

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

DOUG PALUCK and RHONDA PALUCK *
as parents and natural guardians on behalf *
of their minor son, KARL PALUCK, *

Petitioners, *

v. *

SECRETARY OF HEALTH *
AND HUMAN SERVICES, *

Respondent. *

No. 07-889V
Special Master Christian J.
Moran

Filed: December 14, 2011

Entitlement; mitochondrial
disorder; reactive oxygen
species; oxidative damage.

Sheila A. Bjorklund, Lommen Abdo Law Firm, Minneapolis, MN, for petitioners;
Chrysovalantis P. Kefalas, United States Department of Justice, Washington, DC,
for respondent.

DECISION DENYING ENTITLEMENT¹

¹ Because this published decision contains a reasoned explanation for the special master's action in this case, the special master intends to post it on the United States Court of Federal Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002).

All decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When a decision is filed, a party has 14 days to identify and to move to delete such information before the document's disclosure. If the special master, upon review, agrees that the identified material fits within the categories listed above, the special master shall

Doug and Rhonda Paluck allege that vaccinations given to their son, Karl, affected his neurological development. The Palucks seek compensation from the National Childhood Vaccine Injury Compensation Program. 42 U.S.C. § 300aa—10 et seq. (2006).

Karl’s medical history is relatively straightforward.² From when he was born in January 2004 until he was approximately eight months old, Karl appeared to be developing normally. Concerns that something might be wrong with Karl started in September 2004, when he was referred for a developmental assessment. Starting around this time, Karl began to suffer symptoms consistent with viral infections, which waxed and waned over the next few months. Eventually, Karl’s doctors diagnosed him with erythema multiforme. Erythema multiforme is a condition in which a red rash develops due to a reaction “to factors such as viral skin infections . . . agents (including drugs) that are ingested or irritate the skin; [or] malignancy.” Dorland's Illustrated Medical Dictionary (31st ed. 2007) at 651.

On January 19, 2005, Karl received a set of vaccinations, including the mumps-measles-rubella vaccine, the varicella vaccine and Prevnar vaccine. The Palucks contend here that these vaccinations altered Karl’s developmental course.

In March 2005, Karl’s pediatrician noticed deterioration in Karl’s neurological abilities. A neurologist in April 2005 concurred and assessed Karl as having “delayed development.” After these evaluations, there is relatively little information about Karl’s status from May to early July 2005.

On July 12, 2005, Karl experienced his first seizure. Karl has continued to have seizures since then. During his various hospitalizations, Karl’s doctors have attempted to determine what has caused Karl’s problems. They have suggested that Karl suffers from a mitochondrial disorder.

Mitochondria are organelles (parts of cells) that provide energy to the cells, through a process known as oxidative phosphorylation. Dorland’s at 1187. Different cells contain different number of mitochondria because cells that require more energy need to have more mitochondria. Brain cells, for example, consume relatively large amounts of energy and have more mitochondria. Tr. 57-58.

delete such material from public access. 42 U.S.C. § 300aa–12(d)(4); Vaccine Rule 18(b).

² More details about Karl’s history appear in section IV, below.

Medical science is learning more about mitochondria and how dysfunction in mitochondria affects people. “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. Together, these disorders constitute the most common neurometabolic disease of childhood.” Exhibit E (Richard H. Haas et al., “Mitochondrial Disease: A Practical Approach for Primary Care Physicians,” 120 Pediatrics 1326, 1326 (2007)). “Mitochondrial diseases are usually progressive and multisystemic. Typically affected organs are those with a high energy demand, including . . . the central nervous system.” Id. at 1327. When the impaired organ is the brain, a mitochondria defect can affect the “early postnatal development.” Exhibit 21, tab MM (Mark P. Mattson et al., “Mitochondria in Neuroplasticity and Neurological Disorders,” 60(5) Neurons 748 (2008)) at 4.

In this litigation, the Palucks maintain that January 2005 vaccinations made Karl’s mitochondrial disorder worse than it would have been but for the vaccinations.³ To support this position, the Palucks have presented the testimony of Richard Frye, a pediatric neurologist. The Secretary has countered with the opinion of S. Robert Snodgrass, another neurologist.

The Palucks argue that Dr. Frye’s testimony meets the burden set forth in Althen v. Sec’y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005) (identifying three elements). However, for the reasons set forth extensively below, the Palucks have failed to establish any of the required three elements. For the first prong of Althen, the Palucks have not persuasively explained how vaccinations affect mitochondrial function. For the second prong of Althen, Dr. Frye’s testimony does not fully take into account Karl’s health before and after the January 2005 vaccinations. For the third prong of Althen, the Palucks’ case is not persuasive because even if Dr. Frye’s theory were found to be reliable, the theory suggests that Karl’s developmental status would have deteriorated much earlier than it actually did. Consequently, the Palucks have not met their burden of proof and the Clerk’s Office is instructed to enter judgment in accord with this decision unless a motion for review is filed.

³ The Palucks do not allege that the vaccinations caused Karl’s mitochondrial disorder. Tr. 80-81.

I. Procedural History

The case started when the Palucks filed their petition on December 21, 2007. They submitted their first set of medical records approximately one month later. The Palucks continued to gather medical records, which they filed periodically. When they had collected all medical records for Karl, the Palucks filed an amended petition on October 17, 2008.

The Palucks continued to develop their case by filing, on March 31, 2009, the report of Dr. Frye. Dr. Frye received certifications in general pediatrics and neurology with special competence in child neurology in 2004. In 2006, he taught at the University of Texas and in 2007, he was the director of the “Medically-Based Autism Clinic” affiliated with the University of Texas. He has written articles for a range of publications on a diverse set of topics including autism and mitochondrial dysfunction. Exhibit 17a (curriculum vitae).

Dr. Frye’s March 31, 2009 was the first in a series of submissions from Dr. Frye. As discussed below, additional reports were needed to fill gaps in the previous report. The first report is approximately one page. On its face, Dr. Frye’s first report could not carry the Palucks’ burden under Althen. At its most basic level, the report does not assert that vaccines caused Karl’s degeneration. Dr. Frye states that “Karl appeared to demonstrate developmental regression followed by a plateau in his regression, suggesting that an environmental insult that [] Karl was exposed to during this time could have triggered the ongoing mitochondrial based neurodegeneration.” Exhibit 16. Additionally, the report fails to provide information responsive to the other Althen prongs. The report does not offer a theory explaining how a vaccine could trigger the neurodegeneration. The report also does not propose the temporal interval that the medical community would expect to see between a vaccination and the onset of neurodegeneration.

Dr. Frye’s March 31, 2009 report was discussed during a status conference on May 13, 2009. See Vaccine Rule 5. During this status conference, the Palucks stated that a supplemental report from Dr. Frye was appropriate.

The Palucks presented this supplemental report on July 17, 2009. This report suffers from containing too much information in that the report discusses points that Dr. Frye would eventually discard. For example, Dr. Frye cited studies about autoimmunity, exhibit 21 at 1, but Dr. Frye did not present a theory about autoimmunity during his initial testimony. See tr. 164-67. Similarly, Dr. Frye mentions thimerosal, but that is also not pursued here. Tr. 11. Dr. Frye also cited

materials on which experts in the Vaccine Program do not usually rely – a newspaper article and a press release.

Notwithstanding the extraneous information, the July 17, 2009 report disclosed the theory that the Palucks eventually pursued. See Pet'r Br., filed Feb. 18, 2011, at 14 (summarizing Dr. Frye's theory of causation). Dr. Frye asserted that to function properly, mitochondria need to eliminate excessive reactive oxygen species. Dr. Frye also asserted that immunizations can increase the amount of reactive oxygen species, and, in effect, overwhelm the mitochondria. Dr. Frye maintained that Karl, who has a mitochondrial defect, was especially vulnerable to the effects of an immunization. Dr. Frye stated "It is very likely that exogenously provoked metabolic disturbances from environmental insult, in [this] case vaccines, resulted in the uncovering of his genetic susceptibility to push a mild subclinical disorder to a serious clinic[al] disorder with neurodegeneration." Exhibit 21 at 3. Dr. Frye also stated that Karl's case was comparable to another case, the Hannah Poling case, in which a vaccination preceded developmental regression. Dr. Frye's July 17, 2009 report cited 24 articles. Relatively few of these articles addressed the issue that turned out to be a critical part of Dr. Frye's theory – reactive oxygen species.

The Secretary, in turn, responded to Dr. Frye's reports by obtaining a report from another pediatric neurologist, S. Robert Snodgrass. Dr. Snodgrass received his board certification in neurology with special competence in child neurology in 1975. Since then, Dr. Snodgrass has taught at various institutions affiliated with Harvard Medical School, the University of Southern California, the University of Mississippi, and the University of California at Los Angeles. Dr. Snodgrass has written numerous articles. Exhibit B (curriculum vitae).

Dr. Snodgrass summarized Karl's medical treatment, including his treatment before receiving the January 2005 vaccinations. Dr. Snodgrass concluded that "Karl's illness began to cause symptoms gradually in the fall of 2004; it is associated with some kind of mitochondrial abnormality or dysfunction." Exhibit A at 5. This conclusion is at odds with the approach taken by Dr. Frye, whose two reports omitted any discussion of problems that Karl had before the vaccination.

Dr. Snodgrass also discussed Dr. Frye's July 17, 2009 report. Dr. Snodgrass reached the conclusion that "It is unlikely that immunizations aggravated Karl's pre-existing condition." The primary basis is that Karl's symptoms began in the fall 2004, before the vaccination. Exhibit A at 6-7. When Dr. Snodgrass wrote his

original report the importance of reactive oxygen species to Dr. Frye's theory was not clear and Dr. Snodgrass did not discuss reactive oxygen species in his original report at all.

In October 2009, a hearing was set for March 2010, in Houston. A pre-trial conference was held on March 4, 2010. Following this conference, the parties were directed to file certain documents into the record. For example, the Secretary filed her report, pursuant to Vaccine Rule 4, on March 15, 2010.⁴ The Palucks also submitted five additional medical articles.

The hearing commenced on March 22, 2010. Early in the hearing, the Palucks' counsel discovered that her office had not submitted approximately 20 articles on which Dr. Frye was relying but had not disclosed before the hearing. Nevertheless, a good amount of Dr. Frye's testimony was devoted to explaining how vaccines lead to the production of reactive oxygen species and how an abnormal amount of reactive oxygen species can deleteriously affect the functioning of mitochondria. To help explain these connections, Dr. Frye referred to a set of slides that were later filed into the record as exhibit 26. Dr. Frye's oral testimony presented information that was much more detailed than he had presented in his pre-trial reports. After Dr. Frye testified for most of March 22, 2010, the Secretary presented just the beginning of Dr. Snodgrass's testimony.

After the March 22, 2010 session of the hearing, a scheduling order was issued. Pursuant to this order, the Palucks filed the articles that Dr. Frye had identified.⁵ The Secretary submitted a supplemental report from Dr. Snodgrass. In this report, Dr. Snodgrass generally responded to Dr. Frye's March 22, 2010 testimony. In particular, Dr. Snodgrass discussed the significance of a fever after a vaccination and the function of oxidative stress. Dr. Snodgrass also repeated and

⁴ The filing of the Secretary's report just before the start of a hearing reflects an oversight. Typically, the Secretary's report is filed either when the medical records are complete or in conjunction with the report of any expert retained by the Secretary. In any event, the late submission of the Secretary's report did not prejudice the Palucks because Dr. Snodgrass's report placed them on notice as to the Secretary's position.

⁵ When the Palucks filed the articles, they filed only the articles. They did not provide a supplemental report from Dr. Frye explaining the significance of those articles. Eventually, the Palucks explained the relevance of the cited articles in a document filed as exhibit 30.

expanded his point that Karl was having health problems in the fall 2004, before he was vaccinated. Finally, Dr. Snodgrass argued that Karl's case is not comparable to Hannah Poling's case. Exhibit N. The Secretary also submitted other material, including medical articles, into the record.

