alleged mitochondrial disorder played a role in A.K.'s autistic regression, Dr. Shafrir relied on the same articles that Dr. Kendall cited – Shoffner and Poling. Pet. Ex. 63 at 16-17. He also cited the above-discussed Weissman article, as well as Haas, Pet. Ex. 63, Ref.17 (a review article by Hass). *Id*.

Doctor Shafrir's reliance on the Shoffner, Poling and Weissman articles is misplaced for the same reasons discussed above with regard to Dr. Kendall's theory.

The Haas article, Pet. Ex. 63, Ref. 17, does not provide any additional support. This review article's discussion of a causal role for immunizations is limited to a recitation of the Poling case report and the Shoffner study, which are noted in the review to be in contrast to several other studies which failed to show any association between immunization and autism. Pet. Ex. 63, Ref. 17, at 149. Figure 2 of the article obviously played into Dr. Shafrir's theory, positing "a hypothesis for the role of inflammation and mitochondrial dysfunction in the pathogenesis of ASD regression." *Id* at 150. Figure 2 illustrated the theory: the response to a nonspecific stressor (infection/immunization/fever) in the presence of a genetic autistic predisposition and mitochondrial disease or dysfunction, followed by an abnormal immune response or an abnormal metabolic response (or perhaps both), resulting in regression. *Id*. (Fig. 2).

Doctor Haas then reviewed literature pertaining to metabolic and immunologic abnormalities in ASD. However, he also noted that regression was not more common after administration of MMR vaccine (15.6%) than before it (18.4%), in spite of the live viral nature of the vaccine and the enhanced nature of some types of immune response to the vaccine over those of the wild type measles infection. Moreover, although the Haas article does discuss co-morbidities in mitochondrial disorders and ASD, the article ultimately concludes that "the underlying mechanisms of mitochondrial involvement in ASD are unknown, but likely involve neuroinflammation, glial activation and cytokine release." Pet. Ex. 63, Ref. 17, at 151.

Significantly then, just as Dr. Kendall did, Dr. Shafrir acknowledged on cross-examination that he had no basis to claim that the Shoffner study reflected what happened to A.K. Tr. 560-61. Rather, he indicated that "the only thing I said is mitochondrial disorder is a risk factor for autistic regression. I didn't make any other claim, not about the vaccination or about anything else."[231] Tr. 561. Ultimately, Dr. Shafrir argued that the Shoffner study supported an association between mitochondrial disease and autistic regression. Tr. 564-66.

Linking ASD and mitochondrial disorders together as possible comorbidities, however, is insufficient to demonstrate that one causes the other. For example, Casanova, on whom Dr. Shafrir relied regarding the triple hit theory, suggested that the presence of comorbidities such as mitochondrial disorder should not be exclusionary from an ASD diagnosis, but rather that they underscore the heterogeneity of ASD generally and may actually support "the possibility that autism originates early in the first

[231] In his expert report, Dr. Shafrir cited James, Pet. Ex. 117, Ref. 38 (which was also filed as Pet. Ex. 63, Ref. 19) and argued that this paper described how A.K.'s alleged mitochondrial disorder "made him vulnerable to apoptosis and other forms of permanent structural changes in the brain as a result of the activation of the brain immune system induced by the vaccine." Pet. Ex. 63 at 18. Doctor Shafrir described the paper as indicating that "children with autism have been found to have high plasma levels of homocysteine and a biochemical profile of reduced methylation capacity." *Id*. This assertion is best discussed in light of Dr. Deth's presentation, particularly because Dr. Deth discussed the same paper, and Dr. Shafrir acknowledged that he is neither a metabolic specialist nor an expert in oxidative stress and therefore can do no more than cite what he saw as a "significant relationship" reflected in the medical literature. Tr. 547-49.

trimester of gestation." Pet. Ex. 63, Ref. 22, at 422. Ultimately all the Haas and Weissman papers cited by Dr. Shafrir demonstrate is that mitochondrial disorders appear in the autistic population with greater frequency than in the general population. "Comorbid" is not the same as "causal."[232]

b. MTHFR Gene Polymorphism.

The 5, 10-Methylenetetrahydrofolate reductase (MTHFR) gene is involved in folate metabolism. *See* Botto, Res. Ex. MM, Ref. 21, at 1.[233] "Normal MTHFR activity may help maintain the pool of circulating folate and methionine and possibly prevent a buildup of homocysteine." *Id*. The MTHFR gene is involved in the process of DNA methylation. Pet. Ex. 63 at 17; Tr. 1451-52.

It is undisputed that A.K. has two MTHFR gene alterations or variations known as polymorphisms. Pet. Ex. 63 at 17-18; Res. Ex. MM at 3. Specifically, A.K. is heterozygous for a C677T alteration as well as for an A1298C alteration[234], meaning that he has one common and one less common allele at each site. Pet. Ex. 3, p. 301.

Doctor Shafrir contended that the presence of these two polymorphisms is significant, because they are more common among the ASD population than in the general population. Pet. Ex. 63 at 18. He posited that these polymorphisms reduce enzyme activity and, in children with ASD, ultimately lead to reduced methylation capacity, leaving them vulnerable to oxidative stress and brain injury.[235] *Id*. Ultimately, however, Dr. Shafrir acknowledged that he could not say that A.K.'s MTHFR polymorphisms caused A.K.'s autism, only that the polymorphisms are associated with, or are a risk factor for, autism. Tr. 547. I note that there is a wide gulf between "association" and "risk factor." More children with ASD have intellectual disabilities than the general population and in that sense these two conditions are "associated," but intellectual disability is not a risk factor for autism.

Respondent's experts challenged Dr. Shafrir's contentions that these MTHFR polymorphisms are associated with, or are a risk factor for, ASD, pointing out that this

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[232] In any event, Dr. Shafrir's reliance on the role of a mitochondrial disorder as a contributing factor in his development of ASD is further misplaced to the extent that I have concluded that A.K. does not have any mitochondrial disorder or defect. *See* Section VI, above.

[233] Res. Ex. MM, Tab. 21, L. Botto, et al, 5, 10-Methylenetetrahydrofolate reductase Gene Variants and Congenital Anomalies: A Huge Review, AM. J. EPIDEMIOL. 151(9): 862-877 (2000) [hereinafter "Botto, Res. Ex. MM, Ref. 21"]/

[234] The alpha-numeric names refer to two different alleles of the MTHFR gene. Res. Ex. MM, Ref. 21, at 862. An allele is "one of the two or more alternative forms of a gene that can occur at a particular chromosomal locus and that determine alternative characters in inheritance. In humans and other diploid organisms there are two alleles, identical or differing, for each specific locus of an autosomal chromosome, one on each chromosome of a homologous pair." DORLAND'S at. 51.

[235] The mechanism by which this allegedly occurs was explained by Dr. Deth and is addressed in Section IX, below. It is worth noting, however, that to the extent Dr. Shafrir suggested that the polymorphisms resulted in autism by virtue of causing reduced methylation capacity, such supposition actually runs counter to the Wong study, Pet. Ex. 240, which found no overall difference in methylation between twins discordant for ASD. *See* Tr. 1719-24, 1726 (testimony of Dr. Johnson).

association is not supported by medical literature. Res. Exs. MM at 5; XX at 2. Doctor Raymond characterized the literature on MTHFR polymorphisms and developmental disorders, including autism, as "all over the place" and that "any association between MTHFR polymorphisms and autism is unproven." Tr. 1456-57; Res. Ex. MM at 5. Initially, Dr. Shafrir agreed with Dr. Raymond, but then asserted that there is such an association. Tr. 500-01. That is, when asked whether the association between MTHFR polymorphisms and autism is "unproven" as Dr. Raymond asserted, Dr. Shafrir's testimony was confusing. He stated: "I mean, I think it's unproven, but I think that some serious people said that there is a relationship." Thus, Dr. Shafrir conceded that the studies are mixed, but he relied on the studies that showed an association. However, the studies filed with Dr. Shafrir's own expert report were contradictory of one another.

For example, Dr. Boris, one of A.K.'s treating physicians, was the principal author of a 2004 study that looked retrospectively at 168 children with confirmed ASD diagnoses and compared them against a control population of over 5,000 Caucasians.[236] Boris, Pet. Ex. 55 at 106-07. The dual 677CT/1298AC heterozygous polymorphism that A.K. has was present in 25% of the ASD subjects but in only 15% of the controls. *Id.* at 106. Five years later, however, another study looked at a much larger population in an attempt to determine if specific autistic behaviors could be linked to the MTHFR gene.[237] These authors found that the genotype distributions for the ASD subjects were comparable to the general U.S. white population. Goin-Kochel, Pet. Ex. 51 at 105-06. The Goin-Kochel article specifically noted that these findings were in conflict with the prior Boris study and noted that the findings did not support the relationship suggested by Boris.[238] *Id.* at 106. The authors argued that the question of an association remained open and urged even larger studies. *Id*.

Another study cited by Dr. Shafrir indicated that the frequency of compound heterozygous MTHFR 677CT/1298AC only reached "borderline significance" among its sample of autistic children. James, Pet. Ex. 117, Ref. 38.[239]

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[236] Boris, Pet. Ex. 55. Doctor Shafrir did not cite this article in his expert report, but confirmed during his testimony that he believed it demonstrated the link he proposed between MTHFR polymorphisms and autism. Tr. 579.

[237] Pet. Ex. 51, R.. Goin-Kochel, et al, *The MTHFR 677C→T Polymorphism and Behaviors in Children With Autism: Exploratory Genotype-Phenotype Correlations*, AUTISM RESEARCH 2: 98-108 (2009) [hereinafter ["Goin-Kochel, Pet Ex. 51"]. Doctor Shafrir did not cite this article in his expert report, but confirmed during his testimony that he believed it demonstrated the link he proposed between MTHFR polymorphisms and autism. Tr. 579.

[238] Pertinent to this case, the Goin-Kochel authors speculated that the Boris findings could be attributable to the greater presence of those having reported autistic regression among the Boris population. They cautioned, however, that Boris (Pet. Ex. 55) did not identify how regression was "operationally defined" and that a non-standardized approach may have inflated the frequency of regressive cases. Goin-Kochel, Pet. Ex. 51 at 106. This note of caution is similar to the issue I mentioned relative to the Shoffner paper regarding reliance on parental reporting of regression. *See, e.g.*, n.212, *supra*.

[239] In addition, Pet. Ex. 63, Ref. 21, N. Mohammad, et al, *Aberrations in folate metabolic pathway and altered susceptibility to autism*, PSYCHIATR. GENETICS, 19:171-76 (2009), found the frequency of the MTHFR 677T-allele was higher among autistic children than non-autistic children while the 1298C-allele occurred with similar frequency in both groups. However, P. Pasca, et al, *One carbon metabolism disturbance and the C677T MTHFR gene polymorphism in children with autism spectrum disorders*, J.

Moreover, the experts on both sides in this case acknowledge that these MTHFR polymorphisms are common in the general population.[240] Pet. Ex. 63 at 18; Tr. 1449-50. Indeed, Dr. Raymond stressed that not only do many individuals in the general population share A.K.'s MTHFR variances, the majority of them experience no adverse effect from the polymorphism.[241] Tr. 1452-53. This creates an additional interpretative hurdle in finding some causal significance for A.K.'s polymorphisms. Thus, the Boris study cautions that "the high natural prevalence of MTHFR variants in the absence of autistic symptoms could be interpreted in various ways." Pet. Ex. 55 at 107. In addition, the Goin-Kochel study also noted that the distribution of MTHFR varied by many other factors as well, including geographical location, race, and ethnicity. Pet. Ex. 51 at 105. Even Dr. Shafrir, while arguing that an epidemiological relationship exists, nonetheless conceded that the significance of that association is arguable. Tr. 501.

Thus, although there is some literature positing a connection between the MTHFR polymorphisms and ASD, the evidence does not preponderate in favor of an association. The studies in the record are in conflict on that very point, and even if I concluded that an association exists, its significance would remain speculative. Doctor Shafrir himself acknowledged that the fact of the association is as far as he can opine. Moreover, the presence of this polymorphism in the general population, variable by other factors such as race and geographic location, makes any potential significance of an association particularly difficult to establish.

c. Immune System Abnormalities.

Although Dr. Shafrir concludes in his expert report that A.K. has an "abnormal, rare, genetically determined structure of his immune system" (Pet. Ex. 63 at 18), he never actually identified what that supposed genetic structure is or how it was evinced. Nor does he cite any specific abnormality evident in A.K.'s immune system. The closest he came to explanation in his expert report was his broad (and largely unsubstantiated) claim was: "I do not think that there are many physicians and researchers who doubt that a particular expression of an infection in a host, its severity and complication, and at the same token, the severity of immune reaction with its complication and severity (for example they range from fever and irritability to severe devastating and even lethal encephalopathy) are genetically determined." Pet. Ex. 63 at 16.

CELLULAR MOL. MED., 13(10): 4229-4238 (2009), Pet. Ex. 117, Ref. 33, showed a normal distribution of the C677T polymorphism in children with ASD. Finally, Pet. Ex. 63, Ref. 20, X. Lui, et al, *Population- and Family-Based Studies Associate the MTHFR Gene with Idiopathic Autism in Simplex Families*, J. AUTISM & DEVEL. DISORD., 41:938-944 (2011), indicated that the MTHFR gene polymorphisms were elevated among families with only a single instance of autism, but that those results could not be replicated among a group of families with a history of instances of autism.

[240] In fact, that is why these alterations are known as "polymorphisms" rather than "mutations." Tr. 1449-50.

[241] In this regard, Dr. Raymond also distinguished between those who have a homozygous polymorphism, which is thought to be more likely to result in a clinical impact, and a heterozygous polymorphism such as A.K. has, which is viewed as much milder. Tr. 1453-54. Doctor Raymond opined that a heterozygous polymorphism is unlikely to have any metabolic consequences. Tr. 1454. He did note, however, that with the combination of C677T and A1298C variations, A.K. might arguably be considered "somewhat intermediate." Tr. 1454.

Although he cited G. Poland, et al, *Adversomics: The Emerging Field of Vaccine Adverse Events Immunogenetics*, PEDIATR INFECT DIS J., 28(5): 431-32 (2009), filed as Pet Ex. 63, Ref. 12 [hereinafter "Poland, Pet. Ex. 63, Ref. 12"] as support, this paper is not a study or even a literature review. Instead, it is a short opinion piece, advocating for more study of the emerging field of vaccine adverse event immunogenetics or "adversomics." *Id.* at 1.[242] This call to explore a possible role for genetics in accounting for variations in immune reaction and adverse events following vaccination can hardly be said to constitute the general acceptance that Dr. Shafrir claimed. Citing prior work on the role of genetics in susceptibility to infectious disease, the authors indicated that they desire to "further that construct" and "have hypothesized that adverse reactions and events may not be random, but may in fact be, in part, genetically predetermined." Pet. Ex. 63, Ref. 12, at 1. Although the manuscript referenced some prior studies which examined genetic susceptibility to intensified or decreased reactions in Native American populations, the article primarily advocated looking for genetic susceptibilities to certain recognized vaccine reactions, such as the causal relationship between idiopathic thrombocytopenia purpura and the MMR vaccine. *Id*. at 2. Nothing in the article appeared directly relevant to A.K.'s case.

During his direct examination, however, Dr. Shafrir equated the "abnormal immune regulation" he had cited to A.K.'s purported Hashimoto thyroiditis diagnosis. Hashimoto thyroiditis is a type of autoimmune disease, and one which Dr. Shafrir claimed is an "extremely rare condition for a child of this age."[243] Tr. 501. During cross-examination, Dr. Shafrir acknowledged that this condition constitutes the only evidence in A.K.'s medical records supporting the presence of an autoimmune disease. Tr. 556-57. However, he contended that this condition indicated that "there was something unusual about [A.K.'s] immune system" and that the presence of that condition provides "some support," albeit "not strong support," for his contention that A.K. experienced an autoimmune reaction to his influenza vaccinations. *Id*.

Respondent's immunology expert, Dr. McCusker, disagreed. Doctor McCusker, who is far more qualified in this area than is Dr. Shafrir, opined that there is no evidence in A.K.'s medical history indicating that he had any immune deficiency or disorder.[244] Tr. 1401. More specifically, Dr. McCusker disputed that A.K. actually has autoimmune hypothyroidism.

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[242] The filed copy was an "author manuscript" four pages in length. Citations are to the page numbers appearing in the upper right hand corner of each page of the author manuscript. The citation reflects that, when reformatted to the journal pagination, the article is only two pages long (pp. 431-32 of the cited volume (28(5)).

[243] Hashimoto thyroiditis, or "Hashimoto disease," is a "progressive type of autoimmune thyroiditis with lymphocytic infiltration of the gland and circulating anti-thyroid antibodies; patients have goiter and gradually develop hypothyroidism. DORLAND'S at 542.

[244] Although Dr. Shafrir urged an "immunogenetic" understanding of A.K.'s condition, he acknowledged that he is expert in neither immunology nor genetics. Tr. 540-41, 546-47. To the extent Dr. Shafrir argues that his overall theory remains in his wheel-house by virtue of his clinical experience in neuroimmune diseases (Tr. 540-41), that does not qualify him to speak to A.K.'s immunological status overall, particularly not where he bases his opinion regarding the presence of an autoimmune process on a thyroid condition which, obviously, is outside of his area practice area of neurology.

She explained that autoimmune hypothyroidism occurs when autoantibodies formed against the thyroid gland impede the production of the T4 hormone normally produced by the thyroid. Tr. 1407. In A.K.'s case, however, although there is evidence that he had these autoantibodies, multiple thyroid function tests showed normal levels of the T4 hormone.[245] *Id*. Doctor McCusker explained that the ability to produce autoantibodies is inherent to the immune system and is on some level expected even in healthy immune systems. Tr. 1408-1411. Thus, she noted that the presence of anti-thyroid antibodies is not uncommon (occurring in one per 8,000 males per year) and is not in itself evidence of immune dysregulation. Tr. 1410-11. Thus, Dr. McCusker argued that A.K.'s laboratory results are not diagnostic of autoimmune hypothyroidism. Tr. 1407 (citing Pet. Ex. 3, p. 330).

During redirect Dr. Shafrir also raised the fact that on one occasion A.K. tested positive for myelin basic protein antibodies. Tr. 578-79 (citing Pet. Ex. 3, p. 331). Doctor Shafrir argued that this is objective evidence of an autoimmune reaction aimed against A.K.'s nervous system. Tr. 579. Doctor McCusker again disagreed with Dr. Shafrir's conclusions. In addition to her earlier testimony that the presence of autoantibodies is not evidence of immune dysregulation, she testified that "the isolated finding of antibodies in and of itself does not support anything." Tr. 1411. Doctor McCusker stressed that myelin basic protein antibodies can be indicative of multiple disorders, including multiple sclerosis. Tr. 1439-40. These antibodies may be supportive of a diagnosis when accompanied by clinical correlates, but are not in themselves diagnostic. *Id*.

Ultimately, although he did maintain that the autoantibodies were evidence of autoimmune activity, Dr. Shafrir conceded that "I don't' think anybody can say that we understand the significance of the presence of those [antimyelin] antibodies." Tr. 585.

Doctor McCusker also addressed an issue raised by Dr. Boris, but not by Dr. Shafrir. During his testimony, Dr. Boris was asked about the common variable immunodeficiency ["CVID"] diagnosis he made of A.K. He indicated that he believed A.K. fell "into that category," but stopped short of characterizing it as a diagnosis. Tr. 215. He testified that the "diagnosis" was based on laboratory results from July of 2002 which indicated that A.K. had deficiencies in immunoglobulin A ["IgA"] "side chains of Kappa Lambda and Kappa Lambda combinations." Tr. 220 (citing Pet. Ex. 3, p. 375). Doctor Shafrir mentioned these results in his expert report, but did not explain their significance, if any, without explanation. Pet. Ex. 63 at 6. Doctor Boris indicated that this was his sole basis for indicating that A.K. has CVID. Tr. 220.

Doctor McCusker testified that CVID is a condition that represents a "grab bag" of different problems associated with antibody formation. Tr. 1403. She indicated that there are clear diagnostic standards for CVID which include at least two findings of below normal immunoglobulin levels and a failure to produce antibody when stimulated.

[245] Doctor McCusker did note that there is some evidence in the record that A.K. occasionally had "mildly elevated" TSH (Thyroid Stimulating Hormone). She explained, however, that TSH is a signal to produce more T4 and elevated TSH is not considered a concern unless T4 is also abnormal. Tr. 1407-08. But in any event, Dr. McCusker characterized A.K.'s TSH as normal overall. Tr. 1407.

Id. She also noted that it is characterized clinically by recurrent ear, nose and throat conditions. *Id*. She opined that A.K.'s medical records do not support a CVID diagnosis. Tr. 1404. One set of results relied on by Dr. Boris actually showed normal immunoglobulin levels, a point which Dr. Boris conceded. Tr. 220, 1404; Pet. Ex. 3, p. 375. Moreover, she noted that A.K. did not have any functional deficiency, a necessary part of any CVID diagnosis. Tr. 1404. A.K.'s records show that he developed antibodies in response to his MMR vaccine.[246] Pet. Ex. 3, pp. 380-81. And, A.K.'s medical history over his first two years of life showed only the "usual childhood illnesses." Tr. 1401-02. Neither would be likely in a child with CVID.

Thus, Dr. Shafrir's contention that A.K. had a genetically determined abnormal immune system is without support. Doctor McCusker, a pediatric immunologist with far more training and experience than Dr. Shafrir, eviscerated the basis for Dr. Shafrir's conclusions about Hashimoto's thyroiditis or CVID as evidence of a dysfunctional immune system or a genetic propensity to develop autoimmune disease.

3. Doctor Shafrir Has Not Established That the Influenza Vaccine Could Cause an Autoimmune Reaction Resulting in A.K.'s Condition.

The core of Dr. Shafrir's theory was that A.K. had an "abnormal, rare, genetically determined structure of his immune system which produced an immune reaction within his brain to the influenza vaccine." Pet. Ex. 63 at 18. To the extent that Dr. Shafrir relied on this abnormal immune system as a condition precedent to his contention that t A.K. experienced a "brain insult induced by the immune system" (*id*), his theory of causation lacks that necessary predicate. Doctor Shafrir's relied on an abnormal immune system to explain how A.K.'s two doses of influenza vaccine acted as an exogenous or environmental stressor per the third prong of the triple hit hypothesis.

He conceded that there was no direct evidence in A.K.'s case of any abnormal immune reaction. Tr. 545. Indeed, he acknowledged that there is no evidence in the record of this case demonstrating any immune reaction in A.K., abnormal or otherwise, to his influenza vaccinations. Tr. 541-42. Rather, Dr. Shafrir appears to surmise the existence of an autoimmune process triggered by the influenza vaccine based on three circumstantial factors – (1) that A.K. had an abnormal immune system in the first place, (2) that the influenza vaccine is capable of causing neurological injury generally, and (3) that in A.K.'s case, the temporal association between A.K.'s two vaccinations and his regression constitute a challenge-rechallenge response, an immunological concept that demonstrates causation. Looking at these points collectively, Dr. Shafrir argued that despite being unable to identify an "exact immune abnormality" or an "exact mechanism for immune abnormality" it nonetheless "all fits." Tr. 502. Doctor Shafrir fails, however, to persuasively establish any of these three points. The evidence (or lack therof) for an abnormal immune system was addressed in Section VIII.B.2.c, above. The remaining two points are addressed in turn below.

a. Ability of the Influenza Vaccine to Cause A.K.'s Condition.

[246] Doctor McCusker did note that A.K.'s antibody response to the MMR vaccine was "equivocal," but attributed that fact to his lack of any booster dose. She found the antibody response normal under that circumstance. Tr. 1406.

Assuming A.K. was vulnerable to an autoimmune attack, Dr. Shafrir further contended that such an attack can be surmised from the fact that the influenza vaccine is capable of causing a neurological autoimmune injury. To establish this point, Dr. Shafrir cited a number of studies related to recognized autoimmune conditions and to some he claimed were autoimmune in nature: acute disseminated encephalomyelitis ["ADEM"], transverse myelitis ["TM"], Guillain-Barre Syndrome ["GBS"], and narcolepsy. *See* Pet. Ex. 63, Refs. 7-11; Exs. 124, 126, 127.[247] Although he conceded that A.K. did not have any of those disorders (Tr. 542), he argues that the results can be carried over by analogy to A.K.'s condition (Pet. Ex. 63 at 15; Tr. 582-83).

Doctor Shafrir's argument amounted to a "one size fits all" approach to autoimmune reactions. While his analogy may hold at the most superficial level, looking at the details of these conditions makes it impossible to say that what happens in one context carries forward to the context of this case. At the heart of his unestablished assumptions is that A.K.'s ASD is the result of an autoimmune brain injury.

Doctor Shafrir acknowledged that "in order to demonstrate an autoimmune reaction you have to find the actual antibody to isolate it and to show that this antibody is capable of producing the disease." Tr. 584. And, in arguing that A.K. experienced a challenge-rechallenge event, Dr. Shafrir actually quoted language in his expert report from a case report regarding ADEM which specifically associated the symptomology to "production of greater amounts of antibodies to *myelin* after each vaccination" (emphasis added). Pet. Ex. 63 at 16, quoting Pet. Ex. 63, Ref. 8. With the exception of narcolepsy, all of the conditions cited by Dr. Shafrir as analogous are demyelinating conditions. S*ee generally*, Pet. Ex. 63, Refs. 7-11. Doctor Shafrir conceded that A.K.'s his MRI was normal, effectively ruling out a demyelinating brain injury. Pet. Ex. 63 at 12; Tr. 545. Although he stressed that a normal MRI does not completely rule out any brain injury (Tr. 545), Dr. Shafrir did rule out demyelination as a cause of A.K.'s regression (Pet. Ex. 63 at 12).

These studies are therefore of very little relevance to this case. It would be completely speculative to argue that evidence linking the influenza vaccine to demyelination is also evidence that the same process would be the cause other non-demyelinating injuries. In fact, the Immunization Safety Review Committee Report cited

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[247] Pet. Ex. 63, Ref 7, K. Stratton, et al, IMMUNIZATION SAFETY REVIEW: INFLUENZA VACCINES AND NEUROLOGICAL COMPLICATIONS (2004), ["IOM 2004 Influenza Report"]; Pet. Ex. 63, Ref. 8, K. Lapphra, et al, *Adverse Neurologic Reactions After Both Doses of Pandemic H1N1 Influenza Vaccine with Optic Neuritis and Demyelination*, PEDIATR INFECT DIS J., 30(1): 84-86 (2011); Pet. Ex. 63, Ref. 9,.C. Wells, *A Neurological Note on Vaccination Against Influenza,* BRIT MED J., 3:755-56 (1971); B. Willi, et al, *Encephalitis after vaccination against H1N1 influenza virus*, EUROP J PAEDIATR NEUROL., 15: 276-277 (2011); C. Poser, *Neurological complications of swine influenza vaccination*, Acta. Neurol. Scandinav., 66: 413-431 (1982); Pet. Ex. 124, M. Partinen, et al, *Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland*, PLOS ONE 7(3): e33723 (2012) [hereinafter "Partinen, Pet. Ex. 124"]; Pet. Ex. 126, E. Miller, et al, *Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis*, BMJ, 346:f794doi: 10.1136/bmj.f794 (2013) hereinafter "Miller, Pet. Ex. 126"]; Pet. Ex. 127, *Swedish Medical Products Agency publishes report from a case inventory study on Pandemrix vaccination and development of narcolepsy with cataplexy*, EURO SURVEILL, 16(26): 19904 (2011) [hereinafter "Pandemrix Vaccination Study"].

by Dr. Shafrir, indicated that, even if one accepts a causal relationship between the influenza vaccine and GBS and the other demyelinating conditions specifically studied, "the committee concludes that the evidence is inadequate to accept or reject a causal relationship between influenza vaccine and other demyelinating neurological disorders." Pet. Ex. 63, Ref. 7, at 17. Thus, the sources cited by Dr. Shafrir do not advocate that evidence of cause of one demyelinating condition constitutes evidence of a causal role for influenza in other demyelinating conditions, let alone an extension to other conditions in which demyelination is not the mechanism of injury.

Moreover, Dr. Shafrir's citations regarding demyelinating disorders do not even necessarily provide strong support for the general proposition that the influenza vaccine causes a neurologic autoimmune reaction. None of the papers cited by Dr. Shafrir actually concluded that the adverse neurological events caused by the influenza vaccine were autoimmune. For example, although the IOM 2004 Influenza Report acknowledged that molecular mimicry and bystander activation, mechanisms cited by Dr. Shafrir as possibly applicable in AK's case, are possible as causal mechanisms, it characterizes the evidence in favor of those mechanisms as "weak." Pet. Ex. 63, Ref. 7, at 13. Doctor Shafrir himself has acknowledged that "the systematic assessment of the risk for neurological complications from influenza vaccine has multiple barriers" and that "no systematic study controlled in any way was performed in very large population." Pet. Ex. 63 at 14.

Doctor Shafrir cited to an article by Toplak, et al,[248] for the proposition that "there are studies showing the appearance of autoantibodies in certain individuals after influenza vaccine." Pet. Ex. 63 at 16. That study concluded, however, that "influenza vaccination did not increase the percentage of positive autoantibodies in the general healthy adult population." Pet. Ex. 63, Ref. 13, at 138. Only 7 out of 92 study participants had persistently elevated levels of autoantibodies after influenza vaccination. *Id*. The authors concluded that "there were no statistically significant differences" in the percentage of positive antibodies. Pet. Ex. 63, Ref. 13, at 134. Thus, to the extent Dr. Shafrir has not established that demyelinating disorders, mismatched to the facts of this case as they are, even constitute autoimmune injuries in the first instance, his analogy does not hold up on even the most basic level.

Perhaps recognizing these short-comings, on cross examination, Dr. Shafrir stressed his comparison of A.K.'s condition to narcolepsy. Tr. 542. He noted that narcolepsy is "very different from ADEM and GBS" and implied that it is more closely aligned to A.K.'s condition "because it's less acute, it's lifelong, it's disabling, it's very different. And it has no acute presentation." *Id*. Doctor Shafrir's reliance on the narcolepsy studies, however, is equally misplaced.

Although the Partinen article noted that prior research suggested an autoimmune etiology for narcolepsy (Pet. Ex. 124 at 2), none of the studies cited by Dr. Shafrir actually studied that question. *See generally*, Partinen, Pet. Ex. 124; Miller, Pet. Ex. 126; Pandemrix Vaccination Study ,Pet. Ex. 127. Nor do they contain sufficient

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[248] Pet. Ex. 63, Ref. 13, N. Toplak, et al, Autoimmune response following annual influenza vaccination in 92 apparently healthy adults, AUTO IMMUN REV, 8: 134-38 (2008).

discussion of the prior research to allow for evaluation of that contention. Rather, each study sought only to establish an association between onset of narcolepsy and vaccination. *Id*. Thus, contrary to Dr. Shafrir's assertion, the narcolepsy studies do not in themselves show that the disorder is autoimmune in nature. Tr. 582-83. They therefore do not establish, as Dr. Shafrir argues, the capacity of the influenza vaccine to cause a neurological autoimmune injury.

Doctor Shafrir also acknowledged that the findings of the narcolepsy studies were specific to the particular vaccine in question ("Pandemrix" H1N1) and the results were not replicated in non-epidemic influenza vaccines. Tr. 543-44. Although one of the cited articles intimated that the adjuvant contained in that particular vaccine might have been causal, even that point was not widely accepted. Pet. Ex. 126 at 5. Regardless of the cause, however, Dr. Shafrir acknowledged that the implicated vaccine was specific to northern European countries. Tr. 543. There is no evidence to suggest that A.K. ever received the vaccine studied.

Nonetheless, Dr. Shafrir argued that notwithstanding the fact that the narcolepsy studies spoke to a vaccine and injury that are not at issue in this case, he "presented a mechanism that is identical to what we have here in another situation and it can definitely be applied here under the same mechanism that this child developed autism in the same way those kids developed narcolepsy." Tr. 489. His assertion was fervent, but without any support.

Even if narcolepsy is a neurological autoimmune disorder, it does not automatically follow that Dr. Shafrir's analogy holds. As with GBS and ADEM, narcolepsy appears to be caused by factors not relevant to this case. Partinen noted that narcolepsy is typically characterized by a lack of hypothalamic hypocretin production. Pet. Ex. 124 at 2. There has been no suggestion that hypothalamic hypocretin problems are present in either ASD generally or in A.K. in particular. Partinen also suggested that narcolepsy was strongly associated with specific genetic polymorphisms not at issue in this case (HLA DR15 (DR2) and DQBI*0602). *Id*. Thus, even if the narcolepsy studies established as a general matter the type of correlation between genetic susceptibility and vaccination that Dr. Shafrir suggested was present in A.K., neither the genetic vulnerability nor the ultimate neurological impact can be matched up to this case. That is, even if the narcolepsy studies showed that a specific influenza vaccine caused some type of neurological injury, they do not establish that ASD is that type of neurological injury, or that A.K. received the type of vaccine that was causal of narcolepsy.

Doctor Shafrir 's theory is predicated on the presence of a specific, unknowable, antigen being present in A.K.'s influenza vaccine that would interact with his immune system in this particular way. Tr. 554-56. Doctor Shafrir gave an example from his training at St. Louis Children's Hospital wherein 30-40 children presented with cerebral ataxia following chicken pox. Tr. 502-03. He indicated that no one could explain why those particular children succumbed to that particular complication of chicken pox, noting that the immune system is "unique for every person on the face of the earth." Tr. 503. Thus, he argued in effect that the only way to know what happened to those children was to know that cerebral ataxia was a known immune reaction that was

associated with varicella infection. *Id*. Given this framing by Dr. Shafrir himself, it is unclear by what basis Dr. Shafrir contends that the results of the narcolepsy study, or any study using a different vaccine and resulting in a different injury, can be carried over to A.K.'s case by way of analogy, as ASD is not a known complication of or reaction to influenza or influenza vaccine.

b. Doctor Shafrir's Reliance on Challenge-Rechallenge.