The Secretary's submission included two exhibits that the Palucks attempted to have struck from the record. These exhibits, exhibit U and exhibit V, were excerpts of the testimony of Jackson Roberts, M.D. and Dean P. Jones, Ph.D., respectively. Both Dr. Roberts and Dr. Jones testified during the Omnibus Autism Proceeding in the cases presenting theory two.⁶ The Palucks argued in their July 16, 2010 motion that this testimony should not be considered evidence in their case.

The Palucks' motion was discussed in a July 19, 2010 status conference during which the undersigned stated that he had read the decisions regarding theory two. Those decisions, in turn, summarized testimony from Dr. Roberts and Dr. Jones.⁷ The Palucks argued that any reliance on the OAP testimony would, unfairly, deny them the opportunity to cross-examine Dr. Roberts and Dr. Jones. The Secretary, in turn, maintained that the OAP testimony was akin to articles published in a medical journal that special masters typically evaluate even though the authors rarely testify. The Palucks' motion was temporarily denied. The primary basis for denying the motion was to see whether Dr. Snodgrass relied upon the information presented by Dr. Roberts and Dr. Jones in Dr. Snodgrass's testimony. Order, filed July 21, 2010.

The second session of the hearing was held on July 26 and July 27, 2010. The hearing was conducted by videoconferencing as permitted by Vaccine Rule 8(b)(2). During this hearing, Dr. Snodgrass challenged the reliability of the theory presented by Dr. Frye. Dr. Snodgrass discussed oxidative stress and focused on Karl's history. The Palucks also renewed their motion to strike the submission of

⁶ "Theory two" refers to the theory that mercury from thimerosal in some vaccines can cause autism. Dwyer v. Sec'y of Health & Human Servs., No. 03-1202, 2010 WL 892250, at *1 (Fed. Cl. Spec. Mstr. March 12, 2010).

⁷ Dwyer, 2010 WL 892250, *passim*; King v. Sec'y of Health & Human Servs., No. 03-584, 2010 WL 892296, at *55-61 (Fed. Cl. Spec. Mstr. March 12, 2010); Mead v. Sec'y of Health & Human Servs., No. 03-215V, 2010 WL 892248, at *67-80 (Fed. Cl. Spec. Mstr. March 12, 2010).

the testimony of Dr. Roberts and Dr. Jones. This oral motion was also denied. Tr. 269-70; tr. 590-91.

Although the parties had anticipated that a second and third day of testimony would be sufficient to complete the testimony of Dr. Snodgrass and Dr. Frye, another day of testimony was required. During the interlude in the hearing, the parties again filed additional medical articles. For example, the Palucks filed, on September 15, 2010, exhibit 30, which summarized the medical articles on which Dr. Frye relied. Some of these articles related to oxidative stress, a theory that Dr. Frye had mentioned in his July 17, 2009 report and about which he had testified on March 22, 2010. These recently filed articles were discussed during the November 8, 2010 hearing.⁸ Dr. Snodgrass and Dr. Frye completed their oral testimony during this session. However, Dr. Snodgrass referred to an article that was not included in the record. Thus, Dr. Frye was permitted to file a brief report (exhibit 40) and Dr. Snodgrass responded (exhibit BB).

In sum, the amount of evidence in this case is unusually large for a case in the Vaccine Program. The Palucks filed multiple reports from Dr. Frye and more than 50 medical articles on which he relied. The Secretary filed three reports from Dr. Snodgrass and approximately 25 medical articles. The transcript runs 836 pages.

Once the evidentiary record was complete, the parties filed briefs. The Palucks and the Secretary filed initial briefs simultaneously, and both parties filed reply briefs simultaneously. With the filing of the reply briefs, the case is ready for adjudication.

II. Standards for Adjudication

There are at least three distinct parts to evaluating whether a petitioner is entitled to compensation. One part is to articulate the elements of the petitioner's case. These elements are "what" petitioner must establish. A separate part of the analysis is the quantum of evidence that a petitioner must introduce, which is the

⁸ Shortly before the last session of the hearing, the Palucks filed a motion for an award of attorneys' fees and costs on an interim basis. That motion led to a decision, awarding them attorneys' fees and costs. Interim Fees Decision, 2011 WL 1515698 (Fed. Cl. Spec. Mstr. March 30, 2011).

burden of proof. A final aspect is the process of weighing or evaluating the evidence that is submitted. These three portions are discussed separately.

A. Elements of Petitioner's Case

To receive compensation under the Program, the Palucks must prove either: (1) that Karl suffered a "Table Injury"--*i.e.*, an injury falling within the Vaccine Injury Table – corresponding to a vaccine that he received, or (2) that Karl suffered an injury that was actually caused by one of the January 2005 vaccines. See 42 U.S.C. §§ 300aa-13(a)(1)(A) and 300aa-11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1320 (Fed. Cir. 2006). Here, the Palucks are not claiming an injury listed on the Vaccine Table. Therefore, they must prove causation in fact.⁹

When a petitioner proceeds on a causation-in-fact theory, a petitioner must establish three elements. The petitioner's

burden is to show by preponderant evidence that the vaccination brought about [the] injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.

⁹ The parties dispute whether the Karl's case presents a claim for a new injury or a claim for the significant aggravation of a pre-existing condition. The Palucks put forward the standards for adjudicating a claim that a vaccine caused a [new] condition. Pet'r Brief at 23 (citing Althen); Pet'r Reply at 6 ("Petitioners maintain that their claim is an off-Table injury, subject to the three elements of proof of causation as pronounced by the Federal Circuit in Althen.").

In contrast, the Secretary cites to the legal standards for adjudicating cases claiming that a vaccine significantly aggravated an underlying condition. Resp't Brief at 23-24 (citing Loving v. Sec'y of Health & Human Servs., 86 Fed. Cl. 135, 144-45 (2009)). Because three elements from Loving are taken from Althen, this decision addresses those overlapping elements. See Hennessey v. Sec'y of Health & Human Servs., No. 01-190V, 2009 WL 1709053, at *42 (Fed. Cl. Spec. Mstr. May 29, 2009) (recommending an initial evaluation of the Althen factors in significant aggravation cases), motion for review denied, 91 Fed. Cl. 126 (2010).

Althen, 418 F.3d at 1278.

B. Burden of Proof

For the elements that petitioners are required to prove, their burden of proof is a preponderance of the evidence. 42 U.S.C. § 300aa-13(a)(1). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. Moberly v. Sec'y of Health & Human Servs., 592 F.3d, 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between “preponderant evidence” and “medical certainty” is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master’s decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge’s contention that the special master confused preponderance of the evidence with medical certainty). In this regard, “close calls regarding causation are resolved in favor of injured claimants.” Althen, 418 F.3d at 1280.

III. Althen Prong One -- Theory

To explain how the vaccines harmed Karl, the Palucks present a theory dependent upon relatively complex medical knowledge. Special masters have been instructed in how to evaluate this type of evidence.

A. Considerations of Medical Evidence

As Congress authorized, 42 U.S.C. § 300aa-12(d)(2), the judges of the Court of Federal Claims have issued the Vaccine Rules, collectively. The Vaccine Rules, in turn, provide that the special master “must consider all relevant and reliable evidence governed by principles of fundamental fairness to both parties.” Vaccine Rule 8(b)(1); see Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1339 (Fed. Cir. 2010).

Decisions by the Federal Circuit, which are binding precedent, 42 U.S.C. § 300aa-12(e), have provided additional guidance. Within the Vaccine Program, the Federal Circuit expected that special masters would “consider[] the relevant evidence of record, draw[] plausible inferences and articulate[] a rational basis for the decision.” Hines v. Sec’y of Health & Human Servs., 940 F.2d 1518, 1528 (Fed. Cir. 1991).

A particular topic on which the Federal Circuit has guided special masters is the process for evaluating the testimony of expert witnesses. The leading case on this topic is Terran. In Terran, the special master “examined” the expert’s opinion “in light of the four guideposts enumerated in Daubert,” and “conclude[d] that petitioner’s theory of causation is not based on reliable scientific evidence.” Terran v. Sec’y of Health & Human Servs., No. 95-451V, 1998 WL 55290, at *11 (Fed. Cl. Spec. Mstr. Jan. 23, 1998). When Ms. Terran’s appeal reached the Federal Circuit, she argued that “the Special Master improperly applied the Daubert factors to the expert’s testimony.” The Federal Circuit rejected this argument and indicated that the special master reasonably used “Daubert’s questions as a tool or framework for conducting the inquiry into the reliability of the evidence.” Terran v. Sec’y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999). As recognized in Terran, the Daubert factors for analyzing the reliability of testimony are:

- (1) whether a theory or technique can be (and has been) tested;
- (2) whether the theory or technique has been subjected to peer review and publication;
- (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and,
- (4) whether the theory or technique enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2, citing Daubert, 509 U.S. at 592-95.

After Terran, decisions from judges of the Court of Federal Claims have consistently cited to the Daubert criteria as useful in assessing an opinion that a vaccine can cause an injury. E.g. Snyder v. Sec’y of Health & Human Servs., 88 Fed. Cl. 706, 742-45 (2009); Cedillo v. Sec’y of Health & Human Servs., 89 Fed. Cl. 158, 182 (2009), aff’d, 617 F.3d at 1347; De Bazan v. Sec’y of Health & Human Servs., 70 Fed. Cl. 687, 699 n.12 (2006) (“A special master assuredly should apply the factors enumerated in Daubert in addressing the reliability of an expert witness’s testimony regarding causation.”), rev’d on other grounds, 539

F.3d 1347 (Fed. Cir. 2008); Campbell v. Sec'y of Health & Human Servs., 69 Fed. Cl. 775, 781 (2006); Piscopo v. Sec'y of Health & Human Servs., 66 Fed. Cl. 49, 54 (2005).

The reliability of the expert's theory is not presumed. 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 (citing Terran). Furthermore, the reliability of an expert's theory affects the persuasiveness of the evidence. Special masters may "inquir[e] into the reliability of testimony from expert witnesses. Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases." Id. at 1325 (citing Terran).

Petitioners' proffer of any theory does not satisfy their burden on this prong. If the special master finds that the expert's theory is supported by only an "ipse dixit," then the special master may reject this opinion. Snyder, 88 Fed. Cl. at 745, n.66 (2009) (quoting Gen. Elec. Co. v. Joiner, 522, U.S. 136, 146 (1997)); see also Cedillo, 617 F.3d at 1339 (also quoting Joiner).

In evaluating expert testimony and scientific literature, special masters should analyze scientific literature "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." Andreu, 569 F.3d at 1379. "In other words, a finding of causation in the medical community may require a much higher level of certainty than that required by the Vaccine Act to establish a prima facie case. The special master must take these differences into account when reviewing the scientific evidence." Broekelschen v. Sec'y of Health & Human Servs., 89 Fed. Cl. 336, 343 (2009), aff'd, 618 F.3d 1339 (Fed. Cir. 2010).

Generally, the Federal Circuit expects that a special master will present a reasonable basis for rejecting the opinion of an expert. Lampe, 219 F.3d 1361; Burns v. Sec'y of Health & Human Servs., 3 F.3d 415, 417 (Fed. Cir. 1993).

B. Overview of Palucks' Theory

The Palucks have concisely summarized their theory:

[V]accines, by intention, activate the immune system; this in turn leads to the development of potentially toxic elements within the body, namely reactive oxygen species (ROS) and reactive nitrogen species (RNS); ROS and RNS are usually balanced under normal conditions by the (antioxidant) systems of the body; however, if certain parts of the body, namely the mitochondria, are not working properly, more toxic elements will be produced and will be unchecked by antioxidants, resulting in oxidative stress, leading to a cascade of intracellular events leading to apoptosis or cellular death. Brain cells are more vulnerable to this process and with death of brain cells, neurodegeneration and developmental regression are likely.