Finally, Dr. Shafrir argues with regard to adverse neurologic reactions to the influenza vaccine that "their temporal association with the vaccine, when there is a lack of other plausible cause, [is] a convincing argument for causality." Pet. Ex. 63 at 15. Specifically, Dr. Shafrir relies on the concept of challenge-rechallenge to show that A.K. fits a pattern whereby his condition worsened after each of two doses of vaccine, thereby strongly suggesting causation. Pet. Ex. 63 at 16. Although I addressed whether the facts of A.K.'s case in particular fit the challenge-rechallenge model in Section VII.D, above (and find that they do not), I note here that Dr. Shafrir's reliance on the challenge-rechallenge model in this context is conceptually inapt.

The "challenge-rechallenge" concept has been addressed in numerous cases within the Vaccine Program. Most notably, the Federal Circuit succinctly summarized the theory by explaining that "a rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine." *Cappizano,* 440 F.3d at 1322. To successfully establish a challenge-rechallenge theory, a petitioner must show a temporal relationship between the occurrence of petitioner's symptoms and multiple vaccine administrations. *See, e.g., Doe*, 95 Fed. Cl. at 609 (affirming the decision of the special master and noting that "the special master found that petitioner had not established causation by a preponderance of the evidence because neither of his expert's proposed 'challenge events' had the necessary temporal connection to the first or second dose of the vaccine.")

Doctor McCusker explained, however, that challenge-rechallenge is fundamentally an immunological concept. Tr. 1419-20, 1440-41. What the challenge-rechallenge scenario requires is problems associated with an adaptive immune response. The expectation is that an immune reaction will be more muted at the first dose and more pronounced on the second dose as the adaptive immune system's memory allows for a more rapid formation of antibodies. Tr. 1420. Doctor Shafrir described the concept similarly. Tr. 491. Indeed, Dr. Shafrir cited language from a case study regarding ADEM which indicated that "the patient's neurologic symptoms occurred shortly after the first dose of vaccine and resolved and additional symptoms occurred shortly after the second dose of vaccine." Pet. Ex. 63 at 16 quoting Pet. Ex. 63, Ref. 8.

The IOM noted, however, that "[i]t is possible that one or more of the 'challenges' in an individual case patient reporting is related to a coincidental exposure" and that the value of rechallenge reports as evidence of causation "is much greater for monophasic conditions (events that typically happen only once, *e.g*. vasculitis) than for relapsing-remitting conditions, such as multiple sclerosis or rheumatoid arthritis." 2011 IOM Report, Pet. Ex. 223, at 46-47 [hereinafter" 2011 IOM Report"]. I also noted during my questioning of Dr. Shafrir that the idea of challenge-rechallenge depends on the

condition at issue being monophasic. That is, that multiple occurrences of a symptom or condition are only suggestive of causation if they would not otherwise be expected to recur. Tr. 574-75. Doctor Shafrir conceded that he hadn't considered that, but that "there is something in it." Tr. 575.

In this case, Dr. Shafrir relied solely on a parental report that A.K. lost speech after the first dose of vaccine, experienced some improvement in speech, and then demonstrated other symptoms of ASD subsequent to the second vaccine. Pet. Ex. 63 at 3-4. Doctor Shafrir also made a point, however, of noting that speech development is a complex issue and that a notation of "speech delay" only indicates that the milestone is "not happening now" and the ultimate significance of that delay, whether it is mere delay or truly an impairment, usually becomes evident only later. Tr. 462-64. Doctor Miller also intimated that children go through a period of development where they have language – have uttered words – but have not yet progressed to using those words consistently or reliably. Tr. 990-93. And, indeed, [A.K.'s mother] testified that A.K. has had his speech disappear and reappear several times over the years without any suggestion that it was associated with vaccination. Tr. 52.

In that regard, the variability in A.K.'s speech, which respondent's experts indicated may not even have been developed in any meaningful way in the first instance, is a very tenuous indicator that A.K. experienced two distinct immune responses to his vaccinations. Indeed, Dr. McCusker disputes that loss of speech could be considered a manifestation of challenge-rechallenge at all. Tr. 1441.

The problem becomes more obvious when looking at Dr. Shafrir's actual explanation of autistic regression. In his expert report he indicates that some autistic regression patients recover within a few months or years and others "progress to develop various neurodevelopmental syndromes with variable degree of autistic characteristics." Pet. Ex. 63 at 12. With regard to A.K. in particular, he indicated that "there is excellent documentation of appearance of regression of language and behavioral changes typical for the autistic regression such as loss of eye contact appearing after the first and worsening after the second influenza vaccination." *Id*. He stressed during his testimony, however, that a regression is a process that cannot be pinpointed and that he could not say when exactly it started. Tr. 528. He also testified that "autistic behavior fluctuates over time. It's not something [where] a child behaves like this and tomorrow is going to behave exactly the same way." Tr. 478.

Thus, by Dr. Shafrir's own explanation A.K.'s worsening condition, whether identified by delayed or variable speech attainment or onset of other ASD symptoms, is explained by the fact that he was experiencing a variable, yet ongoing condition. Doctor Shafrir stresses that his condition worsened after the second vaccine, but that outcome would have been expected by virtue of his autism with or without the second vaccine. The fact that it happened is therefore not evidence that the vaccine was responsible.

C. Doctor Deth's Presentation Does Not Otherwise Support Either Dr. Kendall or Dr. Shafrir's Theories.

Doctor Kendall's opinion in this case was never more specific than to say that vaccines create oxidative stress and are therefore metabolic stressors capable of

causing a metabolic decompensation. In terms of substantiating that assertion, she offered no proof or explanation beyond asserting that the Shoffner and Poling papers demonstrated a" precedent" for the claimed association. Doctor Shafrir, likewise, ultimately relied in part on mechanisms of neuroinflammation, oxidative stress, and DNA methylation that he did not fully explain. Thus, as indicated above, in addition to Dr. Kendall and Dr. Shafrir's testimony, petitioners have also offered a presentation by Dr. Deth which purported to explain a mechanism by which their respective theories may operate.

Given that the causes of mitochondrial deterioration are not well studied or well understood, Dr. Deth's presentation could have been a viable vehicle for petitioners to prove their theory. That is, if Dr. Deth presented a sound explanation for how a vaccine could be expected to act in the manner Dr. Kendall and Dr. Shafrir each suggested, that might provide sufficient support for one or both of their causation opinions. For the reasons described in Section IX below, however, I have found that Dr. Deth's opinion is fundamentally flawed in a number of key regards and cannot be credited.

Of course, petitioners are not obligated to prove the mechanism of injury as part of their burden of proof. *Knudsen,* 35 F.3d at 549. Nor am I requiring such proof. Nonetheless, "causation in fact requires proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury. A reputable medical or scientific explanation must support this logical sequence of cause and effect." *Grant v. Sec'y, HHS*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). It is therefore significant that the mechanism proposed by Dr. Deth is in itself biologically implausible. *See, e.g. Moberly v. Sec'y HHS*, 85 Fed. Cl. 571, 606 (Fed. Cl. 2009), ***aff'd*** 592 F.3d 1315 (Fed. Cir. 2010) (holding that the Federal Circuit's *Knudsen* decision "does not mean that a special master cannot consider the reliability and soundness of theories of biological mechanisms of causation that are proposed by parties.").

Ultimately, all three of petitioners' experts failed to present any sound scientific explanation supporting petitioners' theory. Therefore, the implausibility of Dr. Deth's proposed mechanism, particularly when coupled with the relative dearth of any other supporting evidence, actually tends, if anything, to suggest that Dr. Kendall's and Dr. Shafrir's theories are *less* likely to be valid.[249]

D. Conclusions Regarding Dr. Kendall's and Dr. Shafrir's Theories.

As indicated above, the context for Dr. Kendall's theory is that there appears to be a generally accepted correlation between metabolic stressors, such as illnesses and surgery, and periods of regression in mitochondrial disorder patients, based on a temporal relationship between such stressors and a regression or decline in health. Yet no one knows exactly how or why this occurs, a point which Dr. Kendall herself acknowledged. In the face of that uncertainty, Dr. Kendall has sought to extrapolate a concrete and very specific cause and effect relationship between vaccines and mitochondrial regression that simply lacks evidentiary support.

[249] I do note, however, that based on the preceding analysis I would find that Dr. Kendall's and Dr. Shafrir's theories were insufficiently supported even in the complete absence of Dr. Deth's presentation.

Doctor Kendall has pointed to no medical literature that actually speaks to this alleged relationship. Rather, the two articles she cited – Shoffner and Poling – suggested only that fever might play a role in mitochondrial decompensation or deterioration. Such a finding is fully consistent with the current state of scientific understanding regarding mitochondrial disorders, but does not establish that any fever, a common event in children, produces a condition that looks like ASD in general or autistic regression in particular. All of the reports of mitochondrial regression in the literature filed, and in the expert reports and testimony in this case, were quite vague regarding the presentations of a mitochondrial decompensation. No one, not Dr. Shafrir and not Dr. Kendall testified that they had seen a mitochondrial decompensation or regression that looked like ASD. The Shoffner paper explicitly disclaimed any connection between vaccination and neurological regression. Moreover, these studies, which are particularly small, are weak evidence in themselves, that autistic regression occurred more often in those with comorbid ASD and mitochondrial disorder conditions.

Contrary to petitioners' claims, vaccines have not been shown to be metabolic stressors at a level sufficient to trigger a metabolic or mitochondrial decompensation or regression. To the extent Dr. Kendall argued that studies positing a temporal connection between fever and regression establish a precedent for such a claim, petitioners have not shown that such a finding could be translated to other potential stressors based on current knowledge. In the absence of such an established connection, petitioners have further failed to convincingly explain how such a connection might otherwise be explained biologically. For these reasons, I find that I cannot credit Dr. Kendall's theory of causation.

For his part, Dr. Shafrir cited the very same purported relationship between mitochondrial regression and vaccination and his argument presented the same weaknesses. In addition, his application of the "triple hit" hypothesis failed on every prong. He failed to demonstrate that A.K. had a genetically-based vulnerability from an abnormal immune system. He failed to demonstrate that MTHFR polymorphisms are associated with ASD or would cause an aberrant immune response to influenza vaccine. Thus, there was nothing unique to A.K. which could have enhanced any reaction to his influenza vaccine.

Doctor Shafrir contended that A.K.'s ASD – which he argued was an etiologically distinct condition of autistic regression – was the result of a brain injury that was autoimmune in nature. He failed to produce any evidence that A.K. had a brain injury caused by a vaccine reaction, that ASD (or autistic regression) is an autoimmune condition, or that A.K. had an autoimmune reaction to his two influenza vaccinations.. Doctor Shafrir acknowledged that there was no evidence of an autoimmune reaction in this case. His attempts to circumstantially demonstrate the capacity of the influenza vaccine to cause such a reaction were not only circular, they utterly failed.

Finally, and most critically, Dr. Shafrir also failed to demonstrate that two years of age represents the "vulnerable period" that the "triple hit" hypothesis contemplates. The available evidence in this regard has not changed since the OAP test cases were decided. Doctor Casanova's triple hit hypothesis squarely places the "vulnerable period" prenatally, not at or near two years of age.

Thus, for all these reasons, I find that the theories espoused by Dr. Shafrir are unreliable, and that the factual predicates for those theories are not present in A.K.'s case.

IX. Dr. Deth Has Not Presented a Plausible Biological Mechanism for Either Theory Advanced.

Doctor Deth's presentation added little to petitioners' case. Had Dr. Deth presented a plausible biological mechanism explaining how A.K.'s influenza vaccinations could have contributed to his alleged injury, his testimony theoretically could have alleviated at least some of the above-discussed shortcomings of Dr. Kendall's and Dr. Shafrir's theories. Though difficult to summarize, Doctor Deth's opinion is that "vaccinations promote inflammation and oxidative stress as integral components of the immune response, and individuals with limited capacity to recovery are at higher risk of long term adverse consequences, including developmental regression in the case of young children." Tr. 751.

That is, Dr. Deth opined that individuals with inhibited ability to produce antioxidants are susceptible to injury due to the metabolic demand created by the inflammation and oxidative stress associated with the immune response to vaccination. He posited that this inflammation and oxidative stress impacts the transsulfuration activity of the body's sulfur metabolism to cause epigenetic changes (*i.e*. alterations in gene expression) associated with autism. Pet Ex. 117 at 10-13. He identified A.K.'s alleged mitochondrial disorder, his MTHFR polymorphisms, and alleged gastrointestinal inflammation as vulnerabilities leading to a whole-body antioxidant deficit that left A.K. at risk for such injury. *Id*. at 3.

Doctor Deth's presentation, however, was ultimately unable to answer the key question of how a vaccination could have produced an *injurious* level of oxidative stress. In addition, as with Dr. Kendall's and Dr. Shafrir's opinions, his theory was predicated on alleged vulnerabilities that simply do not exist in A.K.'s case or the significance of which was not established. And, even if I did accept the presence and significance of those vulnerabilities, Dr. Deth's hypothesis was still implausible from both an epigenetic and metabolic standpoint.

I note in particular that, despite my cautions that I did not intend to permit re-litigation of the same evidence presented in the OAP test cases, much of Dr. Deth's presentation merely recycled a theory of sulfur metabolism that was rejected during the OAP theory 2 test cases. Moreover, the entirety of Dr. Deth's presentation was undercut by his clear lack of candor and credibility.

A. Even Accepting Dr. Deth's Theory as Valid, He Has Not Established That Any Vaccine Could Have Contributed to A.K.'s Injury.

Doctor Deth's presentation in this case did not provide any meaningful support to either Dr. Kendall or Dr. Shafrir's theories. In his expert report, Dr. Deth characterized his opinion as ultimately answering the questions of "how a vaccine causes oxidative stress" and "how such oxidative stress can cause injury to a child with a mitochondrial disorder." Pet. Ex. 117 at 2; Pet. Ex. 239 at 2-3. Even if I accepted all of Dr. Deth's

underlying reasoning, he has failed to satisfactorily answer the threshold question of how the vaccination itself would have contributed to the injury.

Importantly, with regard to oxidative stress, the question is not whether vaccinations produce any oxidative stress at all, but rather whether they produce sufficient oxidative stress to be injurious. Doctor Jones, a witness with far greater expertise in oxidative stress than Dr. Deth, explained that oxidative stress is, in essence, an ever present part of life and that, in moderation, it is not harmful. Tr. 1613-21. Doctor Jones asserted that the term "redox biology" is more descriptive of what happens in the body than the term "oxidative stress." Res. Ex. ZZ at 1. He noted that common daily occurrences such as exercise, eating and exposure to sunlight create oxidative stress. Tr. 1620. An active infection produces a "respiratory burst" that produces ROS (reactive oxygen species) to kill the infecting microorganism, but Dr. Jones explained that the lesser immunological response to a vaccination produces ROS only to the extent of the normal physiological signaling process known as "redox signaling." Tr. 1620-21.

Doctor Deth agreed with Dr. Jones's basic description of redox biology. Tr. 639-40. That is, in his own presentation he explained the distinction between harmful ROS and ROS merely necessary to redox signaling. *Id*. Moreover, he conceded that "vaccination has not been extensively examined with regard to its effects on redox and methylation events."[250] Tr. 736. He characterized that as a "serious problem." *Id*.

Ultimately, Dr. Deth conceded during cross-examination that he did not know: (1) how much oxidative stress was created by an influenza vaccine; (2) the threshold level of oxidative stress necessary to cause autism under his theory; and (3) what level of oxidative stress would be insignificant as a brain insult. Tr. 773. He agreed that transitory oxidative stress, such as that caused by the exercise of a skeletal muscle, does not impact the brain. Tr. 807. Thus, despite his lengthy presentation, Dr. Deth

[250] Although Dr. Deth did not address it, I note that petitioners did file an additional study purporting to show that a live attenuated influenza vaccine produced measurable biomarkers of oxidative stress. *See* Pet. Ex. 97, M. Phillips, et al, *Effect of influenza vaccination on oxidative stress products in breath*, J. BREATH RES. 4: 026001, pp 1-8 (2010) [hereinafter "Phillips, Pet. Ex. 97"]. However, the study's results, which are limited to the detectability of the oxidative stress produced by inhalation of a live, attenuated influenza vaccine, do not support Dr. Deth's theory in any meaningful way or otherwise advance petitioners' case. Nonetheless I asked Dr. Jones about the paper during the hearing. He noted the significant distinctions between administration of a live viral vaccine directly into the lungs and a killed virus administered intramuscularly. Tr. 1676-77. Consistent with Dr. Jones's testimony regarding the distinction between active infection and vaccination, the study authors hypothesized that the live attenuated influenza vaccine in their study impacted oxidative stress by producing reactive oxygen species in the same manner as the body's response to viral pneumonia. Phillips, Pet. Ex. 97 at 3. This suggests that the distinction between a live attenuated and killed influenza vaccine is significant. In testifying that a vaccine does not have the same ability to generate a whole body response as a live infection, Dr. McCusker stressed that a killed virus in a vaccine cannot replicate or spread and cannot enter and activate the body's cells. Tr. 1414-17. Given that the only live, attenuated influenza vaccination was not approved for use until 2003 (PHYSICIAN'S DESK REFERENCE at 1689 (66th ed. 2012)), and A.K.'s influenza vaccinations were administered in 2001 *(see* Pet. Ex. 61, p. 4; Pet. Ex. 118), he could not have received a live viral vaccination.

ultimately conceded that he was unable to opine that A.K.'s influenza vaccines were capable of contributing to his ASD via a theory of harmful oxidative stress.[251]

Notwithstanding these significant problems for his proposed biological mechanism for injury, his opinions regarding the role of inflammation in enhancing the oxidative stress impact of vaccination, ultimately leading to brain injury, is also faulty. Doctor Deth contended that "vaccination produces an inflammatory response that includes changes in antioxidant and methylation pathways, along with increased formation of TNF-α. In concert with the effects of aluminum (and mercury), TNF-α promotes neuroinflammation in the brain and migration of activated monocytes to the brain, especially during the postnatal years. An infectious challenge coupled with immune/inflammatory stimulation increases the adverse consequences for the brain. In combination these events represent an encephalopathy." Pet. Ex. 239 at 96.

The most basic issue is that Dr. Deth's hypothesis was based on an unsupported principle. That is, he contended that the immune system is capable of impacting the brain via the pro-inflammatory cytokine TNF-α (Pet. Ex. 239 at 91-92) and that vaccines have an effect "similar to the effect of TNF-alpha" (Pet. Ex. 239 at 86). He therefore posited, without any apparent support, that the immune response generated by a vaccine must necessarily impact the brain.[252] This argument does not account for the significant differences in immune system challenges presented by vaccines as compared to natural infections.

Dr. McCusker explained that vaccines produce only a transient immune response. Tr. 1417-18. She noted that if a peripheral immune event such as a vaccination created a significant central nervous system response, then one would expect to see specific types of cytokines, known as endogenous pyrogens, acting on the hypothalamus, which would generate a "very high" fever. Tr. 1417. To the extent A.K. experienced any fever at all, petitioners were consistent in characterizing it as "slight" or "low-grade." *See* n. 205, *supra*. Doctor Cohen testified, consistent with Dr. McCusker's opinions, that the reduced antigen load of a vaccine made it unlikely that the vaccine could produce sufficient inflammation to cause a mitochondrial decompensation. Tr. 1311-12. Doctor Deth admitted that he could not opine that an influenza vaccine has an antigen load comparable to an infection. Tr. 792-94.

Moreover, Dr. McCusker also pointed out that Dr. Deth's hypothesis was based in large part on a misreading of the work of Staci Bilbo regarding the effects of immune

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[251] Doctor Deth also indicated that he did not believe there is a specific amount of oxidative stress generated by a vaccine, opining instead that he believed the level of oxidative stress caused by a vaccine would vary from person to person. Tr. 824.

[252] To the extent Dr. Deth's hypothesis relied on the presence of aluminum adjuvant, it was inapplicable to A.K.'s case. Doctor McCusker's testimony that there was no aluminum adjuvant in the 2001-2002 influenza vaccine was unrebutted. Tr. 1418. Although Dr. Deth speculated that any other adjuvant would have the same effect (Tr. 829-31), there was no evidence in this case that the influenza vaccines A.K. received contained *any* adjuvant.

response on brain development. Doctor Deth cited Bilbo & Schwarz,[253] a review article, for the proposition that peripheral immune activation with or without infection could impact brain development during the first three to five years of life.[254] Tr. 742-43. Doctor McCusker pointed out that Dr. Bilbo's work focused on the effects of maternal cytokine inflammation on the fetus. Tr. 1421-26. Doctor McCusker quoted the statement that "these data [referring to data regarding the lack of any impact from infection in later development] indicate that early infection-induced vulnerability is specifically a developmental effect and not a general sensitizing event that can occur at any time. Tr. 1425 (quoting Bilbo & Schwarz, Pet. Ex. 143 at 5). Indeed, the graphic from this paper included in Dr. Deth's presentation explicitly stated that it was reflecting a "neonatal immune challenge." *Compare* Pet. Ex. 239 at 93 and Bilbo & Schwarz, Pet. Ex. 143 at 7, Figure 2. I also note that this review article noted that cytokines in the brain, including TNF-α, are produced in the brain, involved with synapse formation and neurogenesis, and with both injury and repair. Bilbo & Schwarz, Pet. Ex. 143, at abstract.

Doctor Deth cited a study by Mercier, et al,[255] purporting to show that, consistent with this theory, vaccinations ultimately decrease methylation. Tr. 736-37; Pet. Ex. 239 at 86. Doctor Jones pointed out, however, that to the extent the study showed that the vaccinations studied increased transsulfuration and decreased methylation, the actual impact of the vaccinations was less significant than the difference between fasting and fed subjects, suggesting that the impact is extremely small. Tr. 1639-42 (citing Pet. Ex. 132). It would, therefore, be impossible to differentiate between the impact of a vaccination and skipping a meal.

Doctor Deth also cited his own study looking at the pro-inflammatory cytokine TNF-α.[256] *See* R. Deth, et al., *Age-Dependent Decrease and Alternative Splicing of Methionine Synthase mRNA in Human Cerebral Cortex and an Accelerated Decrease in Autism*, PLOS ONE, 8(2): e56927 (2013), filed as Pet. Ex. 135 [hereinafter "Deth, Pet. Ex. 135"]; [257] Tr. 706-08; Pet Ex. 239 at 68. He contended that the study demonstrated that TNF-α "strongly" decreased the amount of methionine synthase mRNA ("MS mRNA").[258] Pet. Ex. 239 at 68; Tr. 708. Doctor Johnson pointed out, however, that Dr.

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[253] Pet. Ex. 143, S. Bilbo & J.Schwarz, *Early-life programming of later-life brain and behavior: a critical role for the immune system*, FRONTIERS BEHAV.NEUROSCIENCE, 3(14): 1-14 (Aug. 2009) [hereinafter "Bilbo & Schwarz, Pet. Ex. 143].

[254] On cross-examination Dr. Deth refused to specify which of the studies discussed in the Bilbo & Schwarz review supported his theory. Tr. 789-92.

[255] Mercier, Pet. Ex. 132.

[256] This is the same study discussed in Section IX.D, below as the post-mortem brain study. Here, Dr. Deth refers to a different aspect of that study conducted not with post mortem brain samples, but with SH-SY5Y neuroblastoma cells which were treated with 30 ng/ml of TNF-α. Pet Ex. 135 at 7; Tr. 708.

[257] Citations will be to the machine-generated page numbers assigned by petitioners, as the actual article's pages are not numbered.

[258] The significance of this finding, per the text of the study, is that "it can be inferred that TNF-α-mediated inflammation is a candidate for causing lower levels of MS mRNA in autism." Deth, Pet Ex. 135 at 11. MS [methionine synthase] mRNA is a redox-responsive multi-domain enzyme that acts as part of the transsulfuration pathway. Deth, Pet Ex. 135 at 1. Within the post-mortem aspect of the study, Dr. Deth

Deth's underlying data, published elsewhere and not presented by Dr. Deth at this hearing, showed that the effects of TNF-α on methionine synthase activity were reversed within six hours, suggesting that TNF-α has little to no long-term effect on methionine synthase activity. Tr. 1714-19.

Doctor Johnson further noted that the study methodology – i.e. directly injecting TNF-α into cells – results in a concentration of TNF-α an "order of magnitude" greater than one would see in cerebral spinal fluid after a vaccination. Thus, Dr. Johnson contended that if such a direct injection cannot produce a sustained inhibition of methylation, then a vaccine would not be able to produce enough oxidative stress to inhibit methylation. Tr. 1727.

In light of Dr. Johnson's testimony, Dr. Deth conceded that the impact of TNF-α on methionine synthase is transient. Tr. 1750-51. Moreover, he indicated that reversal of the decrease in methionine synthase is expected, to the extent that cells have the ability to adapt to external stresses in order to maintain homeostasis. Tr. 1750-52. He speculated, however, that there is an unspecified epigenetic "price to be paid" as a result of the transient stress.[259] Tr. 1752-53.

Finally, respondent's experts stressed that there is no evidence in A.K. of either neuroinflammation or oxidative stress and no evidence to suggest that A.K. had an abnormal immune response to his influenza vaccines. Tr. 1412, 1651-52, 1659-61.

B. Doctor Deth Has Not Established that A.K.'s GI Issues Have Any Significance.

Doctor Deth never actually opined that A.K.'s vaccination alone was sufficient to cause his injury. Like Dr. Shafrir, Dr. Deth asserted that A.K. was vulnerable to the impact of his vaccination due to a number of factors, including both a mitochondrial disorder and MTHFR polymorphisms, which I have already addressed in Section VIII above. In addition, Dr. Deth also relied heavily on the idea that A.K. had gastrointestinal problems leading to a whole-body deficit in antioxidants. For the reasons described

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purported to show that individuals with autism have lower levels of MS mRNA. *See* Deth, Pet Ex. 135 at 6; Pet Ex. 239 at 65; Tr. 706. He also posited that "factors affecting MS activity, such as oxidative stress, can be a source of risk for neurological disorders across the lifespan via their impact on methylation reaction, including epigenetic regulation of gene expression." Deth, Pet Ex. 135 at 1. This theory regarding the possible impact to the transsulfuration pathway recycles Dr. Deth's OAP theory 2 presentation and is discussed further in Section IX.C below. The validity of Dr. Deth's post-mortem study is also discussed further below.

[259] This is one of multiple examples (*see* sections IX.D.2 and E.2, below) of Dr. Deth changing or confusing his theory on rebuttal. In his expert report and in his initial presentation, Dr. Deth asserted that the presence of the TNF-α directly caused an epigenetic change by lowering cysteine uptake, increasing transsulfuration, and inhibiting methylation. Pet. Ex. 117, p. 9; Pet. Ex. 239 at 68; Tr. 708. That is, he testified that "what TNF-α is doing, it's actually shifting the flow of cysteine away from the growth factor regulated $EAAT_3$ pathway, it's decreasing that, whereas it's increasing the alternative transsulfuration pathway, which is usually low in the brain." Tr. 710. Thus, he concluded that the TNF-α is "taking away some of the characteristic features of the brain." *Id*. But once forced to concede that the impact he identified was transient and not as strong as he appeared to suggest, Dr. Deth then contended that it was not the presence of the TNF-α itself that caused a lasting impact, but rather somehow the indirect result of the cell's actual demonstrated ability to clear the stressor that Dr. Deth had identified.

below, I find that Dr. Deth's presentation regarding gastrointestinal inflammation is wholly unpersuasive.

Specifically, Dr. Deth opined that that "to me, in my expert opinion, the perhaps most critical feature predisposing and making [A. K.]'s case a special one of higher risk for vaccination injury is his gut inflammation which has been documented." Tr. at 745. He opined that A.K. had "leaky gut syndrome" and that he was impacted by the presence of gliadomorphin and casomoprhin, food-derived opiate peptides. *Id.* at 745, 818. Ultimately, Dr. Deth opined that the terminal ilium is critical for the uptake of cysteine via the $EAAT_3$[260] transporter and that inflammation of the GI tract inhibits that uptake.[261] Tr. 715-18.

The evidence that A.K. has any chronic GI problem is very limited. A.K. was seen by his pediatrician on August 10, 2000, for a chief complaint of loose stools. His diagnosis was "AGE."[262] Pet. Ex. 61, p. 88. A few days later on August 13, 2000, A.K.'s continued loose stools were the subject of a telephone consultation. Pet. Ex. 61, p. 87. Subsequent notations indicate a report of three weeks of diarrhea as of August 14, 2000, and a "long diet discussion" on September 9, 2000. *Id.* Subsequent records show periodic reports of "loose stool." Pet. Ex. 61, pp. 74, 70, 62. On June 26, 2001, A.K. was seen for an apparent "gastro" complaint, including "liquid diapers" and dehydration.[263] Pet. Ex. 61, p. 61.

On November 12, 2002, A.K. had an intestinal biopsy analyzed by Dr. Harry Ioachim at Lenox Hill Hospital.[264] Pet. Ex. 3, pp. 322-23; Pet. Ex. 61, pp. 129-32. On

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[260] Doctor Deth contended that $EAAT_3$ is the major source of cysteine for the brain. Tr. 666-68. Doctor Jones, however, noted that there are multiple cysteine transporters and questioned Dr. Deth's focus on $EAAT_3$ in particular. Tr. 1654-56. Doctor Deth's focus on $EAAT_3$ appears to stem from the fact that he believes $EAAT_3$ can be associated with both the uptake of cysteine in the GI tract as well as the delivery of cysteine to the brain. Tr. 716-17. That is, he contends that GI inflammation can, via its impact on the $EAAT_3$, ultimately impact the brain. Tr. 713-18. In the Theory 2 test cases, Dr. Deth focused on the $EAAT_3$ transporter because he thought it was the only cysteine transporter available to neurons. That assertion was incorrect, as Dr. Jones demonstrated. *See Dwyer*, 2010 WL 892250 at *121, n.517. Here, as in *Dwyer*, in a matchup between Dr. Deth and Dr. Jones, Dr. Deth fares poorly.

[261] It is worth noting that Dr. Jones challenged Dr. Deth's assertion that $EAAT_3$ is the primary transporter of cysteine in the intestine. Tr. 1654-57. However, since I have concluded that Dr. Deth is not qualified to opine regarding the significance of A.K.'s alleged GI inflammation, it is not necessary to reach the question of whether Dr. Deth or Dr. Jones is correct on that specific point.

[262] "AGE" is a commonly used abbreviation for "acute gastroenteritis." *See, e.g.,* N. Davis, MEDICAL ABBREVIATIONS: 32,000 CONVENIENCES AT THE EXPENSE OF COMMUNICATION AND SAFETY (15th ed.), at 40.

[263] Petitioners interpret that handwritten diagnostic impression as "AGI" which they indicate stands for "acute gastrointestinal symptoms." ECF No. 297 at 6. It may also say "AGE." Pet. Ex. 61, p. 61. Regardless of the interpretation it is clear that this visit reflects that A.K. had a gastrointestinal complaint of some kind.

[264] Petitioners stress that Dr. Iochim found that "A.K.'s intestinal cells showed the presence of 'multiple reactive hyperplastic lymphoid follicles' in three sites in the ilea muscosa, 'fecal mucosa with reactive lymphoid follicles,' 'seven sites with nodular or diffuse inflammatory infiltrates of lymphocytes' and more." ECF No. 297 at 9. They argue that these findings are "all indicative of marked gastrointestinal disease." *Id*. I note, however, that Dr. Levy, the director of the Children's Digestive Health Center at the New York

that same date, he had a colonoscopy exam conducted by gastroenterologist Dr. Arthur Krigsman.[265] Pet. Ex. 8, pp. 59-61. Doctor Krigsman found, *inter alia*, that A.K.'s terminal ileum was "moderately lymphonodular." Pet. Ex. 8, p. 61. Following the biopsy and colonoscopy, Dr. Boris noted lymph node hyperplasia and that A.K. was positive for colitis. Pet. Ex. 3, pp. 133-35. I note that Drs. Boris and Krigsman had offices adjacent to one another, based on their office addresses. *See* Pet. Exs. 3, p. 389 (listing Dr. Boris' office as "77 Froehlich Farm Blvd"); 8, pp. 28, 57 (listing Dr. Krigsman's office as "Woodbury Pediatrics Assoc., 75 Froehlich Farm Blvd" and as simply the same address without the Woodbury Pediatrics reference).

Looking at an image of A.K.'s distal ileum from the November 2002 colonoscopy, and comparing it to a "normal" example, Dr. Deth testified that "so just for contrast, a normal gut epithelium is on the left here. We can see kind of a clean vascular surface, lots of nice mucus, but none of the sort of bulbous lymphoid, which mean, of course, immune cells, white cells. There's some kind of inflammation happening there which I would have to say does not look like it's favorable for the processes that I've just reviewed, the absorption in that area." Tr. 721-22 (discussing Pet. Ex. 13, p 1.). Doctor Deth initially described the reported GI inflammation as "severe," before admitting that the colonoscopy report actually indicated that the inflammation was "moderate." Tr. 760.