Pet'r Br. at 25-26; accord id. at 14. For purposes of analysis, the theory can be divided into a series of simplified propositions. These are:

1. Vaccines stimulate the immune system;
2. The stimulated immune system produces reactive oxygen species and reactive nitrogen species;
3. In people with defective mitochondria, the reactive oxygen species accumulates leading to oxidative stress;
4. Oxidative stress causes cells to die;
5. The killed cells include brain cells and the death of brain cells causes developmental regression.

As discussed below, a critical link is the asserted connection between vaccines and oxidative stress. This step is important because some evidence supports other steps in Dr. Frye's theory. For example, it is commonly understood that immunizations protect from disease by stimulating a response from the immune system. Tr. 63 (Dr. Frye); tr. 429 (Dr. Snodgrass). Thus, the beginning of Dr. Frye's theory is supported.

Similarly, the end of Dr. Frye's theory also appears to have some support. At least in some circumstances, researchers have proposed that oxidative stress causes cell death.¹⁰ Dr. Frye and Dr. Snodgrass agreed that brain cells are

¹⁰ One specific example of how oxidative stress is believed to have deleterious effects is aging. However, the theory that oxidative stress causes aging

particularly vulnerable to oxidative stress. Tr. 69 (Dr. Frye); tr. 80 (same); tr. 428 (Dr. Snodgrass). Medical articles also support this finding. See exhibit Q (Tina Wenz, PGC-1 α Activation as a Therapeutic Approach in Mitochondrial Disease, 61(11) Life 1051, 1052 (2009)); exhibit 21, tab Z (John Shoffner et al., Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression, J. Child Neurol (2009)) at 1.

Consequently, for the Palucks to prevail, they must present preponderant evidence linking a vaccine's stimulation of the immune system to the production of oxidative damage, which may cause neurodegeneration. An analysis of this question requires some understanding of oxidative stress and the precursor to oxidative stress, reactive oxygen species.

has not been validated. Tr. 288; exhibit 21, tab N (Florian L. Mueller et al., Trends in oxidative aging theories, 42 Free Radical Biology & Med. 477 (2007)).

Additionally, in his testimony (tr. 70-72), Dr. Frye relied upon three articles, exhibit 21, tab EE (Douglas R. Green & Guido Kroemer, Cytoplasmic Functions of the Tumor Suppressor p53, 458(7242) Nature 1127 (2009)); exhibit 21, tab FF (Aaron K. Holley & Daret K. St. Clair, Watching the watcher: regulation of p53 by mitochondria, 5(1) Future Oncology 117-30 (2009)); and exhibit 21, tab QQ (Ruth A. Roberts et al., Nitrative and Oxidative Stress in Toxicology and Disease, 112(1) Toxicological Sci. 4 (2009)). There was relatively little testimony about these articles, although Dr. Snodgrass stated that Roberts is not relevant because that article does not discuss oxidative stress in the context of vaccination. See tr. 452-54; tr. 534-35.

C. Reactive Oxygen Species and Oxidative Stress¹¹

An explanation of reactive oxygen species begins with an understanding of chemical reactions.¹² When one atom reacts with another atom, one atom sometimes loses an electron to the other atom. The atom that is missing an electron is considered to be in a state of oxidation. The opposite of oxidation is "reduction," meaning that the atom has gained an electron. Tr. 667-71; Dorland's at 1376 (defining oxidation) and 1633 (defining reduction). When the specific atom that has lost an electron is an oxygen atom, the molecule is known as reactive oxygen species. Tr. 673-74. A similar term is oxygen radical. Dorland's at 1595; see also tr. 532 ("free radicals means things with an unpaired electron.").

Oxidized atoms (that is, atoms that are missing an electron) are unstable. They look to regain their balance by taking an electron from another atom. This sequence of losing an electron then gaining an electron could continue as a series of reactions. A state of perpetual reactivity is potentially dangerous. Normally,

¹¹ Preliminarily, it should be noted that although reactive oxygen species and oxidative stress are the links between vaccinations and neurodegeneration in the Palucks' theory, the evidence on this point was not as robust as it could have been. The principal source of information about reactive oxygen species and oxidative stress is testimony. The Palucks rely upon Dr. Frye. Pet'r Br. at 13-14. However, Dr. Frye did not describe himself as having any special background in reactive oxygen species and oxidative stress. Tr. 33-47 (testimony about Dr. Frye's qualifications); exhibit 17a (curriculum vitae); see also Pet'r Reply at 2 (describing Dr. Frye as "on the cutting edge of research and publication in the areas of mitochondrial disorders and neurodevelopmental regression"). Dr. Frye has not written any publications on oxidative stress. Tr. 159. Similarly, Dr. Snodgrass did not assert any great expertise in reactive oxygen species and oxidative stress. Tr. 245-252 (testimony about Dr. Snodgrass's qualifications); tr. 496.

Although both Dr. Frey and Dr. Snodgrass seem to have a working knowledge of reactive oxygen species and oxidative stress, the autism theory two cases demonstrate that some researchers focus in the field of reactive oxygen species and oxidative stress. See, e.g., King, 2010 WL 892296, at *20. Testimony from experts in this field would seem appropriate when reactive oxygen species and oxidative stress are key parts of the petitioners' theory.

¹² This case's evidence, which is summarized in the following paragraphs, is consistent with the description of reactive oxygen species in the theory two cases. See Dwyer, 2010 WL 892250, at *110-11.

the body is able to prevent the continuation of reactions because other substances (known as anti-oxidants) are capable of donating an electron without becoming unstable. See exhibit 26 (slide 2); tr. 65; tr. 286-87; tr. 676.¹³ An oxidized atom or free radical seeks another electron from something in its vicinity. Tr. 692.

The body regularly produces reactive oxygen species. When there is relatively more reactive oxygen species, the body is in a state of "oxidative stress." By definition, "oxidative stress" comes "in response to excessive levels of cytotoxic oxidants and free radicals in the environment." Dorland's at 1810. Oxidative stress occurs naturally. For example, exercise and drinking alcohol cause oxidative stress. Tr. 160; tr. 280; tr. 532 ; tr. 559. According to Dr. Snodgrass, "everything that lives in this oxygen atmosphere" undergoes oxidative stress. Tr. 279.

The effects of oxidative stress are neither clear nor consistent. Some experts believe that exercise is beneficial because it produces oxidative stress. Tr. 280; tr. 288; tr. 559; exhibit K (Melita M. Nasca et al., Increased Oxidative Stress in Healthy Children Following an Exercise Program: A Pilot Study, 31 J. Developmental & Behav. Pediatrics 386 (2010)). Dr. Frye acknowledged that oxidative stress is not the same as oxidative damage. Tr. 163; tr. 780. Although Dr. Frye recognized that oxidative stress does not always lead to oxidative damage, his theory is that vaccines cause oxidative damage at least in some children with mitochondrial defects. This background in reactive oxygen species, oxidative stress, and oxidative damage is the foundation for examining whether preponderant evidence supports a finding that vaccines can cause oxidative damage.

D. Vaccines and Oxidative Stress

Whether the immune system, when stimulated by a vaccine, causes oxidative stress (as opposed to reactive oxygen species) is an important question in this case. Here, there is a much more vigorous debate. The Secretary titles a significant section of her brief with the argument "Dr. Frye's hypothesis relies on an unsubstantiated link between routinely administered human vaccines and oxidative stress." Resp't Br. at 27.

¹³ One theory to explain cancer is that cancer involves excessive amounts of oxidized atoms. Thus, a way to combat cancer is to increase the amount of anti-oxidants. See exhibit 21, tab P (Ernest K.J. Pauwels et al., Antioxidants: A Tale of Two Stories, 20(9) Drug News Perspect 579 (2007)).

The Palucks' answer to this argument is to cite to Dr. Frye's testimony, which, in turn, relied primarily upon six articles filed as exhibit 37, tab A through exhibit 37, tab E. See Pet'r Reply at 26-27.¹⁴ Due to Dr. Frye's reliance on these articles, they will be discussed in some depth. See Andreu, 569 F.3d at 1379 (when medical literature “is submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination caused a particular injury.”); Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994). There is one article about a study on people, there is one abstract of a study on people, and there are four articles about studies on animals.

The lead author of the article that reports a study on people is Michael Phillips and the article was filed as exhibit 37, tab A (Michael Phillips et al., Effect of influenza vaccination on oxidative stress products in breath, 4 J. Breath Res. 026001 (2010)). Dr. Frye and Dr. Snodgrass strenuously debated the value of this study. Dr. Frye contended that the study showed that people experience oxidative stress for as long as 14 days after receiving a vaccination. Tr. 609-09. In contrast, Dr. Snodgrass maintained that the experiment was flawed. Exhibit BB (Supp. Rep't, filed Feb. 2, 2011) at 1.

In the 2010 study, Dr. Phillips and his team conducted an experiment on 33 people at an air force base. Preliminarily, each person produced a breath sample. Then, the researchers gave each person a dose of the live attenuated influenza vaccine, which comes in a mist form. On two, seven and 14 days after vaccination, the study participants produced additional breath samples. The breath samples were analyzed for the presence of volatile organic compounds. The researchers asserted that volatile organic compounds may be the result of increased oxidative stress.¹⁵ Exhibit 37, tab A (Phillips) at 1-2. The authors concluded that "Treatment with [live attenuated influenza virus] was accompanied by sustained changes in the abundance of [volatile organic compounds] in breath. . . . These findings were consistent with the altered endogenous manufacture of [volatile organic

¹⁴ The articles most directly relevant to whether vaccines cause oxidative stress were filed between the second and third sessions of the hearing.

¹⁵ The basis for asserting that an increase in oxidative stress results in an increase in volatile organic compounds is not entirely clear. Dr. Frye asserted that "several studies" have shown that the hydrocarbon compounds are products of fatty acids that are broken down by oxidative stress. Tr. 608.

compounds] as a physiological response by normal humans to a challenge with [live attenuated influenza vaccine]." Id. at 3.

When Dr. Snodgrass was asked to comment upon the 2010 Phillips study, Dr. Snodgrass stated: "Dr. Phillips in [Exhibit] 37A says LAIV vaccination in healthy humans elicited a prompt and sustained increase in breath biomarkers of oxidative stress. However, I don't believe that holds up if you look into it carefully." Tr. 756-57. Dr. Snodgrass criticized the Phillips study in three respects.

First, Dr. Snodgrass was concerned about drawing a conclusion that the increase in volatile organic compounds found after the vaccination was because of the vaccination. Dr. Snodgrass noted that the study did not appear to control for other variables, such as exercise, that may have affected the amount of volatile organic compounds. Tr. 757-58; tr. 810-11.

Second, Dr. Snodgrass questioned whether the volatile organic compounds studied by Dr. Phillips truly measured oxidative stress. For this criticism, Dr. Snodgrass relied upon a study reported by Dr. Phillips in 2003. Exhibit AA (Michael Phillips et al., Effect of Oxygen on Breath Markers of Oxidative Stress, 21 Eur. Respiratory J. 48 (2003)). Tr. 758-62; tr. 811-12. Dr. Snodgrass testified that "if we go back to his own work when he tried to establish markers in the breath for oxidative stress, these changes that he found do not correspond to what he has published in the past" and "if you go back through Dr. Phillips' own work there appears to be a contradiction between what he confidently says now is evidence of oxidative stress and what he has published in the past." Tr. 761-62.

Third, Dr. Snodgrass differentiated the type of vaccine used in the 2010 Phillips study (a nasal spray) from the vaccines that Karl received in January 2007. Tr. 762.

The Palucks responded to Dr. Snodgrass's criticisms of the Phillips paper. Dr. Frye testified briefly, tr. 814-16, and submitted a supplemental expert report, exhibit 40. The Palucks argue that the Phillips paper was "a peer reviewed article, published in a respected medical journal and relied upon by scientists and medical professionals," and that Dr. Snodgrass's arguments "are rambling, speculative ipse dixit arguments wholly off the mark." Pet'r Reply at 11-12.