Dr. Deth characterized this piece of evidence as "striking" and "obviously relevant." Tr. 721. However, nothing in Dr. Deth's background, training, or experience suggest that he is qualified to offer any opinion regarding the nature of the inflammation depicted, nor its significance in terms of GI function. He conceded that he is neither a pathologist nor a gastroenterologist. Tr. 722. I note again that Dr. Deth holds a Ph.D., not a medical degree.

In that regard, I sought to clarify the nature of Dr. Deth's reliance on this colonoscopy. Specifically, I asked him if he was relying on Dr. Krigsman's expertise and ultimate diagnosis or whether he was offering his own opinion. Tr. 721. At first, Dr. Deth confirmed he was relying on Dr. Krigsman's impression of lymphonodular hyperplasia, but then continued to offer his own interpretation of the image, noting as described above that the depicted inflammation "does not look like it's favorable" to the uptake of cysteine. Tr. 721-22.

Presbyterian Children's Hospital of New York characterized the biopsy findings only as "suggestive of mild colitis." Pet. Ex. 61, p. 123. In any event, Dr. Deth did not at any point cite these findings as supportive of his opinion.

[265] Significantly, Dr. Krigsman testified regarding the possible connection between gut disorders and regressive autism during the OAP. *Synder*, 2009 WL 332044, *83-86. Based on a review of his own patients, Dr. Krigsman testified regarding a concept he referred to as "autistic entercolitis." Respondent's experts rebutted this concept by noting, *inter alia*, that there is no diagnosis of "autistic entercolitis" recognized in gastroenterology and that epidemiological evidence does not support the contention that children with regressive autism experience inflammatory bowel disease more frequently than those without regression. *Id.*

In light of his insistence, I again gave Dr. Deth an opportunity to cite something – anything – to support his argument that the depicted inflammation would result in this particular loss of function. Tr. 722. Doctor Deth then claimed that he is "a knowledgeable scientist" in the relevant field and that he knows "enough about GI epithelial function in regard to cysteine uptake." Tr. 722. Despite this protest, he nonetheless conceded that he could not cite anything to support his claim and instead stated that generally speaking "without being too concrete about that . . . the cell's normal function will be impaired when it's inflamed. So I'd have to leave it at that." Tr. 722-23.

Doctor Deth attempted to further link his claim regarding A.K.'s GI inflammation to A.K.'s overall medical record, indicating that "there's other evidence to that effect including a medical history of GI problems, and those problems could be related to his other metabolic abnormalities affecting the terminal ileum because that is the place that was most inflamed." Tr. 745. Doctor Deth also offered opinions that the GI disturbances noted in earlier portions of A.K.'s medical history "seemed not to be at the same level of importance" as subsequent findings. Tr. 804. He claimed to know the significance of a finding regarding "irritable bowel disease."[266] Tr. 803. When challenged regarding his analysis of A.K.'s medical history, Dr. Deth conceded only that he has no expertise relative to the timing of the cited GI inflammation, but insisted that he was nonetheless qualified to speak to its potential impact. Tr. 747.

His testimony regarding the significance of GI inflammation in A.K.'s medical history was confusing and inconsistent. In his expert report, Dr. Deth indicated that A.K.'s alleged GI dysfunction was a factor predisposing him to harm from his vaccinations. Pet. Ex. 117 at 14. In his subsequent trial presentation, however, Dr. Deth indicated that A.K. developed GI inflammation after his vaccinations. Pet. Ex. 239 at 98. When I questioned Dr. Deth regarding the discrepancy, he acknowledged that the reference to the inflammation being after the vaccine was based on the fact that the

[266] On cross-examination, Dr. Deth was asked whether A.K.'s testing negative for "*irritable* bowel disease" would affect his opinion. Tr. 803. This appears to be a reference to *inflammatory* bowel disease ("IBD"). Doctor Deth clarified that respondent's counsel was not referring to irritable bowel syndrome ("IBS") before indicating that a negative finding for irritable bowel disease would not change his opinion. *Id.* Significantly, however, Dr. Deth cited a review paper on Crohn's disease, a type of IBD, to support his contention that TNF-α is responsible for the type of GI inflammation A.K. experienced. Pet. Ex. 239 at 77 (citing Pet. Ex. 260, S. Peake, et al, *Mechanisms of Action of Anti-tumor Necrosis Factor α Agents in Crohn's Disease,* INFLAM. BOWEL DIS., 19: 1546-55 (2013) [hereinafter "Peak, Pet Ex. 260"]. When Dr. Johnson indicated that this paper had nothing to do with autism and was not relevant to his theory (Res. Ex. JJJ at 3), Dr. Deth replied that the article indicated that "the proinflammatory cytokine TNF-alpha contributes to GI inflammation. GI inflammation has to do with autism and with [A.K.]." ECF No. 281 at 5. Doctor Deth's citation, however, indicated that TNF-α has been examined in Crohn's disease because it is a regulator of the innate immune response and the chronic gut inflammation of inflammatory bowel diseases such as Crohn's disease or ulcerative colitis is known to occur via an immunopathogenic mechanism. Peake, Pet. Ex. 260 at 1546. To the extent Doctor Deth's statement was that the presence or absence of IBD would not alter his opinion, this suggests that he is not aware of that distinction. Indeed, during his initial presentation Dr. Deth indicated that TNF-α is broadly implicated in many forms of GI inflammation. Tr. 724-25. That statement goes well beyond the Peake article, which is the only cite he provided for that assertion. Although A.K. may have had some signs of colitis, he did not have ulcerative colitis. Pet. Ex. 61, p. 124; Tr. 96.

colonoscopy, the only explicit evidence of inflammation cited, occurred over a year after the vaccinations in question. Tr. 746. He then suggested that earlier notations in A.K.'s medical records were indicative of prior inflammation, before finding himself unable to cite any specific notations and ultimately acknowledging that he did not have the expertise to so opine. Tr. 746-47. He also indicated that the question of whether A.K.'s inflammation occurred before or after the vaccine was important, but nonetheless seemed to opine, quite unconvincingly in light of the above, that he could reconcile either scenario with his theory. Tr. 747.

Doctor Deth also cited urine samples showing gliadomorphin and casomorphin peptides as evidence that A.K. has "leaky gut syndrome." Pet. Ex. 117 at 13. "Leaky gut syndrome," also known as "autistic enterocolitis" is not a recognized diagnosis. Rather, it is a hypothesis initially advanced by the now-discredited Andrew Wakefield. *See, e.g., Synder*, 2009 WL 332044 at *79-87. Moreover, Dr. Deth's own expert report indicated that these peptides are, if anything, diagnostic of celiac disease, not irritable bowel syndrome or inflammatory bowel disease. Pet. Ex. 117 at 14. To the extent Dr. Deth claimed that his own research has shown that these same peptides inhibit $EAAT_3$, his only citation is to one of his own publications: *Autism: A Neuroepigenetic Disorder*, filed as Pet. Ex. 117, Ref. 46.[267] Although the article is best characterized as a review article, Dr. Deth nonetheless referenced his own original research within the text, without reporting any of his actual data. Particularly in light of his selective presentation of his other studies (*see* Section IX.D, below), this is not a persuasive piece of evidence.

I also note that one of A.K.'s own treating gastroenterologists, Dr. Levy, expressed serious doubts about the pursuit of a "leaky gut" "diagnosis." Pet. Ex. 61, p. 124. Doctor Levy, writing in April of 2003, specifically noted that as of that date A.K. was negative for serological markers of celiac disease and cautioned against pursuing the "leaky gut" theory to connect A.K.'s autism to either food allergies or immunizations. *Id.* In contrast, Dr. Deth's sole citation in support of his claim that A.K. had gliadomorphin and casomorphin peptides was a much later hand written notation by Dr. Boris from January of 2005. Pet. Ex. 117 at 13 (citing Pet. Ex. 3, p. 45). Neither Dr. Deth nor petitioners have cited any testing to substantiate that notation. Moreover, I find the notation Dr. Deth relied upon (Pet. Ex. 3, p. 45) to be illegible.

Doctor Deth also cited a finding in A.K. of low cystine in August of 2008 as evidence that A.K. had a deficit of antioxidants caused by his GI inflammation. Tr. 749; Pet. Ex. 239 at 101. The actual result was not characterized as low; it was characterized as below the detection limit of the test, according to Dr. Jones. Tr. 1643-45. Moreover, Dr. Jones noted that measurements of cystine are incredibly unreliable absent specific protocols, and cystine values vary by both time of day and diet. Tr. 1645-48. For these reasons, as well as the absence of information regarding the lab's handling of the samples, Dr. Jones did not trust the reported cystine values. *Id*. In his rebuttal testimony, Dr. Deth did not address any of Dr. Jones's concerns, but stated only that Dr. Jones's concerns "struck me as shooting the messengers if you don't like the

[267] AUTISM SCIENCE DIGEST: THE JOURNAL OF AUTISMONE, 3:8-19. The filed copy of the article indicates that it is reprinted with permission, but does not identify the source document or the year of publication.

delivery of the package" before stating without any apparent support that "there's no reason to disparage the validity of those results and they speak for themselves." Tr. 1743.

The fact that Dr. Deth's testimony strayed a bit from his precise area of expertise is not, in itself, highly significant. I note that many of the respondent's experts occasionally did the same. Indeed, there is an extent to which the interconnectedness of these topics requires it. *See, e.g*., Dr. Johnson briefly discussing the immunologic topic of the impact of vaccines versus active infection as it related to neurotoxicity. Tr. 1732. But Dr. Deth's testimony is unique in this case both for the significant extent to which his opinion is ultimately built upon this overreaching, as well as the extent to which he has attempted to assert – without any apparent basis – sufficient knowledge in the area of gastroenterology to opine knowledgeably and reliably, despite his lack of credentials. Indeed, Dr. Deth asserted that A.K.'s purported GI inflammation was the "most important" piece of evidence regarding the presence of oxidative stress in A.K.'s case. Tr. 801. He also persisted in claiming expertise regarding the impact of gastrointestinal inflammation, despite being unable to provide any supporting source for his assertions and his tenuous grasp on what the medical records actually reflected. [268] The wide latitude afforded to an expert "is premised on an assumption that the expert's opinion will have a reliable basis in the knowledge and experience of his discipline." *Daubert*, 509 U.S. at 592.[269] This assumption does not apply when an expert is opining outside of his discipline.

During the OAP I observed that while Dr. Deth has a Ph.D. in pharmacology most of his research prior to 1998 focused on hypertension and cardiovascular problems, not neurotoxicology, neuropharmacology, autism, or sulfur metabolism. *Dwyer*, 2010 WL 892250 at *108. I found that respondent's competing experts offered more persuasive testimony in part because, unlike Dr. Deth, they carefully restricted their testimony to their areas of expertise. *Id*. The same dynamic plays out in the instant case. Doctor Deth's credibility in this case is greatly reduced by his unapologetic attempts to testify well beyond his expertise. *See, e.g.,* Tr. at 628-29 (toxicology), 722 (pathology and gastroenterology), 733-34 (immunology). As described herein, this tendency was particularly pronounced with regard to Dr. Deth's claims regarding gastroenterology. Indeed, as noted above, I felt compelled to challenge Dr. Deth's overreach on this subject numerous times (Tr. 722-23, 747, 751),and, after he had opined that the two influenza vaccinations were responsible for A.K.'s "neuro developmental injury," "regressive encephalopathy," and "severe early developmental regression," I commented that Dr. Deth's diagnoses and causation opinions constituted

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[268] Interestingly, despite his forays into gastrointestinal diagnosis, Dr. Deth acknowledged that upon his review of A.K.'s medical records, he did not recognize the importance of "AGE" notations. Tr. 753. Even [A.K.'s father], a lay witness, testified that he understood what the abbreviation "AGE" meant. Tr. 94-95. While not terribly significant in itself, this does provide a tidy illustration of why I am highly skeptical of Dr. Deth's claimed, yet un-credentialed and unsubstantiated, knowledge of gastrointestinal function.

[269] The Federal Circuit has approved the use of the *Daubert* factors by special masters in evaluating the reliability of and the weight assigned to expert opinions in Vaccine Act cases. *See Moberly,* 592 F.3d at 1324 (Fed. Cir. 2010); *Andreu*, 569 F.3d at 1379; *Terran*, 195 F.3d at 1316.

"practicing medicine without a license" (Tr. 751).[270] Doctor Deth's medical opinions regarding A.K.'s gastrointestinal inflammation and its purported relationship to two vaccinations were outside his expertise and unsupported by other evidence. I find them inherently unreliable based on Dr. Deth's lack of qualifications to diagnose this child and to opine on the cause of a neurodevelopmental condition.

C. Doctor Deth's Opinion Remains Predicated on Concepts Rejected During the OAP.

The remainder of Dr. Deth's presentation largely recycled concepts and ideas he previously presented during the OAP theory 2 test cases, particularly with regard to sulfur metabolism. During the OAP, all three special masters who heard him found his testimony lacked sufficient indicia of reliability to be credited.[271] *King*, 2010 WL 892296 at *54-61; *Dwyer*, 2010 WL 892250 at *108-142; *Mead*, 2010 WL 892248 at *64-80.

In the OAP Theory 2 cases, Dr. Deth hypothesized a biochemical process by which mercury can produce an oxidizing environment in the brain, described the biochemical processes involved in neuroinflammation, and explained that only a small fraction of children vaccinated with TCVs develop autistic symptoms because of "genetic and epigenetic differences between individuals." *Dwyer*, 2010 WL 892250 at *108. He testified "that 'the most critical problem in autism' involves maintaining a normal 'redox' status in cells" and attempted to explain the underlying cellular metabolism relating to this problem. *Id.* He also asserted that children with autism have an impaired ability to handle oxidative stress. *Id.*

Then-Special Master Campbell-Smith "found that the particular limitations that Dr. Deth recognized in his own testimony significantly diminished the weight that could be accorded to the theory he presented." *Mead*, 2010 WL 892248 at *6. Special Master Campbell-Smith also found Dr. Deth's own research to be of questionable reliability. *Id.* at *73-74. Special Master Hastings similarly, but more forcefully, stated

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[270] In light of petitioners' arguments against consideration of Dr. Miller's testimony, I find it ironic that they proffered the testimony of a pharmacologist with no background in gastroenterology, neurology, or immunology to opine in all three fields. While toxicology is certainly grounded in biochemistry and related to pharmacology, it does constitute a separate discipline. I am certainly not requiring that a witness have a medical degree in order to offer an opinion in a Vaccine Act case. Indeed, I have permitted, considered, and credited the testimony of Ph.D. witnesses who lack a medical degree in the past. *See, e.g. Synder*, 2009 WL 332044 at *17, *20-21 (crediting the testimony of, *inter alia*, Dr. Thomas MacDonald, a Ph.D. specialist in gastroenterology; Dr. Michael McCabe, a Ph.D. toxicologist, Dr. Steven Bustin, a Ph.D. molecular geneticist.) Here, however, Dr. Deth's opinions were so far outside his areas of education, training, research, and experience to be per se unreliable. Had this been a jury trial, I would not have let him testify, based on the requirements of *Daubert*. Unlike Dr. Deth, Dr. Miller clearly possessed the education, training, and expertise necessary to opine on the matters about which she testified.

[271] The OAP special masters were not the only judicial officers to express concerns about the reliability of Dr. Deth's opinions based on his lack of expertise to opine. In one of the autism cases tried outside the Vaccine Program, Maryland Circuit Court Judge Berger found Dr. Deth's testimony inadmissible because "his opinion 'that exposure to mercury [from] thimerosal-containing vaccines causes autism,' would have required him to delve into fields of toxicology, epidemiology, neurology, and genetics—all fields with which he had little or no expertise." *Blackwell v. Wyeth*, 408 Md. 575, 625-26 (2009). The highest court of Maryland upheld this ruling. *Id.* at 630.

that the testimony of Dr. Deth "was not persuasive in any event." *King*, 2010 WL 892296 at *28. He observed that Dr. Deth "did not explain his opinion well, and relied heavily on questionable *in vitro* experiments and on his own laboratory's work, part of it unpublished." *Id.* at *55. I stressed that "the scientific studies upon which [Dr. Deth] relied provided, at best, only tangential support for his hypothesis" and that his own research was "poorly performed and scientifically implausible." *Dwyer*, 2010 WL 892250 at *109. I also noted that "in the course of the hearing, nearly every premise of his causation theory, other than that of the ubiquity of mercury exposure in children (with or without autism), was seriously undermined, where not completely demolished." *Id*. at *110.

In *Dwyer*, I summarized Dr. Deth's theory in pertinent part as contending that mercury depletes glutathione levels, which in turn increased oxidative stress. Oxidative stress turns off methionine synthase activity, resulting in less methionine. Lowered methionine levels result in reduced "SAM" production and that leads to fewer methylated products available for DNA methylation. [272] It also impacts the D4 dopamine receptor on neuronal cells, decreasing synchronization for neuronal activity. According to Dr. Deth, both impaired methylation and the negative impact on dopamine receptor can produce autistic symptoms. *Dwyer*, 2010 WL 892250 at *113.

Except for mercury as the trigger for oxidative stress, this is the same process Dr. Deth described in this case. Doctor Deth testified that ultimately the most important aspect of his present theory is the level and state of glutathione oxidation in the brain. Tr. 772. He opined that "a decrease in [methionine synthase] activity inhibits methylation reactions by lowering the SAM/SAH ratio" and that "any factor that significantly alters [methionine synthase] activity will exert significant epigenetic effects." Pet. Ex. 117 at 8. He also opined, as he did in the OAP, that the reduction in methionine synthase activity results in both a decrease in D4 receptor phospholipid methylation and DNA methylation, which both in turn lead to autism. Tr. 689; Pet. Ex. 239 at 55.

Indeed, Dr. Deth made the overlap with his OAP testimony quite clear when he indicated during his presentation in this case that his current theory is reflected in his 2008 review article. Tr. 646; Pet. Ex. 239 at 24; Pet. Ex. 117 at 9, 12 (citing Pet. Ex. 117, Ref. 11, R. Deth, et al, *How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis*, NEUROTOXICOL. 29: 190-201 (2008). In *Dwyer*, I noted that at the time of his participation in the OAP, this review article was Dr. Deth's only publication on oxidative stress. *Dwyer*, 2010 WL 892250 at *108, n. 456. The problems with the article and the theory behind it were discussed extensively in *Dwyer*,

[272] "SAM" refers to S-adenosylmethionine, a methyl donor. Pet. Ex. 117 at 8. As in the OAP, Dr. Deth contended here that the level of methionine synthase has a direct relation to the level of SAM while being inverse to "SAH" or S-adenosylhomocysteine. *Id.* That is, he contended that increased methionine synthase activity promotes methylation by increasing the SAM/SAH ratio while decreased methionine synthase activity inhibits methylation by lowering the SAM/SAH ratio. *Id*. Methylation of DNA is responsible for alterations in gene expression, producing the epigenetic changes that Dr. Deth referenced. Pet Ex. 117 at 7.

and like much of Dr. Deth's other testimony, was given very little weight. *Dwyer*, 2010 WL 892250 at *111, 113, 114, 116, 121, 133, 135, 140.

During the OAP, I discussed Dr. Deth's peculiar views regarding both the methionine-methylation cycle and his D4 receptor methylation hypothesis. *Dwyer*, 2010 WL 892250 at *115-19. I discussed at length the short-comings of Dr. Deth's own study regarding the D4 receptor (the Waly study) on which he relied heavily.[273] Doctor Deth claimed to have discovered an unusual extracellular methylation cycle at the D4 receptor. *Dwyer*, 2010 WL 892250 at *118-19. Based on the profound flaws of that study, coupled with Dr. Deth's unsupported extrapolation of its findings, I found the evidentiary value of this paper to be essentially nil.[274] *Id.* Despite continuing to rely on that same study, Dr. Deth has presented very little new information on these points in this case and has failed to remedy any of the deficiencies I identified.[275] *See, e.g.,* Pet. Ex. 117 at 9 (Dr. Deth's expert report's reliance on the conclusions from the Waly study as a basis for much of his later work). And, his opinion and his underlying research work were, once again, thoroughly and extensively rebutted by Dr. Johnson. S*ee* Res. Ex. XX at 6-9 (Dr. Johnson's expert report, identifying twelve flaws with the Waly paper before concluding, "[t]his single paper, the whole foundation of Dr. Deth's theory in this case, has no data on either oxidative stress or methylation. This lack of data indicates that, once again, Dr. Deth's hypothesis is simply speculation without scientific foundation.").

But perhaps the most glaring flaw Dr. Deth has carried forward from his discredited OAP theory is the concept of the cystathionine block. As noted above, Dr.

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[273] Waly, Pet. Ex. 117, Ref. 9. For some reason, the actual paper was filed in the OAP but, in the present case, the on-line early release version was filed. In comparing page number citations to the article in the two proceedings, the present case's page 1 corresponds to page 358 in Dwyer. Since the Waly paper continues to play an important role in Dr. Deth's opinion in the present case, I take note that this original paper was rejected by three journals before it was published by a fourth. Dwyer, 210 WL 892250 at *108 n.457.

[274] In *Dwyer*, I described the Waly paper as having two distinct parts, one related to the effects of insulin-like growth factor 1 and dopamine on methionine synthase activity and one related to the inhibitory effects of heavy metals on DNA methylation. *See Dwyer*, 2010 WL 892250 at * 116-17, 119. My focus here is primarily on the first part.

[275] Although he did cite the Waly study multiple times in his expert report (*see* Pet. Ex. 117 at 8-9), Dr. Deth attempted to gloss over his reliance on the study during his testimony. He presented a slide depicting "the D4 receptor that our lab discovered," but then stated that "while I've published a number of papers about this, I don't recount them here." Tr. 684. He also tried to deflect the criticisms of his work by claiming that the critique offered by Dr. Johnson constituted an attempt to redo the peer-review process, stating that "at this point in time I find it inappropriate as well as off target to some extent to review the way we did our experiments and to suggest other controls that we could have done. There was a time for that, but that time was when the paper was published, and if somebody wants to pick up and add to our data and test it, that's what science is." Tr. 764-65. Such an argument is, of course, absurd. By Dr. Deth's logic, all peer-reviewed literature is of precisely equal quality and value simply by virtue of having met the minimum criteria for publication. That is clearly not true. Moreover, Dr. Jones pointed out that the peer-review process is not perfect and that results in works of variable quality. Tr. 1664-65. I also note, for example, that Dr. Cohen, in contrast to Dr. Deth, was quite forthright in testifying regarding his opinion that a paper for which he was a participating author had significant methodological flaws. S*ee, e.g.,* Tr. 1227-29, 1356-59.

Deth has indicated that his theory is ultimately based on how the body supplies glutathione to the brain. Tr. 772. Respondent's experts have noted, however, that the human brain has compensatory systems, that the transsulfuration pathway does not operate via a single transporter, and that it is not plausible for the mechanism that Dr. Deth described to impact the brain and only the brain. *See, e.g.,* Tr. 1514-19, 1728-32, 1654-57. In that regard, Dr. Deth relied on what he characterized as the "cystathionine block" in the human brain to explain both that the brain is uniquely susceptible to oxidative stress and dependent upon the $EAAT_3$ transporter to provide cysteine. Tr. 666-68.

Cystathionine is the first of the two intermediate steps on the transsfulfuration pathway, between homocysteine at one end and glutathione on the other. Cysteine is the second intermediate step, failing between cystathionine and glutathione. *Dwyer*, 2010 WL 892250 at *197, n.520; Tr. 668-69. As in the OAP, Dr. Deth cited a 1958 study showing that the human brain has a much higher level of cystathionine than other species, such as monkeys, rats and ducks.[276] *Dwyer*, 2010 WL 892250 at *121-22; Tr. 669-70; Pet. Ex. 239 at 37. He contended that this study shows that "evolution has gradually tightened the noose around transsulfuration, has gradually reduced the ability of homocysteine to be converted into cysteine, thereby gradually increasing the importance of the $EAAT_3$-mediated cysteine uptake pathway." Tr. 669-70.

But, as in the OAP, Dr. Deth's description of a cystathionine block remains completely unsupported. *See, e.g.,* Tr. 1735-36. As I noted in *Dwyer*, "Dr. Deth jumped from high cystathionine levels to the conclusion that there was a blocked metabolic process without any data that such a block actually exists. He did not rely on any measurements of lower cysteine and glutathione levels in human brains; he simply concluded that they must be low as a result of high cystathionine levels. It is equally likely that cysteine and glutathione levels are also higher in humans." *Dwyer*, 2010 WL 892250 at *122. Indeed, Dr. Deth still has not offered any explanation as to why one would even expect a duck to have the same level of cystathionine in the brain as a human such that any explanation was called for in the first place. In the OAP Dr. Johnson also challenged the study's finding. In this case, Dr. Deth claimed that he had recently replicated the findings of this 1958 study (Tr. 669-70), but did not cite to any specific study, much less one that had been published.

While I am mindful of the fact that the results from the OAP test cases are not binding on any other litigant currently or formerly in the OAP, I cautioned petitioners' counsel on several occasions that I did not intent to permit Dr. Deth to present anew here what he presented (and I rejected) in the OAP, absent new evidence. Here, Dr. Deth's theory in this case simply shares too many similarities with his prior discredited testimony to ignore. *See Hodges*, 9 F.3d at 961 (noting that Congress contemplated

[276] Pet. Ex. 117, Ref. 15, H. Tallan, et al., *L-cystathionine in human brain*, J. BIOL. CHEM., 230(2):707-716 (1958).

the special masters would use their accumulated expertise in the field of vaccine injuries to judge the merits of individual claims).[277]

Petitioners argue in effect that Dr. Deth's prior OAP testimony should not be a factor in my decision. ECF No. 302 at 9-10. They note that "Dr. Deth's testimony in the OAP focused on mercury and its effect on oxidative stress, hardly the issue herein."[278] *Id* at 10. And while it may be true, as petitioners stress, that "the OAP cases did not involve mitochondrial disease or the influenza vaccine" (*id*.), the fact remains that Dr. Deth's opinion still focuses on oxidative stress and relies on the same flawed understanding of sulfur metabolism and on many of the same concepts and studies. Indeed, upon my review of the record of this case, it appears as though Dr. Deth ultimately posited the same core mechanism as in the OAP, merely substituting a new source of oxidative stress in place of his previously discredited theory regarding thimerosal.[279] Petitioners' argument that this case involves mitochondrial disease rather than mercury misses the point. There was substantial overlap in Dr. Deth's two presentations.

Petitioners stress that in the five years that have passed since the OAP "an overwhelming abundance of medical literature has emerged supporting Dr. Deth's medical theory of causation." ECF No. 302 at 10. And while it is no doubt true that further studies have been published since the time of the OAP, Dr. Deth has simply failed to establish that any subsequent literature actually supports his view in any meaningful way.

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[277] Petitioners have argued that OAP evidence should be barred, because consideration of expert witnesses and evidence not before the Court in the instant case violates the confrontation clause. S*ee*, *e.g.,* ECF No. 302 at 10. While I previously addressed that objection in my prior ruling on motions (*See* Motions Ruling, filed on Sept. 28, 2015 (ECF No. 319), at Section II.D), I note here that this argument is particularly misplaced with regard to Dr. Deth's testimony. My analysis is focused on the weaknesses inherent to Dr. Deth's own opinion and Dr. Deth has, of course, testified in both cases. Indeed, the critical point is that Dr. Deth's testimony *in this case* remains flawed, a problem which petitioners had ample opportunity to address. Although the OAP results are not binding, the analysis it contains remains highly persuasive, and moreover, was equally available to both sides, as both the OAP documents and testimony remain publically available. Petitioners have long been on notice that claims that merely repeat the theories presented during the OAP will not be compelling. Moreover, three of the same experts arrayed against Dr. Deth during the OAP theory two cases (Drs. Jones, Johnson, and Mailman) submitted reports in this case as well, and two of those three (Drs. Jones and Johnson) also testified.

[278] However, in withdrawing from the OAP, petitioners specifically reserved the right to present evidence on the mercury causation theory. *See* Motion to Withdraw as a Test Case, April 10, 2008, (ECF No. 40), at 1.

[279] In fact, Dr. Deth's presentation in the instant case is so similar to his OAP presentation that he failed to even completely eliminate references to mercury as a causal agent. References remain two of the PowerPoint slides used in this case. *See* Pet. Ex. 239 at 89, 96. Moreover, Dr. Deth raised mercury several times in his testimony. *See, e.g.,* Tr. at 740 (irreversible binding to thioredoxin reductase), 744 (three factors at play here: mercury, TNF-alpha, and aluminum); 783-85 (influence of mercury on oxidative stress); 786-89 (elevated mercury levels in one of A. K.'s tests), and 829 (additive effect with other stressors). Petitioners cannot present evidence on the mercury theory, against my express orders, and without notice to the court and opposing counsel and then bar my consideration of evidence refuting it.

For example, immediately following his veiled reference to the above-discussed Waly study, Dr. Deth referenced three subsequent studies which he claimed confirm his hypothesis. Tr. 685-86; Ex. 239 at 51. In a supplemental report[280], however, Dr. Johnson pointed out that the three studies discuss the dopamine D4 receptor only as it relates a completely different point, and not with regard to the methylation activity Dr. Deth was discussing. Res. Ex. JJJ at 2. Doctor Johnson commented that Dr. Deth's testimony regarding dopamine D4 receptor-mediated methylation remains "complete speculation." *Id*. In response, Dr. Deth admitted in his own supplemental rebuttal report that his theory of dopamine-stimulated phospholipid methylation has "not been proven," but argued that the observations of the studies were nonetheless somehow relevant to his theory. ECF No. 281 (incorrectly filed as Pet. Ex. 239) at 4.

Indeed, Dr. Johnson's supplemental report persuasively established that much of the late-filed literature by Dr. Deth was simply irrelevant or not related to Dr. Deth's theory in the manner that Dr. Deth suggested.[281] S*ee* Res. Ex. JJJ, *passim*. For the most part, Dr. Deth's responses to Dr. Johnson's criticisms confirmed, either directly or indirectly, that the literature was only related to his theory in the broadest of senses and did not offer any significant confirmation of his ideas. ECF No. 281, *passim*; Post-hearing Order, filed Sep. 9, 2013 (ECF No. 278). For example, where Dr. Johnson pointed out that an article Dr. Deth relied upon was "not physiologically relevant" in that its results "would never be achieved *in vivo*," Dr. Deth responded only that the study illustrated as a general manner that "enzymes are modified by glutathionylation." ECF No. 281 at 3. When Dr. Johnson criticized Dr. Deth's reliance on a study to show that autism is epigenetically caused, Dr. Deth responded that the relationship in question is "complex and currently not completely understood," but that the article is relevant because epigenetics is considered a driver of development generally. *Id*. Neither these responses, nor Dr. Deth's presentation overall, persuade me that Dr. Deth's theory in this case has any better grounding in the relevant science than did his OAP theory. [282]

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[280] Due to the fact that Dr. Deth included references to many medical and scientific journal articles in his hearing presentation that had not been cited in his report nor previously filed into the record—in violation of my prehearing order (*see* Prehearing Order, February 21, 2013 (ECF No. 199)) and my letter to each of the experts (including Dr. Deth) that all journal articles they expected to rely upon must be filed before the hearing—I afforded respondent the opportunity to address those studies in writing. S*ee* Scheduling Order, filed Jun. 6, 2013 (ECF No. 270).

[281] Doctor Deth's penchant for citing a study for a matter that it did not support was abundantly clear during the Theory 2 test cases and it is precisely why I required petitioners to file the studies referenced on Dr. Deth's slide presentation (*see* Pet Ex. 239) and allowed respondent the opportunity to respond to Dr. Deth's numerous citations in his hearing presentation in writing after the hearing.

[282] It is worth noting that as a general matter, Dr. Deth was either unable or unwilling to directly answer many of the challenges to his theory raised by respondent's experts. For example, Dr. Johnson questioned Dr. Deth's reliance on a particular study regarding oxidative stress, noting that he felt the results were more consistent with acute damage or injury and not a chronic or delayed process such as autism. Res. Ex. JJJ at 2 (citing Pet. Ex. 239 at 23; Pet. Ex. 246, T.R. Hurd, et al, *Complex I Within Oxidatively Stressed Bovine Heart Mitochondria is Glutathionylated on Cys-531 and Cys-704 of the 75-kDa Subunit: Potential Rolse of CYS Residues in Decreasing Oxidative Damage*, J. BIOL. CHEM.: 283(36)(September 5): 24801-24815.). Rather than actually address the point raised by Dr. Johnson, Dr. Deth replied that "once again Dr. Johnson rejects a scientific finding because it supports a theory that he does not support. The finding obviously supports a theory whereby mitochondrial activity is regulated by

D. Doctor Deth was Not a Credible Witness.

It is also highly significant that whatever the advances in the relevant fields since the OAP, and whatever the alterations to Dr. Deth's original hypothesis, he remains an inherently unreliable witness. There are numerous instances in this case where I found that Dr. Deth had attempted to gloss over information which further complicated, if not disproved, his underlying hypotheses. These examples further undermine the basic premise of Dr. Deth's theory, but perhaps more importantly, they also undermine his credibility as a witness. This was most egregious with regard to Dr. Deth's own post-mortem study.

During the OAP, Dr. Deth described unpublished post-mortem brain studies conducted by his lab as the strongest piece of evidence in favor of his opinion. *Dwyer*, 2010 WL 892250 at *109. Significant concerns were raised regarding the quality and reliability of the data generated.[283] *Dwyer*, 2010 WL 892250 at *126. The study was published by the time of this hearing. *See* Deth, Pet. Ex. 135;[284] *see also* Tr. 695-706; Pet. Ex. 239 at 62-65 (discussions of the study and findings). Nothing in the present testimony cleared up any of the concerns from the OAP.