The most salient of Dr. Snodgrass's criticisms is whether volatile organic compounds demonstrate oxidative stress. Dr. Snodgrass has stated, without any

contradiction, that the volatile organic compounds measured in the 2010 study are not the same as the volatile organic compounds discussed in the 2003 study. This difference means that the volatile organic compounds used in 2010 have not been shown to measure oxidative stress. Although the Palucks charge Dr. Snodgrass with making a "rambling, speculative" argument, this characterization is not accurate. Dr. Snodgrass pointed to a specific gap in the Phillips study and the Palucks have not filled this gap. Dr. Frye asserted that there are studies to validate the methodology, tr. 608, but Dr. Frye did not identify those studies even after writing a supplemental report addressing Dr. Snodgrass's criticisms, see exhibit 40.

The absence of information showing that volatile organic compounds can be used as a measurement for oxidative stress is also notable because other methods to measure oxidative stress are available. The best way to detect oxidative stress is to measure the level of a substance known as F2-isoprostane. Tr. 280; tr. 435-37; tr. 579; tr. 608; tr. 697. F2-isoprostanes can be found in urine, which makes testing for oxidative stress non-invasive. Tr. 436. According to Dr. Snodgrass, this type of testing would make the Phillips study more credible. Exhibit BB at 1-2.

The other evidence submitted by the Palucks regarding vaccinations and oxidative stress was not as informative as the Phillips study. One exhibit is merely an abstract of approximately 400 words. Dr. Frye stated that an abstract is usually peer-reviewed, although he did not have any specific information about this journal's practice. Tr. 749-49; see also tr. 212 (Dr. Frye's testimony that whether poster presentations are peer-reviewed depends upon the organization sponsoring the meeting); tr. 680. Dr. Snodgrass asserted the opposite. Dr. Snodgrass said that abstracts from conferences (sometimes known as poster presentations) are not peer-reviewed. Tr. 771-72. Testimony reported in another special master's decision supports Dr. Snodgrass's view. Hennessey, 2009 WL 1709053, at *32 n.112 . Whether this abstract was subject to peer-review is just one factor to consider in evaluating it. See Daubert, 509 U.S. at 593-94 (citations omitted).

In the experiment reported in this abstract, Dr. Ratanamaneechat and colleagues gave H1N1 influenza vaccination (in either a 15 mcg dose or a 30 mcg dose) to 33 people with severe asthma and 25 people with non-severe asthma. Approximately 60 percent of the people who received a dose of the vaccine reported having an adverse event (usually related to their respiratory system) within 42 days of receiving the vaccination. Exhibit 37, tab F (S. Ratanamaneechat, Serum Superoxide Dismutase Activity as a Predictor of Adverse Events After H1N1 Vaccination, 181 Am. J. Respiratory & Critical Care Med. A6791 (2010)).

To Dr. Frye, the Ratanamaneechat study showed that people who "may have increased oxidative stress, . . . were more vulnerable to actually have adverse effects from the vaccine." Tr. 610. The Secretary argues that "Dr. Frye oversimplified and overstated the results of this study." Resp't Br. at 37.

The Secretary's argument with regard to the Ratanamaneechat study is accurate. As discussed by Dr. Snodgrass, a flaw in the Ratanamaneechat experiment is that the study lacked any controls, meaning people who were similar to the participants but who did not receive the vaccine. Tr. 771. Control groups are a basic part of scientific experiments. "[O]utcome figures from a treatment group without a control group reveal very little and be misleading. Comparisons are essential." David H. Kaye and David A. Freedman, "Reference Guide on Statistics" in Reference Manual on Scientific Evidence (2d ed. 2000) at 93.¹⁶ Here, without knowing the incidence of respiratory events among asthmatics who did not receive an H1N1 vaccination, the report that approximately 60 percent of 58 people did have some adverse event is not meaningful. Without a control group, the Ratanamaneechat study is not a work on which a persuasive expert opinion can be based.

The other bases for Dr. Frye's opinion that vaccines lead to the production of oxidative stress are four articles reporting results of studies on animals.¹⁷ See tr. 603-07; Pet'r Reply at 11 n.8. Whether the Palucks find these articles to be

¹⁶ This point is repeated in the recently published third edition of the Reference Manual on Scientific Evidence. David H. Kaye and David A. Freedman, "Reference Guide on Statistics" in Reference Manual on Scientific Evidence (3d ed. 2011) at 220.

¹⁷ These are exhibit 37, tab B (Sindhu Saraswathy & Narsing A. Rao, Photoreceptor Mitochondrial Oxidative Stress in Experimental Autoimmune Uveitis, 40 Ophthalmic Res. 160 (2008)); exhibit 37, tab C (Guey-Shuang Wu et al., Photoreceptor Mitochondrial Tyrosine Nitration in Experimental Uveitis, 46(7) Investigative Ophthalmology & Visual Sci. 2271 (2005)); exhibit 37, tab D (E. Philip Jesudason et al., Anti-inflammatory effect of melatonin on A β vaccination in mice, 298 Molecular & Cellular Biochemistry 69 (2007)); and exhibit 37, tab E (Asuncion Ramos et al., Evolution of oxidative/nitrosative stress biomarkers during an open-field vaccination procedure in sheep: Effect of melatonin, 133 Veterinary Immunology & Immunopathology 16 (2010)).

meaningful is not clear. After respondent's brief presented a fairly lengthy attack on these four articles, see Resp't Br. at 30-34; the Palucks did not defend the relevance of the animal studies. The Palucks mentioned them only in a sentence appearing in a footnote of their reply brief. Pet'r Reply at 11 n.8. Nevertheless, they have been considered. Dr. Snodgrass persuasively demonstrated that each of these animal studies provides little basis for opining that vaccines lead to the production of oxidative stress in humans. Tr. 763-70; see also tr. 435-36.

In addition to asserting that vaccines cause oxidative stress in everyone, the Palucks appear to present a more limited theory, that people with mitochondrial defects experience oxidative stress from vaccines. The Palucks assert that "if certain parts of the body, namely the mitochondria, are not working properly, more toxic elements will be produced and will be unchecked by antioxidants, resulting in oxidative stress." Pet'r Br. at 25. The Palucks' briefs omit any extensive discussion about whether people who have mitochondrial defects respond to vaccines differently from otherwise healthy people. Nevertheless, an independent review of the record reveals that Dr. Frye presented this theory in his expert report. Exhibit 21 at 2. The most comprehensive testimony from Dr. Frye on this point appears to be from the first day of the hearing when Dr. Frey presented his slides. See tr. 73-75; see also tr. 200.¹⁸

There are two difficulties with asserting that people with mitochondrial disorders are more vulnerable to developing oxidative stress due to a vaccination. First, mitochondrial disorders are variegated. What happens in one mitochondrial

¹⁸ During a cross-examination of Dr. Frye, the following exchange took place:

Q: [F]or your hypothesis, do you need mitochondrial dysfunction? Do you need a finding of mitochondrial dysregulation or disorder?

A: That's what it appears to be. The cases seem to be linked to mitochondrial dysfunction. Could there be other reasons that we could think about? If you have severe over-activation of the immune system with some type of immune abnormality, that could be something. If you have some type of abnormality in the antioxidant system where you have actually, . . . no protection, . . . that's a possibility, too. So there's many possibilities, but what seems to be the – the empirical evidence seems to suggest that mitochondrial dysfunction is one of the key pieces.

Tr. 200-01.

disorder may not happen in the next person with a mitochondrial disorder. Tr. 286; exhibit 21, tab Z (Shoffner) at 4. Second, exercise, which causes oxidative stress (tr. 280; tr. 288), produced beneficial effects in people with mitochondrial DNA mutations. Exhibit S (Julie Murphy et al., Resistance training in patients with single, large-scale deletion of mitochondrial DNA, 131 Brain: J. Neurology 2832 (2008)); see also tr. 347-48; tr. 450. Based upon this article, the Secretary argues that "Dr. Frye's contention has no objective support and is objectively contradicted." Resp't Br. at 40. The Palucks did not address the Murphy article in their reply. To the extent that the Palucks' theory is premised on an assertion that people with a mitochondrial disorder respond differently to vaccines than other people, the Palucks have not presented persuasive evidence for this point.

E. Additional Evidence

Section D discussed evidence pertaining to the step in the Palucks' theory that vaccines cause oxidative stress. As such, section D is like examining a tree in the forest. Other evidence is relevant to the overall theory that vaccines cause neurodevelopmental problems. This other evidence is like examining the forest. The evidence relating to the general point includes an article about vaccination and mitochondrial disorders, an article about Hannah Poling, and an article containing a series of cases.

1. Barshop

In this study, the authors surveyed members of the Society for Inherited Metabolic Disorders to ascertain their views about the effects of vaccination on metabolic diseases, including ones with a mitochondrial dysfunction. The number of people responding to the e-mail survey was 111.¹⁹ It appears that the consensus view of the respondents was that vaccines do not affect metabolic diseases. The authors reported that:

[It] is clear that the general opinion held by practitioners in the field of Clinical Biochemical Genetics favors the full schedule of vaccination for their patients. The overwhelming majority also feel that the benefits of the

¹⁹ The authors describe the people responding to the survey as "specialists in the field of Medical Biochemical Genetics," most of whom were board certified in pediatrics, biochemical genetics, and/or medical genetics.

current schedule outweigh the risks to individuals with undiagnosed metabolic disease. Most have never observed any significant adverse event which was attributed to a vaccine reaction. Some respondents have seen the association once or seldom in their careers, but none felt it to be frequent. The fact that there were few encountered events of long-term deterioration due to a disease for which vaccination is available probably simply reflects the low incidence of those diseases, due to the effectiveness of vaccination practices. A panoply of questions remain, however, and there is a great need for more data.

Exhibit 21, tab A (Bruce A. Barshop & Marshall L. Summar, Attitudes regarding vaccination among practitioners of clinical biochemical genetics, 95 *Molecular Genetics & Metabolism* 1 (2008)).

Dr. Frye was questioned about this study during the first session of the hearing. Dr. Frye stated the people responding to the survey probably had not heard of the Hannah Poling case. Tr. 188-89. However, a report about the Hannah Poling case actually prompted the survey. Exhibit 21, tab A (Barshop) at 1.

The information presented in the Barshop article is responsive to one of the criteria identified by the Supreme Court for assessing the reliability of an expert's opinion, which is whether a theory is generally accepted in the relevant scientific community. See Daubert, 509 U.S. at 594. Special masters may use this criterion in weighing the persuasiveness of an expert's testimony in the Vaccine Program. Moberly, 592 F.3d at 1324; Terran, 195 F.3d at 1316. The general acceptance of a theory is not dispositive in determining its reliability, Andreu, 569 F.3d at 1378-79, but can be probative, Terran, 195 F.3d at 1316.

2. Hannah Poling

The Palucks cite to the case of Hannah Poling as supporting the theory that a person with a mitochondrial defect is more vulnerable to environmental stressors that can cause a metabolic decompensation. Pet'r Brief at 21. This argument is based upon testimony from Dr. Frye. Tr. 121-23; tr. 141; tr. 181; tr. 189-94; tr. 240; tr. 620; tr. 715-16.

The information about Hannah Poling comes from an article that reports details about her. See exhibit 21, tab Q (Jon S. Poling et al., Developmental Regression and Mitochondrial Dysfunction in a Child With Autism, 21(2) J. Child Neurology 170 (2006)); see also tr. 477 (testimony of Dr. Snodgrass). The authors of this paper were Dr. Jon Poling, who is Hannah’s father; Dr. Frye, who knew Dr. Poling in medical school; Dr. John Shoffner, who authored another paper on which the Palucks rely; and one other doctor. Tr. 121; tr. 123; tr. 208.²⁰ The parties appear not to rely upon information about Hannah that became known to the public through her case in the Vaccine Program.²¹

²⁰ After the journal learned that Hannah’s father had a financial interest in her case because of the claim in the Vaccine Program, the journal commented that Dr. Poling should have disclosed his interest. Exhibit X (Jon S. Poling, Correspondence on “Developmental Regression and Mitochondrial Dysfunction in a Child with Autism, 23(9) J. Child Neurology 1089 (2008)). This criticism did not question the accuracy of the information presented in the article co-written by Dr. Poling. See id.; see also tr. 715.

²¹ The Office of Special Masters has made two documents from the Poling case available to the public. The first is a ruling on a motion to release information. Poling ex rel. Poling v. Sec’y of Health & Human Servs. No. 02-1466V, 2008 WL 1883059, at *1 (Fed. Cl. Apr. 10, 2008). The second is a decision awarding attorneys’ fees and costs to the Polings. Poling ex rel. Poling v. Sec’y of Health & Human Servs. No. 02-1466V, 2011 WL 678559, at *1 (Fed. Cl. Jan. 28, 2011).

These documents indicate that the Secretary conceded that the Polings were entitled to compensation because Hannah suffered an on-Table injury. The special master in Poling did not have occasion to determine whether a preponderance of the evidence shows that vaccines cause regression in children with mitochondrial defects because causation is presumed in on-Table cases. See Cedillo, 617 F.3d at 1335. In contrast, the Palucks have not alleged that Karl suffered an on-Table injury. Thus, the legal standards for establishing causation are completely different. Shalala v. Whitecotton, 514 U.S. 268, 270-71 (1995); Grant v. Sec’y of Health & Human Servs., 956 F.2d 1144, 1147 (Fed. Cir. 1992) (stating “[t]he Vaccine Act distinguishes Table injuries, which presume causation, from injuries requiring proof of causation by the vaccine.”). The Palucks’ plea that justice demands that the result in their case match the result in Hannah’s case (Pet’r Reply at 19) overlooks the distinction between on-Table and off-Table cases.

An abbreviated summary of Hannah’s case as set forth in the articles cited above is that she appeared to be developing normally for her first 19 months. Then, she received a set of vaccinations and, within 48 hours, developed a fever. The fever lasted 12 days. Within four days, Hannah lost her ability to climb stairs. She developed behaviors consistent with autism. A muscle biopsy revealed that she had a mitochondrial disorder, which presumably was present when she was born. In the four years after her initial regression, she made “slow yet steady improvements” in various areas. Exhibit 21, tab Q (Poling).²²

Based upon Hannah’s experience, the authors retrospectively evaluated records from approximately 250 children with autism or other neurologic disorder. The authors searched laboratory reports for measurements of liver function. The researchers determined that levels of a particular liver enzyme, aspartate aminotransferase, were much higher in autistic children than in non-autistic children. *Id.* at 171. Given other laboratory studies, the authors stated that the elevation in aspartate aminotransferase “might reflect abnormal mitochondrial function in skeletal muscles.” *Id.* at 172.²³

The article presents a qualified opinion about a link between mitochondrial disorders, vaccination and autism.

This patient exemplifies important questions about mitochondrial function in autism and developmental regression. . . . If such [mitochondrial] dysfunction is present at the time of infections and immunizations in young children, the added oxidative stresses from immune activation on cellular energy metabolism are likely to be especially critical for the central nervous system, which is highly dependent on mitochondrial

²² Dr. Snodgrass testified that Hannah’s course differed from Karl’s course. Tr. 322; tr. 344; tr. 349; tr. 478-79; tr. 784. This is also the position that the Secretary advances. Resp’t Brief at 43, 60.

For purposes of evaluating the Palucks’ theory, comparing and contrasting Hannah’s and Karl’s histories is not necessary. This analysis is taken up in Section V, discussing the third prong of Althen.

²³ Aspartate aminotransferase is found in tissues that are highly metabolic. Kathleen D. Pagana and Timothy J. Pagana, Mosby’s Manual of Diagnostic and Laboratory Tests, 125 (4th ed. 2010).

function. Young children who have dysfunctional cellular energy metabolism therefore might be more prone to undergo autistic regression between 18 and 30 months of age if they also have infections or immunizations at the same time. Although patterns of regression can be genetically and prenatally determined, it is possible that underlying mitochondrial dysfunction can either exacerbate or affect the severity of regression.

Id. at 172 (emphasis added).

In short, the authors conclude that it is possible that immunizations may cause an autistic regression in a child who has a mitochondrial disorder. In his testimony, however, Dr. Frye acknowledged that this article is essentially a report of one case and that case reports provide little information about causation. Tr. 716; tr. 234. Dr. Snodgrass agreed that case reports are not very helpful in determining causation. Tr. 323. Additionally, Dr. Snodgrass pointed out that Karl is not autistic. Tr. 321.

3. Shoffner Series

Like the article about Hannah Poling, the Palucks rely upon an article by John Shoffner to support their theory that vaccines can cause problems for a child with a mitochondrial disorder. In this study, the researchers retrospectively identified 28 children who had both an autism spectrum disorder and a mitochondrial disorder. “Autistic regression” occurred in 17 children (approximately 60 percent).²⁴ Of those 17 children, 12 children (or approximately 70 percent) had autistic regression with fever. And of those 12 children who had autistic regression with fever, the fever was associated with a vaccination in 4 cases. Exhibit 21, tab Z (Shoffner) at 3; see also tr. 124 (Dr. Frye’s summary of this article). An association between fever and regression means that the regression began within two weeks of a fever that did not involve meningitis or encephalitis. Exhibit 21, tab Z (Shoffner) at 2; see also tr. 320 (Dr. Snodgrass).

²⁴ “Autistic regression” was defined as “loss of developmental skills that included speech . . . and social interests in individuals [less than] 3 years of age.” Exhibit 21, tab Z (Shoffner) at 2; accord tr. 194 (Dr. Frye); tr. 430 (Dr. Snodgrass’s definition of regression).

From these observations, the authors made the following conclusion:

Although the number of patients in this pilot study is small, the data suggest that a subgroup of patients with mitochondrial defects may be at increased risk of autistic regression. The rate of autistic regression in this highly selected group of individuals was approximately twice the rate of regression reported in the general population of patients with autistic spectrum disorder. This risk of autistic regression may be enhanced by prolonged fever that occurs with or without vaccinations.

Exhibit 21, tab Z (Shoffner) at 4. The authors recommended additional studies on this topic.²⁵

Dr. Frye maintained that “the inciting event that could be identified was a vaccine.” Tr. 124. Later, in rebuttal testimony, Dr. Frye stated that Shoffner showed that “vaccines, routine vaccines, can cause neurodegeneration in children, into autism, in children that have an underlying mitochondrial disorder.” Tr. 621. On cross-examination, Dr. Frye presented a slightly more nuanced point. He said that the fever was critically important and that a vaccine caused the fever in four cases. Tr. 196-97.

Dr. Snodgrass criticized the Shoffner paper.²⁶ Dr. Snodgrass noted that it provided very few details about any children. Dr. Snodgrass also maintained that even to the extent that Shoffner connected a vaccine to autistic regression, the Shoffner paper provides relatively little, if any, information that is useful in Karl’s case because Karl did not suffer autistic regression. Tr. 320-21; tr. 344-50; tr. 430.

²⁵ The authors also noted that “In our patients with mitochondrial disease and autistic spectrum disorders, the vaccines did not appear related to the neurologic regression.” Exhibit 21, tab Z (Shoffner) at 4. The basis for this statement is not entirely clear, see tr. 196, but one inference is that the authors were distinguishing between their own patients and the people whose charts they reviewed for the study.

²⁶ One group, Autism Speaks, ranked the Shoffner paper as one of the top 10 autism research achievements in 2009. Exhibit 36 (printout from website).

F. Summary Regarding *Althen* Prong 1

The Palucks “must provide a reputable medical or scientific explanation that pertains specifically to [their] case, although the explanation need only be legally probable, not medically or scientifically certain.” Moberly, 592 F.3d at 1322 (citation and quotation marks omitted). Here, the Palucks have not met their burden.

Preliminarily, the presentation of the “medical or scientific explanation” was not persuasive. Dr. Frye’s March 31, 2009 report presented a conclusion that Karl’s vaccinations “could have triggered the ongoing mitochondrial based neurodegeneration.” But, the March 31, 2009 report was missing a medical theory. Exhibit 16. Dr. Frye’s supplemental report was ordered to correct this deficiency. The July 17, 2009 report suffered from including too much information. The report presented the oxidative stress theory that the Palucks eventually presented at trial. However, this theory was hidden among other ideas, such as autoimmunity, that were largely ignored during trial. Likewise, although Dr. Frye’s supplemental report cited many medical articles, the Palucks did not elicit much testimony about these articles during the hearing. Instead, in his initial testimony Dr. Frye referred to articles that he had provided to the Palucks’ attorney only shortly before the hearing. The second set of articles, however, did not address the critical point of oxidative stress and vaccination. The articles most responsive to this topic were not filed until before the third session of the hearing. The overall impression is that Dr. Frye’s theory was not well thought-out. It may turn out that if Dr. Frye acts as an expert witness again, he might present his opinion and the basis for his opinion more clearly from the beginning.

Regardless, the more fundamental problem is that the evidence in the record does not support a finding that the Palucks have presented preponderant evidence that vaccines cause oxidative damage. It is important to recall that oxidative damage is not the same as oxidative stress. Oxidative stress naturally comes from the production of reactive oxygen species that occurs in normal biologic processes, such as those associated with exercise. People have the natural ability to prevent oxidative stress from progressing to a state of oxidative damage.

The Palucks’ evidence did not establish that it is probable that vaccines can cause oxidative damage. The primary article on which Dr. Frye relied to connect vaccines to cause oxidative damage, the Phillips article, was flawed in several respects. Although the Palucks need not present literature to verify every opinion offered by their expert, the Palucks must present an opinion that is reliable.

Moberly, 592 F.3d at 1325. The Palucks have failed to meet their burden of persuasion. The Palucks also did not establish, on a more likely than not scale, that mitochondrial defects make a person more vulnerable to oxidative stress. In sum, the Palucks have not met their burden of proof regarding the first prong of Althen.

IV. *Althen* Prong Two – Logical Sequence of Cause and Effect

A. Introduction

The second element in a petitioner’s case is to submit preponderant evidence establishing “a logical sequence of cause and effect showing that the vaccination was the reason for the injury.” This prong has been interpreted to mean an inquiry into whether the vaccine “did cause” the injury to the vaccinee. Pafford, 451 F.3d at 1354. Under this prong, the relevant evidence tends to be evidence specific for the petitioner, as opposed to evidence about causation in general. The types of evidence that may be probative on second prong include the statements of treating doctors and evidence of challenge-rechallenge. Capizzano, 440 F.3d at 1326.

As a matter of logic, the first and second prongs relate to each other. See Capizzano, 440 F.3d at 1327 (“We see no reason why evidence used to satisfy one of the Althen III prongs cannot overlap to satisfy another prong.”). If it is found that the vaccine “did cause” an injury, then the vaccine must be capable of causing the injury. Conversely, if there has not been a showing that the vaccine “can cause” an injury, then the vaccine cannot be said to have caused the injury for a specific petitioner. See Caves v. Sec’y of Health & Human Servs., ___ Fed. Cl. ___, No. 07-443V, 2011 WL 2523438, at *23 (June 24, 2011), appeal docketed, No. 2011-5108 (Fed. Cir. July 13, 2011).

The parties have significantly different positions regarding Karl’s health, particularly his developmental status in October 2004, before he received vaccines in January 2005. Although the Palucks acknowledge that Karl had delays in his gross motor abilities in October 2004, the Palucks maintain that he was “making progress in his overall development.” Pet’r Brief at 18. The Palucks claim that the January 2005 vaccinations “significantly changed the course of Karl’s development by significantly exacerbating an underlying mitochondrial disorder.” Pet’r Brief at 12; tr. 657 (Dr. Frye’s opinion that there was evidence of regression in Karl’s development in April 2005).