1. Doctor Deth Selectively Presented the Results of His Own Study on mRNA Splicing.

As Dr. Deth described it, the post-mortem study showed that, among neurotypical subjects, mRNA for methionine synthase in the brain decreased 500-fold over the course of a lifetime.[285] Tr. 702. Despite this, the study also showed that the level of protein produced by the mRNA remained constant during the life span. *Id.* Doctor Deth described the finding as "surprising," but offered the interpretation that an age-dependent slowing of metabolism resulted in the production of less new protein with an accompanying longer longevity for the proteins produced. Tr. 702-03.

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oxidative stress status. Simply because Dr. Johnson doesn't support a theory, however, does not provide a basis to reject sound science." ECF No. 281 at 3. Doctor Deth's very unhelpful "shoot the messenger" comment in response to Dr. Jones's concerns regarding the collection and measurement of cystine would be another similar example. Tr. 1743. In yet another instance, Dr. Deth responded to a challenge regarding the relevance of an illustration he pulled from a study by focusing first and foremost on Dr. Johnson's use of the word "cartoon" to describe the graphic. ECF No. 281 at 5. "Cartoon" is a term frequently used to distinguish graphics or diagrams (as opposed to photographs or charts) used to illustrate concepts or points, and is not pejorative. Doctor Johnson's use of the term "cartoon" was clearly not intended to be derogatory, and he used the same term to describe a graphic in his own expert report. S*ee* Res. Ex. UU at 5. The lack of substantive response to Dr. Johnson's criticisms is telling.

[283] Many of the illustrations and charts presented in *Dwyer* and the other Theory 2 test cases were replicated in the article.

[284] Citations will be to the machine-generated page numbers assigned by petitioners, as the actual article's pages are not numbered.

[285] Doctor Deth explained that his study looked at mRNA as a substitute for actually measuring methionine synthase activity, because he felt that the enzyme could not be measured reliably in the post-mortem brain. Tr. 778-81.

In subsequent testimony, however, Dr. Johnson explained the significance of the alternative RNA splicing aspect of Dr. Deth's study. Tr. 1698-1708. He noted that portions of Dr. Deth's study, which Dr. Deth did not mention in his testimony (referring specifically to a figure showing the epithelium bromide-stained gel data), showed that 95% of methionine synthase mRNA was retained in older subjects and that there was no difference in methionine synthase protein levels between the different groups, indicating that the total methionine synthesis activity between the groups was the same. Tr. 1708-14. He contended that the data that Dr. Deth omitted constituted contradictory data, possibly suggestive of a technical failure. Tr. 1712. He further indicated that he did not find Dr. Deth's explanation – that proteins among the aged simply stop degrading - to be viable, noting that it is inconsistent with aging. Tr. 1713-14.

Doctor Deth's chief response in rebuttal was to claim that the criticism is irrelevant, because the data Dr. Johnson cited is not data from the autistic group.[286] Tr. 1754. This response is simply inadequate. Doctor Deth's ultimate conclusion regarding the autistic group was couched as a comparison to the neurotypical group, so data calling those results into question is relevant to his ultimate conclusion. Moreover, regardless of which aspects of the study on which Dr. Deth ultimately relied, he testified about the results in the neurotypical group. By failing to mention the contradictory data he implicitly overstated the viability of the data about which he testified. And finally, regardless of Dr. Deth's intentions, to the extent Dr. Johnson contended that the data reflected a technical failure, that calls into question the overall quality of the study and the weight it should be accorded.

In sum, Dr. Deth failed to mention that data he was presenting was potentially contradicted by other findings within the same study.

2. Doctor Deth's Claim of a "Compensating" Mechanism to Explain Away His Inconsistent Results is Unsubstantiated Speculation and Not Credible.

In discussing the significance of his post-mortem study with regard to the autistic group, Dr. Deth testified that this group had lower levels of the mRNA necessary for creating methionine synthase. Tr. 705-07. From this result he concluded that "levels of methionine synthase mRNA are lower in autism, consistent with a premature progression to a more oxidized state." Pet. Ex. 239 at 65. On cross-examination, however, Dr. Deth acknowledged that despite testing for markers of oxidative stress, the post-mortem study did not find any elevation of any markers of oxidative stress in the autistic population (specifically noting hydroxyl guanosine). Tr. 781-82. Providing further detail, Dr. Jones noted that this study found no difference in GSH, GSSG,[287] cysteine, cystine, or their respective ratios, the markers of oxidative stress used in other studies. Tr. 1651.

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[286] Doctor Deth also claimed that the criticism is not valid because the sample was normalized for "product" rather than for brain material. Tr. 1754. He stopped short, however, of explaining how that distinction could account for the contradictory data Dr. Johnson revealed.

[287] GSH refers to the reduced thiol form of glutathione and GSSG to the oxidized disulfide form. DORLAND'S at 809.

On redirect, Dr. Deth acknowledged that Dr. Jones was correct in his interpretation of the lack of oxidative stress markers, testifying that: "we were, I would say, somewhat surprised, to not find the biomarker that we used for oxidative stress to be elevated, and in fact many of the metabolites that we thought might be abnormal were not abnormal, but we then appreciated that the large changes in the mRNA that we observed are probably compensating successfully for the otherwise expected oxidative stress." Tr. 827. That is, he speculated that "the large decrease in autism subjects of methionine synthase was how they accommodated or adapted to the oxidative stress and probably relieved their oxidative stress sufficiently so that they didn't have biomarkers, but what they did have was lower levels of methionine synthase messenger RNA." *Id.*

Doctor Deth's later testimony suggests that he was attempting to mislead in his initial testimony that this study supported his theory. He presented the depressed mRNA levels as "consistent with" a state of increased oxidation (*i.e*. "a progression to a more oxidized state"). Pet. Ex. 239 at 65. Yet, on cross-examination he first admitted that the study failed to show that autistic brains had that increased oxidative state (Tr. 781-82) and on rebuttal, acknowledged that the study included findings contradictory to his hypothesis and that they came as a "surprise." Tr. 827. On direct examination Dr. Deth indicated that decreased mRNA is "consistent with a premature progression to a more oxidized state;" in rebuttal he actually speculated, in complete contradiction to his initial presentation, that the decreased mRNA is actually a sign of the subject's ability to relieve or cope with oxidative stress.

This is not an insignificant point. Doctor Deth indicated that "I think the evidence for epigenetics being related to oxidative stress and oxidative stress being a common feature of autism, make the persuasive argument that is certainly a reasonable hypothesis if not the primary most logical explanation that's at hand right now." Tr. 758. Although this study was not the only basis by which Dr. Deth contended that markers of oxidative stress are associated with autism, it does undercut his hypothesis to a significant degree.

It appears that Dr. Deth's study simply failed to generate results consistent with his initial hypothesis. The fact that he posited an untested after-the-fact hypothesis to explain away the discrepancy does not excuse his unqualified statement in his initial presentation that the mRNA levels are themselves indicative of "a more oxidized state," a statement which he knew to be incomplete.

E. Doctor Deth's Theory is Implausible from an Epigenetic Standpoint.

Epigenetics is the bedrock of Dr. Deth's theory.[288] That portion of his theory was not well-developed in the Theory 2 test cases, and his epigenetics presentation in this

[288] "Epigenetic" is defined as the alteration of "the activity of genes without changing their DNA sequence." DORLAND'S at 632. Alternatively, it can be described as something that affects phenotype without changing the genotype. *Id*. Epigenetics is "the study of heritable changes in the function of genes that occur without changes in the DNA sequence, occurring during development and cell proliferation and including mechanisms such as DNA methylation, histone modification, and RNA interference. *Id.*; Tr. at 1457. Epigenetics helps explain how identical twins can differ with respect to diseases that are considered genetic in nature, but not related to a single gene. By affecting gene

case was one of the few areas where his testimony was different and new. He stressed that knowledge about epigenetics has increased greatly in the past decade. Tr. 620; Pet. Ex. 239 at 8. Yet, even if I accepted that A.K. had all of the vulnerabilities Dr. Deth relied upon, and even if I accepted as accurate his explanation of sulfur metabolism, oxidative stress and inflammation as they relate to vaccination, his hypothesis would still not make sense from an epigenetic standpoint.

Doctor Deth posited that ASD is an epigenetic disorder wherein environmental factors impact gene expression. Tr. 613, 617-18. Asserting that children with ASD show evidence of decreased DNA methylation, he reasoned that DNA methylation, which is particularly sensitive to oxidative stress, was altered by oxidative stress. Tr. 625, 639, 689-92. Petitioners summarized his testimony as describing "the mechanism by which a vaccine administered to a two year old child could and did cause epigenetic changes in the child's brain giving rise to autistic-like symptoms . . ." ECF No. 297 at 63.

Respondent's experts challenged his assertion that there is an association between autism and depressed DNA methylation as well as arguing that other evidence suggests that a post-natal/early childhood insult resulting in epigenetic changes is unlikely.

1. Doctor Deth's Theory is Not Plausible as a Postnatal Occurrence.

Although he indicated that epigenetics operates in all phases of human development from pre-conception through adulthood, Dr. Deth stressed that epigenetic changes occurring in earlier development have a larger impact. Tr. 628-31, 813-14. In particular, he contended that epigenetic changes occurring in early childhood, when significant brain and immune development is occurring, are the most critical. Tr. 628-31. He maintained that the acute inhibition of DNA methylation (a process whereby enzymes control gene expression by attaching single carbon molecules to specific DNA sites) by oxidative stress can have long-term consequences to growth and development. Tr. 622-25.

Doctor Raymond noted that petitioners' theory ignores the critical distinction between pre- and postnatal development.[289] Doctor Raymond explained that during early prenatal development, epigenetic activity occurs in the context of cell division, regulating the process to create different kinds of tissue. Tr. 1461-64. At that stage, epigenetic changes from methylation can be carried on by the further replicating cells. *Id.* Postnatally, when epigenetic regulation acts on non-dividing cells, the changes are not carried forward (heritable) as they would have been during early prenatal development. Tr. 1464-68.

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expression, but not the underlying DNA structure of the gene, epigenetic changes can produce significant differences, and differences that can be inherited. Methylation turns genes on or off (or partially on or off).

[289] Although Dr. Raymond agreed that epigenetic regulation occurs throughout life, he asserted that the most significant epigenetic activity occurs from conception through the second trimester of gestation. Tr. 1457-59.

Doctor Raymond therefore contended that, even though it is undisputed that epigenetic changes occur throughout a person's lifetime, Dr. Deth's theory is implausible, because the type of disruption in methylation he describes – occurring at around 2 years of age on non-dividing neural cells – would have to be systematic to have such a significant impact to the brain. Tr. 1464-68. That is, the likelihood that *only* the genes necessary to cause autism would be activated postnatally and that they would be activated uniformly throughout the brain (e.g., to remove all Purkinje cells) is "not plausible." [290] Tr. at 1461, 1467-68. Thus, Dr. Raymond maintained that Dr. Deth cannot account for the "impossible" chance occurrence necessary for the methylation disruption he posited to impact a specific phenotype in the context of that type of systemic whole body deficit. Tr. 1467-68. That is, Dr. Raymond contended that Dr. Deth cannot explain how his theory would result in autism, and only autism, without impacting other body tissues.[291] Tr. 1468-69.

And indeed, Dr. Deth effectively conceded Dr. Raymond's point, testifying that "if that disturbance of development in methylation occurs early it's going to have a larger impact because the earliest cells give rise to whole pathways, whole regions of development, whereas later in life, later in development, abnormalities can be expected to have a more discrete I'll call it localized impact. This is evident by the comparison between let's say fetal abnormalities, which again can be related to epigenetic consequences, as opposed to let's say postnatal or even adolescent abnormalities, which while they might result in disease certainly have a more limited repertoire of outcomes compared to earlier defects." Tr. 628.

Nonetheless, Dr. Deth contended without apparent basis that "different organs have different vulnerability to epigenetic insult" and that the brain is unique in that it is "restrained from development until the postnatal period." Tr. 629-30. His citations regarding epigenetics and brain development, however, actually contradict his ultimate conclusion. For example, Dr. Deth cited *DNA methylation signatures in Development and Aging of the Human Prefrontal Cortex* by Numata et al., from THE AMERICAN JOURNAL OF HUMAN GENETICS, but that study found that "the fastest changes occur during the prenatal period" and "slow down markedly after birth."[292] He also cited an

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[290] Doctor Raymond noted in particular that Dr. Deth's reliance on Wong, Pet. Ex. 240, is misplaced. Tr. 1470. In Wong's methylomic manuscript, the profiles were gathered from blood samples. Tr. at 1471. In order for the blood profiles to correspond to the expected autistic methylation profiles in the brain, the methylation events that resulted in the triggering of autism would have to occur early on, before the stem cells differentiated. Tr. at 1472. Doctor Raymond describes the Wong paper as "a stellar paper… It has limitations, but it clearly makes the point that [the epigenetic event that results in autism is] way back there" in prenatal development. Tr. 1473.

[291] On cross-examination, Dr. Deth indicated that under his theory there would be oxidative stress in the whole body, but that because A.K. had a neurological injury, his focus was on the brain. Tr. 772-73. Doctor Deth did not explain what impact he would expect on the rest of the body under his theory. Nor did he attempt to show that A.K. experienced any other medical issues beside his ASD that were potentially explained by this whole-body oxidative stress.

[292] *See* Pet Ex. 242, Numata, et al, *DNA methylation signatures in Development and Aging of the Human Preffrontal Cortex*, AM. J. HUM. GENET. 90(2)(Feb. 10, 2012): 260-72. Doctor Deth included this article in his slide presentation but had not previously submitted it into the record. It was subsequently filed by petitioners on May 31, 2013, but no exhibit number was assigned at filing. *See* ECF No. 260. Upon my

author manuscript by Colantuoni, et al, titled *Temporal dynamics and genetic control of transcription in the human prefrontal cortex*, which likewise indicated that "the rate of expression change during fetal development is much faster than at any other stage in human life." [293] Clearly, these studies do not support Dr. Deth's assertion that from an epigenetic perspective the postnatal period is the most critical phase of brain development.

Ultimately, Dr. Deth cited 13 studies which he indicated all have findings "indicative of body-wide oxidative stress" among children with autism. Pet. Ex. 117 at 12. Further describing those studies, Dr. Deth opined that "we have these two partners, oxidative stress, impaired methylation, that were yoked together by their shared metabolic pathways as being very common and evident in autism. This implies that factors which cause oxidative stress and impaired methylation are primary suspects, or misfactors, or targets for causation of autism and should be investigated as such." Tr. 692. Yet, when discussing the role of environmental insults in epigenetic development of developmental disorders in his expert report, Dr. Deth cited a review article limited exclusively to prenatal environmental exposures. *See* Pet. Ex. 117, Ref. 7, F. Perera, *Prenatal Environmental Exposures, Epigenetics, and disease*, REPROD. TOXIOCOL., 31: 363-273 (2011). Thus, Dr. Deth's attempt to extend these epigenetic concepts to the onset of ASD in early childhood remains unsupported and speculative.

Doctor Johnson also cast further doubt on the significance Dr. Deth ascribed to the claimed association between autism and oxidative stress. Doctor Johnson pointed out that among the 13 studies Dr. Deth cited to link autism and oxidative stress as a general matter, at least one of those studies, one by James, et al,[294] showed that both the autistic and control subjects had the same metabolic patterns as their mothers, strongly suggesting that contrary to what Dr. Deth implied, there is no relationship between this state of oxidative stress and post-natal environmental factors such as vaccines. Specifically, to the extent Dr. Deth contended that the studies show that "factors which cause oxidative stress and impaired methylation are primary suspects, or misfactors, or targets for causation of autism," Dr. Johnson pointed out that the James study suggests that the metabolic profile Dr. Deth described is a genetically determined "baseline" for these individuals and not likely associated with vaccines. Tr. 1692, 696-98.

In rebuttal, Dr. Deth contended that "the assumption here that Dr. Johnson seemed to be making is all of it – sort of the causative factor for autism lies within the metabolic features of their parents, and I think this is . . . not true." Tr. 1759-60. Doctor Deth opined that Dr. Johnson was overstating the role of genetics and not accounting sufficiently for the environmental factors that also contribute. Tr. 1760. Consistent with Dr. Raymond's testimony, however, the James paper highlighted by Dr. Johnson

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order, petitioners' subsequently filed an updated exhibit list identifying this article as Pet. Ex. 242. *See* Exhibit List, June 25, 2013 (ECF No. 271).

[293] *See* Pet Ex. 243, C. Colantuoni, et al, Temporal Dynamics and Genetic Control of Transcription in the Human Prefrontal Cortex, NATURE 478 (7370)(2012):519-23. As with the Numata study, this document was not given an exhibit designation at the time of filing. *See* n. 292, *supra*.