The Secretary does not see the January 2005 vaccinations as altering Karl’s development. She contends that “Karl was not developing normally before his

January 2005 immunizations” and that Karl did not dramatically worsen after those vaccinations. She further argues that “Karl’s condition may well have followed invariably from his mitochondrial disorder.” Resp’t Brief at 65.

B. Review of Karl’s Medical History

1. Before and through Vaccination

Karl was born in January 2004. His routine well-baby examinations at two, four and six months did not detect any problems. Exhibit 3 at 1-2; exhibit 5 at 59-61.

In September 2004, a local education program screened Karl for developmental progress. Karl had some delay in his gross motor skills. He also may have had some problems with speech and language. He was referred to the K.I.D.S. Program at St. Joseph’s Hospital. Exhibit 5 at 111.

Karl was nine months old at the time of the K.I.D.S. evaluation and he was assessed as functioning as a seven month old. Gross motor function was one area of deficit. The K.I.D.S. team also assessed Karl as delayed in his ability to communicate. The K.I.D.S. team recommended “infant development services . . . targeting his speech/language, gross motor, and the delays in fine motor related to low muscle tone.” Exhibit 15 at 4-5.

In the fall and winter of 2004, Karl’s doctors diagnosed him as having otitis media several times. Karl also suffered from repeated instances of erythema multiforme. Exhibit 3 at 38, 57-61. The erythema multiforme demonstrates that his immune system was activated. Tr. 98; tr. 295.

On January 19, 2005, Dr. McDonough evaluated Karl as part of a one-year well baby appointment. Dr. McDonough used the Denver Developmental Screening Test, a commonly used method to see whether Karl was making developmental progress. Dr. McDonough assigned Karl an “F” in two skills under the “Personal-Social” domain, playing pat a cake and wave bye bye. (In the same domain, Karl received a “P” for three other activities --- indicate wants, play ball with examiner, and initiate activities.) For the domain of language, Dr. McDonough gave Karl one “F” for speaking one word and gave him one “P” for “dada/mama specific.” Exhibit 5 at 35. Although Dr. Frye challenges how Dr. McDonough rated Karl (see tr. 630-39), special masters should consider carefully the views of treating doctors. Capizzano, 440 F.3d at 1326. Dr. McDonough was

the doctor responsible for caring for Karl and Dr. McDonough examined Karl in January 2005. Dr. Frye did not examine Karl in the relevant time. Tr. 189. The Palucks have not offered a persuasive reason to second-guess Dr. McDonough's evaluation.

In addition to the Denver test, Dr. McDonough recorded other information on his office's form. There is a circle around the word "babbling" with a handwritten notation saying "not yet no words." There is also a circle around the word "crawl" and handwriting saying "4 point." Dr. McDonough also recorded "Karl doesn't hold cup well."

Dr. McDonough physically examined Karl. In the neuromuscular area, Dr. McDonough checked abnormal. The notes say "muscle tone [increased] upper and lower extremities. 2 beats clonus [in] [right] ankle." The same area of the form has a normal box checked for hips with a note, which is difficult to read, apparently saying "got [decreased] ROM." ("ROM" means range of motion. Neil M. Davis, Medical Abbreviations (15th ed. 2011) at 284.).

Dr. McDonough assessed Karl as having "gross motor delay and recurrent erythema multiforme." He referred Karl to an early development center where Karl could receive physical therapy and occupational therapy services. Exhibit 5 at 62.

Karl also was given a set of vaccinations. Id., exhibit 4 at 18.

2. Late January to Early February 2005

In the days immediately following the January 2005 vaccinations, Karl was fussy, did not eat well, and was lethargic. The source of this information is the record from Karl's daycare center. Karl's daycare provider also noted on two occasions, two days after vaccination and nine days after vaccination, Karl had a temperature. For the period from January 21, 2005 to February 4, 2005 (inclusive), staff from daycare made an entry for Karl for every weekday except one (Thursday, January 27, 2005). None of the other entries mention Karl having a fever on other days. Exhibit 22 at 1-2. The experts agreed that Karl's immune system was active during this time with both pointing to the fever as evidence for immune system activation. Tr. 103-05 (Dr. Frye), tr. 338 (Dr. Snodgrass), tr. 429 (same), tr. 624-28 (Dr. Frye).

The more relevant questions are what caused the immune activation, and what effect, if any, did the immune activation have on Karl? Dr. Frye asserts that the January vaccinations caused Karl's fever. Tr. 103-05; tr. 196-97; tr. 624-28. Dr. Snodgrass disagrees. Dr. Snodgrass points out that children in daycare frequently have fevers, so that Karl having a fever is not unexpected. Dr. Snodgrass also suggests that the erythema multiforme, which Dr. McDonough recognized in the January 17, 2005 visit, is the possible cause for Karl's fevers. Finally, Dr. Snodgrass stated that when the varicella and MMR vaccines cause fevers, the fevers usually appear seven or eight days after the vaccination. Tr. 338-39. Karl's fevers were not necessarily caused by the vaccines because fevers can have many causes. Tr. 291; exhibit J (Ellen R. Wald et al., Frequency and severity of infections in day care: Three-year follow-up (pt. 1), 118(4) J. Pediatrics 509 (1991)).

A finding that the January 17, 2005 vaccinations caused Karl to have a fever on January 21, 2005, and a fever on January 28, 2005 does not mean that either fever had any lasting consequence on Karl. The record shows that Karl attended daycare on January 21, 24-26, 28, 2005 and February 1-4, 7, 8, 2005. Exhibit 22 (Karl's infant gram).²⁷ These records do not show any consistent problem with Karl's health.

3. March 2005

On March 3, 2005, Ms. Paluck brought Karl to the Dickinson clinic where he was seen by Dr. Kamille Sherman. (This visit appears to be the first time that a doctor saw Karl after his January 2005 vaccinations.) Ms. Paluck was concerned that Karl had been a "little bit fussy," had been coughing, and had "a bit of rhinorrhea for the past couple of weeks." Karl's temperature was 97.3 degrees. Dr. Sherman observed that Karl was not in acute distress and he was interacting appropriately with his mother. Dr. Sherman did not note any developmental concerns, although the reason for this visit was not to discuss Karl's development. Dr. Sherman assessed Karl as having bronchitis with irritability and recommended that if Karl had more problems, he should be seen "sooner." Exhibit 3 at 63.

²⁷ In a status conference held on July 22, 2011, the undersigned requested that petitioners investigate whether there were daycare records not submitted into the record. On August 22, 2011, petitioners filed a status report indicating that Ms. Paluck stated that there were no additional daycare records to be obtained.

Some information about Karl's development was recorded in a pediatrician office's note from a telephone call with Karl's parents on March 22, 2005. They reported that Karl has "some brief crawling," is "not sitting on his own," "leans to one side" and is "babbling more." Exhibit 5 at 72. Karl's lack of ability to sit on his own is not new. In the K.I.D.S. evaluation in October, Karl could not sit without support for 60 seconds. Exhibit 15 at 5. The daycare records indicate that on February 2, 2005, Karl's parents were "concerned about Karl not sitting up yet." Exhibit 22 at 2.

On the other hand, developing the ability to crawl is progress. At the December 27, 2004 visit, Dr. McDonough stated that Karl "tries to crawl." Exhibit 3 at 5. The chiropractor's February 7, 2005 record says that Karl is not crawling. Exhibit 12 at 1-2. Similarly, the February 8, 2005 entry from daycare says that Karl "tries to crawl [by] pulling his body." Exhibit 22 at 2. Thus, when the parents communicate that Karl is doing "some brief crawling," Exhibit 5 at 72, the parents are saying that Karl is doing something that he could not do before. The parents' observations are corroborated in the April 2, 2005 note from the chiropractor, which says that Karl has been "taking few crawling steps." Exhibit 12 at 7. Another telephone record, this one from April 11, 2005, shows that Mr. Paluck reported that "Karl is crawling about 2 wks ago." Exhibit 5 at 76.²⁸

The March 22, 2005 record from a telephone call also states that Karl is "babbling more." Exhibit 5 at 72. The "more" portion of "babbling more" also suggests some progress. Karl was noted to be babbling in the January 19, 2005 visit with Dr. McDonough. Exhibit 3 at 3; see also exhibit 3 at 7 (letter from Dr. McDonough, dated March 24, 2005).²⁹ Thus, Karl improved, at least a little bit, between January 19, 2005 and March 22, 2005. See tr. 793-94 (Dr. Snodgrass's discussion of fluctuations in Karl's progress, providing babbling as an example of how Karl got better).

²⁸ Karl's ability to crawl appears to be limited because on April 26, 2005, Dr. McDonough stated that Karl did not crawl. Exhibit 3 at 13. After Karl's first seizure, Dr. McDonough stated that Karl had not been able to crawl. Exhibit 5 at 56-57 (report dated July 12, 2005).

²⁹ On April 19, 2005, Karl's neurologist, Dr. Kriengkrairut, reported that Karl could not babble. Exhibit 3 at 84. In July 2005, Dr. McDonough stated that Karl had some babbling. Exhibit 5 at 56-57.

A primary part of Dr. Frye's opinion is that the January 19, 2005 vaccinations started Karl on a consistent decline. The following passage captures this opinion:

[F]rom looking at the temporal evolution that right after the vaccines it seemed that he had immune activation very much like we've seen in previous cases^[30] and following that he has devastating regression that continues until April, and continued after that with the development of seizures and him continuing to lose function.

Tr. 657 (emphasis added). In saying that Karl had a regression that continued until April, Dr. Frye is mistaken and this error diminishes the persuasiveness of Dr. Frye's opinion. See Brooke Group Ltd. v. Brown & Williamson Tobacco Corp., 509 U.S. 209, 242 (1993); Perreira, 33 F.3d at 1376 n. 6; Bradley v. Sec'y of Health & Human Servs., 991 F.2d 1570, 1574 (Fed. Cir. 1993).³¹

4. Mid-April, May & June 2005

In April 2005, Karl saw Dr. Kriengkrairut for the first time and Dr. McDonough for the fifth time. The Palucks claim that these visits show Karl regressed from January 17, 2005. Pet'r Brief at 20-21 and 28-29. The Secretary and Dr. Snodgrass countered that Karl did not regress from January 17, 2005 to April 19, 2005 and that Karl "got worse in April/May." Tr. 367; tr. 577.

³⁰ The "previous cases" to which Dr. Frye refers are the Shoffner series and Hannah Poling. The similarities and differences between Karl's case and those other cases are discussed in section V.

³¹ The Palucks' briefing also overlooks reports of Karl's progress in March 2005. Their recitation of facts omits the note from the March 22, 2005 telephone call, the April 2, 2005 chiropractor's note, and the record from the April 11, 2005 telephone call. See Pet'r Brief at 7. After the Secretary argued that Karl's "post-vaccination clinical course was more variable than Dr. Frye portrayed," Resp't Brief at 56, the Palucks had a chance to respond. However, the Palucks' reply brief also skips over reports of Karl's progress in March and focuses on Karl's status in April. See Pet'r Reply at 20.

A preponderance of the evidence supports a finding that Karl was worse in April 2005. The primary basis for this finding is the report of Dr. McDonough, who saw Karl both in January and in April. On April 13, 2005, Dr. McDonough reports that Karl has “global developmental delay.” Exhibit 3 at 9. This finding means that Karl has deficits in more than one area, tr. 651, and consistent with this definition, Dr. McDonough said that Karl had developmental problems in “speech and fine and gross motor development.” Exhibit 3 at 10. Dr. McDonough’s assessment of global development delay shows that Karl had deteriorated from Dr. McDonough’s evaluation in January, when Dr. McDonough said that Karl had only “gross motor delay.” Exhibit 5 at 62.