[294] James, Pet. Ex. 117, Ref. 36.

indicated that to the extent the authors saw their results as supportive of an epigenetic theory of autism causation, they felt the results were suggestive of epigenetic alterations occurring during fetal development. James, Pet. Ex. 117, Ref. 36, at 1971. Thus, regardless of whether Dr. Johnson overstated the role of genetics or not, this James paper – cited by Dr. Deth himself – undermines his theory with regard to the timing of the epigenetic changes he asserts.

2. Doctor Deth's Theory Is Predicated on an Unproven Association Between Hypomethylation and Autism.

Doctor Deth further opined that "during oxidative stress [methionine synthase] activity is inhibited, resulting in a decrease of SAM/SAH and inhibition of all methylation reactions, including DNA methylation." Pet. Ex. 117 at 8. Thus, he concluded that "any factor that promotes oxidative stress has the potential to cause a significant decrease in global DNA methylation, disrupting the normal pattern of epigenetic regulation." *Id*. Doctor Deth cited the Wong study,[295] as evidence supporting the link between epigenetics and autism, noting that "this paper did show that the degree of changes in DNA methylation of epigenetic regulation was associated with differences in the severity of the autism." Tr. 621; Ex. 239 at 9.

Doctor Johnson noted, however, that the Wong study actually contradicted Dr. Deth's theory with regard to the expected methylation outcome. That is, while Dr. Deth posited that autism is caused by depressed methylation, the Wong study showed that twins discordant for autism showed no overall difference in methylation and in fact that different genomes are variously over or under methylated. Doctor Johnson contended that Dr. Deth's theory cannot account for that outcome and that, contrary to Dr. Deth's hypothesis of depressed methylation, the Wong study shows that methylation is either increased or decreased among autistic subjects with a majority of the genes becoming over-methylated. Tr. 1719-24, 1726. That is, Dr. Johnson noted that the Wong study showed that of the ten genes experiencing the largest change, only three experienced decreased methylation. Tr. 1724.

In rebuttal, Dr. Deth initially stated that his theory of hypomethylation was still consistent with the Wong article, because the manuscript only looked at gene and promoter methylation, which accounted for less than 5% of the genome. He concluded that, looking at the entire genome would show that hypomethylation was still present.[296] Tr. 1757-58. Doctor Deth was incorrect in this statement, however, as the article clearly indicates that changes in *global* methylation were not found to be correlated with autism. Wong, Pet. Ex. 240 at 3.

Subsequently, Dr. Deth seemed to acknowledge that the Wong paper indicated that there was no consistent pattern of global hypomethylation among the autistic subjects. Tr. 1765-66. He then completely backtracked on his claim that decreased or hypomethylation was required for autism, stating that "I would say that changes in or

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[295] Wong, Pet. Ex. 240.

[296] Doctor Deth also stressed a distinction between blood DNA and brain DNA, but he could not explain the difference. Tr. 776-77, 1764.

dynamic changes over time in DNA methylation is a more accurate term to use rather than essentially trying to paint me into a box here of saying, oh, it has to be hypomethylation, and I never said that it has to be hypomethylation, and indeed, even if I did, I'll say here that changes in the pattern, the normal pattern of methylation are sufficient to have epigenetic effects rather than simply always being hypomethylation. Tr. 1766.

This admission, however, completely undermines Dr. Deth's entire presentation. Contrary to his later rebuttal testimony, Dr. Deth was quite clear in asserting that he was relying on studies which he claimed showed a 28% decrease in the SAM/SAH ratio among autistic subjects, which he argued was evidence of impaired methylation. *See, e.g.,* Pet. Ex. 239 at 59. He was also clear in stating that it was the relationship between oxidative stress and impaired methylation, and the fact that they could both be associated with autism, that supported his theory. *Id*. Specifically, he testified that "we have these two partners, oxidative stress, impaired methylation, that were yoked together by their shared metabolic pathways as being very common and evident in autism. This implies that factors which cause oxidative stress and impaired methylation are primary suspects, or misfactors, or targets for causation of autism and should be investigated as such." Tr. 692.

This is highly significant, because Dr. Deth's opinion ultimately was that "any factor that promotes oxidative stress has the potential to cause a significant decrease in global DNA methylation, disrupting the normal pattern of epigenetic regulation." Pet. Ex. 117 at 8. Absent the alleged association between autism and impaired DNA methylation, it is not clear how Dr. Deth purports to complete his connection between oxidative stress and autism. Even if he established that reduced methionine synthase activity could create some form of epigenetic consequence, he would have no basis to conclude that the outcome would be autism. Indeed, as described above, Dr. Raymond's testimony regarding prenatal versus postnatal epigenetics makes that outcome unlikely.

F. Conclusion and Findings Regarding Dr. Deth's Presentation.

For all of the above reasons, I decline to credit Dr. Deth's testimony in this case. Doctor Deth failed to candidly address the science underlying his hypothesis; attempted to testify beyond his expertise; and relied to a significant degree on previously discredited concepts and ideas. *Snyder*, 88 Fed. Cl. at 718 (quoting *Ryman*, 65 Fed. Cl. at 40-41(special masters perform gatekeeping function when determining "whether a particular petitioner's expert medical testimony supporting biological probability may be admitted or credited or otherwise relied upon" and as a "trier-of-fact [a special master] may properly consider the credibility and applicability of medical theories")).

Moreover, even accepting Dr. Deth's testimony as at least minimally credible, he still has not presented a plausible theory. By his own admission his opinion stops short of actually contending that vaccines cause harmful oxidative stress. Moreover, his theory is fundamentally flawed in its understanding of basic metabolic and epigenetic concepts. And, in any event, the mechanism proposed by Dr. Deth is predicated on the

existence of vulnerabilities not present in this case. Thus, even considering Dr. Deth's presentation at face value, it remains highly unpersuasive.

X. Analysis under *Althen, Pafford and Loving.*

A. *Althen* Prong 1: A Reliable Theory.

Althen requires that a petitioner in an off-Table causation case present a reliable medical theory by explaining how the vaccines administered can cause the injury in question. *Althen*, 418 F.3d at 1278. This first prong of *Althen's* three part causation test has also been characterized as the equivalent of the "Can it cause?" inquiry used in toxic tort litigation. *See Pafford*, 2004 WL 1717359, at *4.

The medical theory must be a reputable one, although it need only be "legally probable, not medically or scientifically certain." *Knudsen,* 35 F.3d at 548-49. The Supreme Court's opinion in *Daubert* likewise requires that courts determine expert opinions to be reliable before they may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." 509 U.S. at 590 (footnote omitted). The Federal Circuit has stated that a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly,* 592 F.3d at 1324.

Here, petitioners' experts strained to stretch the idea of mitochondrial regression to encompass vaccines as triggers of such regression. As described above, that extension is completely unsupported by any scientific literature; it was presented in this case almost entirely through the opinion of Dr. Kendall, supported by one case report (Poling, Res. Ex. MM, Tab 14). Doctor Kendall's and Dr. Shafrir's further reliance on the Shoffner and Weissman papers was misplaced and their opinions that vaccines can act as triggers of mitochondrial regression were unpersuasive.

Evidence that regression in ASD, a well-described phenomenon involving the loss social communication and behavior, "looks like" mitochondrial regression was also nearly non-existent. "Mitochondrial autism" may someday be accepted as a descriptor for co-morbid autism and mitochondrial disorder diagnoses, but there is little evidence that autism itself is caused by such disorder, and no evidence that autism causes mitochondrial disorders. While Dr. Kendall is one of the few mitochondrial disorder specialists in the U.S., her opinion that vaccines can trigger either onset of a mitochondrial disorder with symptoms looking like ASD, or ASD via a mitochondrial regression are insufficiently supported and remain speculative.

To the extent Dr. Shafrir alternatively sought to establish that A.K.'s condition could be explained by a constellation of vulnerabilities contributing to an autoimmune reaction, he failed to demonstrate that any of the alleged vulnerabilities have the significance he maintains. He failed to articulate any basis for claiming that an influenza vaccination could lead, via autoimmunity, to the type of injury A.K. experienced. He also failed in his attempts to extend the so called "triple hit" hypothesis beyond the pre-natal context. Contrary to Dr. Shafrir's theory, there is no basis upon which to argue that regressive autism can be linked to a postnatal environmental factor. Moreover, his reliance on challenge-rechallenge is not persuasive in the context of this case wherein

A.K. was experiencing an ongoing and continuous condition (i.e. ASD) with a variable course.

To the extent petitioners attempted to otherwise establish a causal relationship through Dr. Deth's presentation regarding oxidative stress and inflammation – intended to establish a plausible biological mechanism – they failed. Doctor Deth's opinion suffered far too many serious flaws to be credited. Notably, having acknowledged that not all oxidative stress is injurious, Dr. Deth conceded that he could not opine what level of oxidative stress is created by a vaccination or what level of oxidative stress would be necessary to cause the type of neurological injury he described. Respondent's experts persuasively addressed these same questions, contending that the oxidative stress created by a vaccination is likely to be quite small. In any event, Dr. Deth also failed to credibly or persuasively address those aspects of his theory based on gastrointestinal function, epigenetics, and sulfur metabolism. To the extent Dr. Deth's presentation appeared coherent at a superficial level, it simply collapsed at the slightest challenge.

B. *Althen* Prong 2: A Logical Connection.

Even if petitioners had provided a theory which satisfied the first prong, to satisfy the second prong of the *Althen* test, petitioners must establish a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. In other words, petitioners must show that the received vaccine did, more likely than not, cause the injury in the case at bar. *Pafford*, 451 F.3d at 1356. The sequence of cause and effect need only be "'logical' and legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49; *accord Capizzano*, 440 F.3d at 1326. Evidence from a treating physician may assist petitioner in meeting her burden of proof under the second *Althen* prong. *Capizzano*, 440 F.3d at 1326.

Most significant to *Althen* Prong 2, there is strong evidence in the record suggesting that A.K.'s condition predated his vaccinations. A.K. was showing signs of both ASD and speech delay well before receiving either dose of his two dose series of influenza vaccinations. Moreover, the actual timeline of events do not support petitioners' claim of a regression. This is fatal to both Dr. Kendall's and Dr. Shafrir's opinions in that each relied on fact of a temporal relationship between the onset of A.K.'s ASD and his vaccinations as proof of vaccine causation. Doctor Shafrir, in particular, sought to rely on a challenge-rechallenge response as evidence that A.K.'s vaccines caused his condition. Absent such a reaction, Dr. Shafrir acknowledged that there was no other evidence upon which to causally link A.K.'s vaccinations to his alleged injury.

Additionally, all of petitioners' experts relied at least in part on the fact that A.K. was vulnerable to vaccine injury due to his alleged mitochondrial disorder. For the reasons described above, however, I have determined that that reliance was in error. Although petitioners' cited Dr. Shoffner's finding of a Complex I defect in A.K.'s medical history, as well as clinical reports by multiple treating physicians referencing that finding, these medical records did not provide support for petitioners' contention, particularly in light of respondent's presentation of multiple expert witnesses who interpreted Dr. Shoffner's findings as tentative, based on the need for further testing, and showing on

their own no abnormality. This finding is fatal to Dr. Kendall's opinion in this case and also highly significant to Dr. Shafrir's opinion as well.

Moreover, contrary to the opinions of Drs. Shafrir, Deth and Boris, I have also found that A.K. did not have an abnormal immune system. Doctor McCusker fully rebutted Dr. Shafrir's claims regarding Hashimoto's thyroiditis and myelin basic protein antibodies as well as Dr. Boris's specious diagnosis of common variable immunodeficiency. Dr. Deth likewise failed to establish that A.K.'s gastrointestinal complaints are significant to his immune status or otherwise contributed to the cause of A.K.'s autism.

Additionally, A.K.'s MTHFR polymorphisms have not been shown to cause or contribute to autism as several of petitioners' experts claimed. Although some studies have suggested a possible *association* between MTHFR polymorphisms and autism, respondent's expert, Dr. Raymond, noted that the overall body of studies on the subject have generated conflicting findings. Moreover, Dr. Raymond also noted that most people with these polymorphisms experience no ill-effect, and that the only established consequence of these polymorphisms relates to cardiovascular health.

C. *Althen* Prong 3: A Proximate Temporal Connection.

Merely showing a proximate temporal connection between a vaccination and an injury is insufficient, standing alone, to establish causation. *Grant,* 956 F.2d at1148. A proximate temporal relationship, even when coupled with the absence of any other identified cause for the injury, is not enough to demonstrate probable cause under the Vaccine Act's preponderance standard. *Moberly*, 592 F.3d at 1323 (citing *Althen*, 418 F.3d at 1278). Therefore, since petitioners have failed to establish *Althen* prongs 1 and 2, they cannot prevail even if they did establish a temporal connection. Nonetheless, I note again that, as described above, respondent has established that A.K.'s speech delay and autism predated his vaccinations. Moreover, I have determined that A.K. did not regress following his vaccinations. These findings preclude any temporal relationship between the onset of A.K.'s ASD and his influenza vaccinations.[297]

D. *Loving* Factors: Significant Aggravation.

Although the above analysis is itself dispositive, since petitioners' claim is that "one or more vaccines significantly aggravated an underlying mitochondrial disorder" (Petition (ECF No. 237) ¶ 74), I will briefly address the additional *Loving* factors necessary to proving such a claim. To demonstrate aggravation of a pre-existing

[297] In their post-hearing brief, faced with respondent's evidence regarding the onset of A.K.'s ASD, petitioners alternatively cite earlier vaccinations administered in May of 2001 as potentially causal. ECF No. 297 at 125. Notwithstanding the fact that these vaccines were mentioned in the operative petition, this after-the-fact argument is patently insufficient. Petitioners cite to no medical opinion by any expert or treating physician in support of this claim. Moreover, the focus of this case has clearly been on A.K.'s two influenza vaccines in November and December of 2001. Indeed, petitioners' experts not only failed to opine that these earlier vaccines contributed to A.K.'s condition, they explicitly based their causation opinions on the temporal relationship they believed was present between the November and December 2001 influenza vaccines and A.K.'s alleged regression. In fact, Dr. Shafrir explicitly confirmed during the hearing that he was not opining that the May 2001 vaccines were casual. Tr. 527-28.

condition, petitioners must show: (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. *See Loving,* 86 Fed. Cl. at 144 (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.,* 704 F.3d at 1357 (applying the six-part *Loving* test).

Petitioners claim fails under this analysis first and foremost, because petitioners have failed to establish that A.K. had any mitochondrial disease or defect at all. That is, they have failed to show that A.K. even had the condition they allege to have been aggravated. Moreover, to the extent petitioners claim that the aggravation ultimately resulted in ASD with onset post-dating his vaccinations, respondent has established that A.K.'s ASD predated his vaccinations. Thus, petitioners have failed to establish both of the first two Loving factors relating to A.K.'s condition before and after the vaccination. That is, petitioners have failed to establish that A.K. was in two distinct states before and after the vaccination rather than experiencing an ongoing disorder, albeit one with a naturally variable course.[298]

Moreover, even if A.K. did have a mitochondrial disorder, petitioners still would have failed to show that A.K.'s current condition constitutes a significant aggravation of that disorder. As noted above, there is insufficient evidence to suggest that mitochondrial decompensation results in autism or autism-like features. Moreover, as noted in the *Althen* analysis above, there is no evidence demonstrating that any of A.K.'s vaccinations would have been the cause of such aggravation.

XI. Conclusion.

ASD can be a devastating injury, and that is certainly true in A.K.'s case. Only a heartless individual could remain unmoved by the testimony of petitioners in this case. If sympathy alone were a basis to award compensation, such an award would certainly issue in this case.

It is not. Petitioners, like every other petitioner to claim that vaccines cause or substantially contributed to a condition that led to an ASD diagnosis, have been unable to muster preponderant evidence in support of vaccine causation. As such, I have no choice but to dismiss their vaccine injury claim.[299]

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[298] To the extent petitioners argue in the alternative that A.K. may have had minor pre-existing developmental delays that were subsequently exacerbated by his influenza vaccines (ECF No. 297 at 128-30), I further note that I have found that A.K. did not regress in the manner petitioners alleged.

[299] I am aware of two cases in which petitioners have prevailed on a Table injury theory, where the child in question developed an acute encephalopathy meeting the strict Table definition of that condition, within the requisite time frame after administration of specific vaccinations. One is the Poling case, discussed at length in the motions ruling in this case and in this decision, in which respondent conceded the Table injury. The other is a recent decision I issued in *Wright v. Sec'y, HHS*, No. 12-423V (Fed. Cl. Spec. Mstr. Sept. 21, 2015) (ECF No. 83), in which respondent contested the presence of a Table injury. In another case, *Banks v. Sec'y*, *HHS*, No. 02-738V, 2007 WL 2296047 (Fed. Cl. Spec. Mstr. Jul. 20, 2007),

This case is dismissed. The Clerk shall enter judgment accordingly.

IT IS SO ORDERED.

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

petitioners prevailed on their theory that the viral vaccine administered to the child caused encephalitis, which manifested with symptoms sufficient to warrant an ASD diagnosis. None of those cases resemble the facts and theories proposed in this case.