Even in the specific field of gross motor skills, Karl was getting worse. Dr. McDonough stated in April that Karl’s “hips are tight with decreased hip flexion to about 70 degrees bilaterally with increased [sic, it appears that a word is absent] in the lower extremities. This is a change of hip movement over the last couple of months.” Exhibit 3 at 10. Although some time was spent trying to interpret Dr. McDonough’s January 17, 2005 notes for the range of motion in Karl’s hips, tr. 332-33 (Dr. Snodgrass), the answer to this question is found in Dr. McDonough’s April 13, 2005 report. Dr. McDonough states that Karl’s hip movement had “change[d].” There is no reason to second-guess Dr. McDonough’s comparison.

Additionally, six days later, Dr. Kriengkrairut found that Karl had “marked spasticity of the extremities.” Exhibit 3 at 84. “Spasticity” means that the muscles are so hypertonic (that is, rigid) that movements are limited. Tr. 825; see also tr. 647. Dr. Kriengkrairut’s report, when combined with Dr. McDonough’s determination that Karl’s hip flexion had changed, constitutes a persuasive basis for finding that Karl’s gross motor skills had deteriorated between January and April.

The finding that Karl was worse in April than he was in January must be placed in context. This comparison examines only two points and ignores Karl’s health in February and March, when he was either the same or improving.

Some evidence of additional progress comes from May 2005, when Karl was receiving therapy. Karl’s speech therapist, Ms. Trisha Getz, indicates that Mr. Paluck stated that Karl’s “strength is increasing.” The therapist also recorded that “Karl is producing much more eye contact with therapist and laughed while appearing to enjoy play with a ball.” Exhibit 6 at 33; see also tr. 359-60 (Dr. Snodgrass).

5. July 2005 and Afterward

Karl's status deteriorated dramatically in July 2005. In that month, he had a seizure in which his eyes rolled back and during which he was not responsive. Exhibit 6 at 62 (St. Joseph's Hospital & Health Center – Discharge Summary). When hospitalized for this seizure, Karl was again seen by Dr. McDonough. Exhibit 5 at 56-57. At discharge on July 16, 2005, Dr. McDonough “suspect[ed] that [Karl] has an underlying seizure disorder.” Exhibit 4 at 15. From July 2005 until the present, Karl has made minimal, if any, developmental progress.

The details of Karl's appointments with doctors and therapists over the ensuing five years are not relevant to determining whether the January 17, 2005 vaccinations caused Karl's developmental problems. See Pet'r Brief at 10-11 (discussing Karl's history from October 2005 to November 2010).³² The relevant time is from Karl's birth until July 2005.

6. Synthesis

In the first year and a half of Karl's life, his development fluctuated. He had developmental problems before the January 17, 2005 vaccinations. He made some improvements but remained delayed when he was vaccinated. Within the two weeks following vaccination, Karl had fevers on two occasions. Otherwise, Karl was more-or-less in his usual state of health. By the end of March 2005, Karl was developing the skill of crawling, an ability that he had not shown previously. In April 2005, Dr. McDonough stated that Karl was worse than he was in January. But, Dr. Kriengkraitut recounted that Karl had gotten better in some respects and this view was supported by Karl's speech therapist. The limited progress essentially stopped in July 2005.

The question is does Karl's history match what the experts have assumed to be the case? In determining whether a petitioner presents persuasive testimony from an expert, a special master may take into account disparities between the facts and what the experts assumes to be facts. See Burns v. Sec'y of Health & Human

³² The work up during this time included testing that led Karl's treating doctors to think that Karl may have a mitochondrial disorder. Dr. Frye and Dr. Snodgrass agree that it is “probable” that Karl has a mitochondrial disorder. Tr. 84-89; tr. 260; tr. 413-21.

Servs., 3 F.3d 415, 417 (Fed. Cir. 1993) (stating “The special master concluded that the expert based his opinion on facts not substantiated by the record. As a result, the special master properly rejected the testimony of petitioner’s medical expert.”).

Dr. Frye’s opinion is that the pattern for Karl’s developmental progress “looked like . . . a progressive hill downward for about six months.” Tr. 231. This image of a continuous downward slope is not accurate in two respects. First, it fails to account for Karl’s developmental problems before the vaccination. Second, a “continuous downward slope” fails to capture periods when Karl seemed to be remaining the same and fails to reflect the (brief) instances of progress. The Palucks bear the burden of presenting a “logical sequence of cause and effect showing that the vaccination was the reason for the injury,” Althen, 418 F.3d at 1278. Here, Dr. Frye’s testimony does not carry the Palucks’ burden because Dr. Frye’s view of Karl does not match what actually happened to Karl.

A contrary image of Karl’s developmental progress was offered by Dr. Snodgrass. In this view, Karl’s progress from September 2004 to July 2005, was up and down. See Exhibit N (Supp. Rep’t) at 4. Although the Palucks’ cross-examination of Dr. Snodgrass revealed that the exact graphical depiction (in terms of slopes of ascent and descent) could be seen as arbitrary, tr. 454-55, the Palucks did little to rebut the basic point, which was that Karl’s development was not linear. A non-linear depiction of Karl’s progress is consistent with the facts but not consistent with Dr. Frye’s theory.

7. Treating Doctors

With regard to the second prong of Althen, the Federal Circuit has instructed special masters to consider carefully any statements from treating doctors. Capizzano, 440 F.3d at 1326. The Secretary argues that the collection of information from treating doctors does not support any affirmative finding on prong two. The Secretary argues: “Here, although physicians had a plethora of opportunities to associate Karl’s vaccination to various injuries, dictated notes concerning the etiology of Karl’s condition, and were asked by Karl’s parents about the reasons for his illness, not once did any treating physician causally associate Karl’s vaccination with any of his injuries.” Resp’t Brief at 52.

In rebuttal, the Palucks identify two medical records. See Pet’r Reply at 20. First, the Palucks cite to the report from Karl’s second MRI, which occurred on

July 22, 2005. The doctor who reviewed the MRI reported that the “Findings are consistent with a progressing leukodystrophy (consider hereditary, toxic or metabolic etiologies).” Exhibit 11 at 91. Second, the Palucks cite a note from the chiropractor, stating “discussed poss. [a]dverse rx [reaction] / vaccine.” Exhibit 12 at 7. Neither document cited by the Palucks presents a probative statement from a treating doctor that the medical professional considered the vaccines as the cause of Karl's problems.

C. Summary Regarding *Althen* Prong 2

For the second element, the Palucks bear the burden of presenting preponderant evidence “showing a logical sequence of cause and effect showing that the vaccination was the reason for the injury.” In this case, the Palucks have not met their burden. The Palucks’ expert presented a view of Karl’s development that is not consistent with the medical records. To Dr. Frye, the January 2005 vaccinations started Karl’s developmental regression and this regression continued. Actually, Karl was showing signs of developmental problems months before the vaccinations. Then, after Karl received the vaccinations, his most precipitous decline did not occur until July 2005. Thus, even if Dr. Frye’s theory passed Althen prong 1, the Palucks have not established Althen prong 2 because Karl did not act in a way predicted by Dr. Frye. See Ricci v. Sec’y of Health & Human Servs., ___ Fed. Cl. ___, No. 99-524V, 2011 WL 5438654, at *7 (Oct. 26, 2011) (finding that special master did not error in finding that petitioners’ evidence on Althen prong 2 was lacking despite the special master’s assumption that the petitioners prevailed on Althen prong 1). Furthermore, the records from Karl’s treating doctors do not overcome the gap in the Palucks’ proof. From all of Karl’s extensive records, the Palucks advance two notes as potentially helpful. However, these comments are not persuasive evidence that the 2005 vaccinations caused Karl’s problems. Consequently, the Palucks have not satisfied Althen prong 2.

V. *Althen* Prong Three - Timing

A. Standards for Adjudication

Petitioners are required to establish a “showing of a proximate temporal relationship between vaccination and injury.” Althen, 418 F.3d at 1278. The Federal Circuit has elaborated that the third prong of the Althen test requires “preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically

acceptable to infer causation.” Bazan v. Sec’y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). Thus, the two components of this prong are (a) the timeframe for which it is “medically acceptable to infer causation,” and (b) the onset of the condition for which petitioner seeks compensation. See Shapiro v. Sec’y of Health & Human Servs., No. 99-552, 2011 WL 1897650, at *13 (Fed. Cl. Spec. Mstr. April 27, 2011), aff’d in relevant part, vacated in non-relevant part, ___ Fed. Cl. ___, 2011 WL 5543699, at *11 (Oct. 31, 2011).

B. Analysis of the Evidence

1. Time Expected by Medical Science

The first component is to determine the time in which, given what is understood about Karl’s disorder, a causal connection between the vaccine and the injury may be inferred. Citing Dr. Frye’s testimony, the Palucks propose that two periods are relevant. The initial period is when the vaccine leads to the production of oxidative stress, which happens within one week. The second period is when the signs and symptoms of oxidative stress become apparent. For this second period, Dr. Frye did not mark any boundaries because when the clinical manifestations of oxidative stress become apparent will vary with the severity of the mitochondrial dysfunction. Pet’r Brief at 29, citing tr. 127-128, 131-32, 232. According to Dr. Frye, the damage caused by oxidative stress can become apparent “days or weeks or months” or even years or decades after the oxidative stress. Tr. 129.

There is little, if any, evidence that the general medical community would expect to see evidence of neurodegeneration months or years after a vaccine induced an increase in oxidative stress. The articles that were cited by Dr. Frye suggest that the temporal connection between the vaccination and the resulting damage would be much more direct, a period measured in weeks, not months. These articles include:

a) Edmonds

Dr. Edmonds and colleagues studied 40 patients with mitochondrial disease. The doctors attempted to determine how frequently these patients experienced neurodegeneration after an infection. The article reports that “[i]n most patients (10/13), the neurological event occurred 3 to 7 days after the onset of the infection and frequently appeared at a time when the infection was resolving.” A graphical presentation of this discovery is presented in figure 3 of the article. The authors also commented that “[t]he pattern was similar to that reported for Reye syndrome,

now known to be frequently associated with mitochondrial defects in fatty acid oxidation.” Exhibit 21, tab D (Joseph L. Edmonds et al., The Otolaryngological Manifestations of Mitochondrial Disease and the Risk of Neurodegeneration with Infection, 128 Archives of Otolaryngology - Head & Neck Surgery 355 (2002)) at 360.

Dr. Snodgrass incorporated figure 3 from Edmonds into his supplemental report. Exhibit N at 5. Dr. Snodgrass testified that the Edmonds article could provide some information in Karl’s case if an analogy were drawn between infections and vaccinations. If this comparison were valid, then Dr. Snodgrass testified that “we would think that it should follow the general time course that we see in figure 3.” Tr. 541; accord tr. 524. Dr. Frye did not address this aspect of the Edmonds paper.³³

b) Shoffner

Dr. Frye relies upon the Shoffner series. Tr. 125. Dr. Shoffner and colleagues reviewed the files of 28 people with autistic spectrum disorders and mitochondrial diseases. The authors investigated whether regression occurred after a fever. The authors’ definition of regression was limited to “regression as beginning within 2 weeks of a febrile episode without the suggestion of infectious meningitis or encephalitis.” Exhibit 21, tab Z (Shoffner) at 2.

³³ When Dr. Frye testified in rebuttal, the Palucks’ attorney raised a question about the Edmonds paper, prefaced with the comment that “the Edmonds paper was written in the context of sepsis.” Tr. 619. This comment was mistaken because the paper written in the context of sepsis to which the Palucks’ counsel probably intended to refer is Exhibit 21, tab QQ (Ruth A. Roberts et al., Nitrative and oxidative stress in toxicology and disease, 112(1) Toxicological Sci. 4-16 (2009) and/or exhibit 21, tab PP (Alessandro Protti & Mervyn Singer, Bench-to-bedside review: potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure, 10 Critical Care 28 (2006)). Unfortunately, this error was repeated by counsel for the Secretary and the undersigned. Tr. 776; tr. 818.

c) Hannah Poling

Dr. Frye compared Karl's case to Hannah Poling's case. As previously mentioned, the article describing Hannah's case contains the report about her experience and also a report about a study of approximately 250 children. Information about the course of the illness is available only for Hannah. Hannah experienced a temperature of 38.9 degrees Celsius within 48 hours of receiving a set of vaccinations. In this time, she also had "inconsolable crying, irritability, and lethargy, and refused to walk." The fever lasted for the next 12 days. Ten days after vaccination, Hannah developed a rash. For three months, Hannah was "irritable" and lost her ability to communicate during the three months after vaccination. Exhibit 21, tab Q at 171.

d) Animal Studies on Experimental Autoimmune Uveitis

Among the articles cited by Dr. Frye to support the theory that a vaccination can cause oxidative stress and oxidative stress can damage the function of mitochondria, there are several studies involving experimental autoimmune uveitis.³⁴ See tr. 616. In brief, the animals (Lewis rats) were injected with a substance that was designed to prompt their immune systems to attack their photoreceptors. Tr. 604-05 (Dr. Frye's description of the rodent model); tr. 750-51 (additional information from Dr. Frye about the rodent model); tr. 763-65 (Dr. Snodgrass's discussion of these articles).

For purposes of finding the appropriate temporal interval, the important point from these studies is that the animals experienced the adverse effect within 14 days of injection of the substance stimulating the immune system. Exhibit 21, tab J (Khurana) at 3302; exhibit 37, tab B (Saraswathy) at 160; exhibit 37, tab C (Wu) at 2271-72; see also tr. 300-01 (Dr. Snodgrass's testimony that damages

³⁴ These studies include Exhibit 21, tab J (Rahul N. Khurana et al., Mitochondrial Oxidative DNA Damage in Experimental Autoimmune Uveitis, 49 (8) Investigative Ophthalmology & Visual Sci. 3299 (2008)); ex. 37, tab B (Sindju Saraswathy & Narsing A. Rao, Photoreceptor Mitochondrial Oxidative Stress in Experimental Autoimmune Uveitis, 40 Ophthalmic Res. 160 (2008)); ex. 37, tab C (Guey-Shuang Wu et al., Photoreceptor Mitochondrial Tyrosine Nitration in Experimental Uveitis, 46(7) Investigative Ophthalmology & Visual Sci. 2271 (2005)).

occurs “early on”); tr. 487-88 (same); tr. 605 (Dr. Frye’s testimony); tr. 742 (same).

e) **Finding Regarding Appropriate Medical Interval**

The evidence coalesces around a finding that two weeks from vaccination is an appropriate interval between vaccination and the onset of neurological problems.³⁵ Dr. Frye’s opinion that there is an intervening period of months between the initial production of oxidative stress and the (consequential) neurological injury is found not persuasive. Dr. Frye has not identified any studies that present this pattern.

2. Onset of Karl’s Signs and Symptoms

Petitioners bear the burden of presenting persuasive evidence that the onset of symptoms began within the medically appropriate time. Bazan, 539 F.3d at 1352. Given the finding above, the Palucks have the burden of showing that Karl’s neurodegeneration began within two weeks of the January 17, 2005 vaccinations.

As discussed in section IV.B.2 above, Karl did not experience signs or symptoms of neurodegeneration within two weeks of the January 17, 2005 vaccinations. It appears, more likely than not, that Karl had a significant step backward in his development in April 2005, which is outside the amount of time expected by the medical community.

For a sign or symptom of neurodegeneration that occurred within two weeks of the January 15, 2005 vaccinations, the Palucks elicited the following testimony from Dr. Frye in rebuttal:

³⁵ In the context of discussing the medically appropriate interval, Dr. Frye testified that oxidative stress causes diseases that appear later in life, such as Alzheimer’s disease, Parkinson’s disease and aging. Tr. 128-29. Dr. Frye’s opinion about the relevance of Alzheimer’s disease is, frankly, confusing. In his report, Dr. Frye cited studies from Alzheimer’s disease and in his initial testimony, he discussed Alzheimer’s disease. Exhibit 21, tab M (Paula I. Moreira et al., An integrative view of the role of oxidative stress, mitochondria and insulin in Alzheimer’s disease, 16 J. of Alzheimer’s Disease 741 (2009)); tr. 67. Much later in his testimony, Dr. Frye stated that “Alzheimer’s disease . . . doesn’t have the same biological mechanism to the same extent as we’ve argued that occurs with vaccines and induction of oxidative stress and inflammation.” Tr. 694. Thus, Dr. Frye was “not testifying on Alzheimer’s disease.” Tr. 696.

What we seem to see [in] the pattern of regression is that of fever, irritability, what we call encephalopathy, and then regression, and then to start to see regression of cognitive abilities over weeks to months after that, those are the patterns that seem to have emerged from the literature. We see spasticity emerging at Karl on February 11th, which is about three weeks after he has the vaccines. So we have documented evidence that within three weeks he actually has neurological changes in his motor system.

Tr. 659-60. The source of “spasticity” mentioned by Dr. Frye is the chiropractor’s February 11, 2005 note. Exhibit 12 at 5; see also tr. 646-48.

This argument rests too heavily on a single word appearing in the notes of a chiropractor. See 42 U.S.C. § 300aa—13(a) (stating that the special master should consider the “record as a whole.”). On the same page of notes, the chiropractor has two entries (February 16 and February 18) that Karl is “less rigid.” Exhibit 12 at 5. If, on February 11, 2005, Karl truly had “neurological changes in his motor system” as advanced by Dr. Frye, then those changes would have not been ameliorated within seven days.

Additionally, there is the confounding fact that Dr. McDonough reported that Karl had increased muscle tone and inconsistent ankle clonus in January 2005. Exhibit 3 at 3. As Dr. Snodgrass testified, Karl’s spasticity is not an absolutely new problem. Spasticity, hypertonicity and clonus are related problems, each suggesting a difference in degree. Tr. 333-35; tr. 789. As a treating doctor who examined Karl in both January and April 2005, Dr. McDonough is capable of detecting and reporting changes in Karl’s gross motor skills. See section IV.B.4, above. The same assessment cannot be made for Karl’s chiropractor because – regardless of the chiropractor’s training and experience – the chiropractor did not examine Karl before the January 15, 2005 vaccinations. For these reasons, a single report of spasticity on February 11, 2005 does not meet the Palucks’ burden of showing that Karl evidenced his neurodegeneration within two weeks of his vaccination.³⁶

³⁶ Additionally, the chiropractor reports spasticity on February 11, 2005, and February 11, 2005, is 27 days after the January 15, 2005 vaccinations. This

The Palucks emphasize that Karl's course resembles Hannah Poling's case. They argue that Karl developed problems similar to Hannah's problems at roughly the same time as Hannah. Pet'r Brief at 30; Pet'r Reply at 19; see also exhibit 27 (chart comparing the two cases).

The evidence does not support a conclusion that Karl's course is like Hannah's course. There are two important differences. One is that Hannah started having problems immediately. She had a fever within two days of the vaccine, which is also what happened to Karl. However, Hannah's fever continued for 12 days. For Karl, there is only evidence that he had a second fever on the ninth day after vaccination. Hannah had (new) problems with her gross motor functions within one week of her vaccination. Karl's gross motor problems were evident before the vaccination and did not meaningfully worsen until April.

The other primary difference between Karl and Hannah is that Hannah's immediate problems persisted. Hannah was irritable for the following three months. Although Karl was reported to be irritable at different times in the three months after vaccination, Karl was also improved sometimes. Hannah's ability to verbalize decreased throughout the three months. Karl, who was not talking when he received the vaccinations, had "more babbling," in March 2005. For all these reasons, Hannah's case is not a "precedent" for finding that Karl's neurodegeneration developed within a medically appropriate time.³⁷

amount of time (27 days) falls outside the medically appropriate time, which is two weeks.

³⁷ It bears repeating that Hannah's case is not a precedent in a legal sense. The Secretary conceded that Hannah's case met the definition of an encephalopathy developing 5-15 days after an MMR vaccination. See 42 C.F.R. § 100.3 paragraph III. When the injury occurs within the time specified in the Vaccine Injury Table, causation is presumed. Shalala, 514 U.S. at 270-71; Munn v. Sec'y of Health & Human Servs., 970 F.2d 863, 865 (Fed. Cir. 1992). Given this presumption, neither the Secretary nor the special master had occasion to evaluate whether the MMR vaccination actually caused Hannah's encephalopathy.

C. Summary Regarding Althen Prong 3

To the extent that there is support for the theory that vaccines can lead to the production of oxidative stress as a step toward neurodegeneration, it appears that the neurodegeneration would be apparent within two weeks. However, Karl did not show signs of neurodegeneration until after two weeks had passed. Consequently, the Palucks have not met their burden of proof regarding prong 3.

VI. Alternate Causes

The parties also raised the issue of whether a factor, other than the January 15, 2005 vaccinations, caused Karl's neurodegeneration. The Secretary argues the legal point that the Palucks bear the burden of ruling out other potential causes of Karl's problems. Resp't Brief at 62, citing Munn, 970 F.2d at 865, and Doe v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1356-58 (Fed. Cir. 2010). This legal point is the foundation for the Secretary to discuss two different ideas from Karl's case. The Secretary's first point builds upon Dr. Frye's theory that oxidative stress, when combined with a mitochondrial disorder, can lead to neurodegeneration. For Dr. Frye, the source of the oxidative stress is the January 15, 2005 vaccines. The Secretary, in contrast, proffers that other substances could have triggered oxidative stress in Karl. These other substances include bacteria, viruses, or the April 2005 MRI. Resp't Brief at 62-64. The Secretary's second explanation does not depend upon Dr. Frye's theory. Instead, the Secretary contends that Karl's development "could be due to mitochondrial dysfunction' alone." Id. at 65, quoting tr. 374 (Dr. Snodgrass).

The Palucks' answer to the Secretary's arguments is primarily a legal argument. The Palucks maintain that in the circumstances of Karl's case, they do not bear the burden of ruling out alternative causes. Pet'r Reply at 21-22, citing Walther v. Sec'y of Health & Human Servs., 485 F.3d 1146, 1150 (Fed. Cir. 2007) and Cedillo, 617 F.3d at 1338. Apart from this argument about where the law places the burden of proof, the Palucks present a single sentence: "Respondent has not come forward with any evidence, let alone a preponderance of the evidence to show that is/was more likely than not some other cause for Karl's condition." Pet'r Reply at 22.

An extended discussion of whether some factor other than the vaccines caused Karl's neurodegeneration is not needed because the Palucks have not established any of the Althen prongs. Nevertheless, it is worth noting that even if

oxidative stress were shown to cause neurodegeneration in some infants, there is the confounding question of the source of any damage-causing oxidative stress.

Sources of oxidative stress vary. Dr. Frye explained that residents in pediatric neurology learn that people with mitochondrial disorders are vulnerable to “environmental stressors.” When asked to give examples of environmental stressors, Dr. Frye responded “Traditionally it’s taught that those would be bacterial or viral illnesses, so things that activate the immune system.” Tr. 90.

These environmental stressors are issues in this case because Karl encountered many bacteria and/or viruses. In the fall 2005, when Karl first starting showing signs of developmental delay, he suffered from several instances of otitis media. He developed erythema multiforme that continued intermittently for months. Dr. McDonough said that the erythema multiforme was present the day Karl was vaccinated. Dr. Snodgrass testified that Karl’s erythema multiforme was more likely to produce oxidative stress than the vaccines. Tr. 356-57.

Separating the effects of different sources of oxidative stress might be difficult but, in this case, the Palucks seem not to have attempted to do so. The Palucks’ challenge appears to resemble a portion of the cases in which petitioners claimed that mercury from vaccines caused their children’s autism. Each special master deciding those cases noted that children are exposed to mercury from many sources. See Cedillo v. Sec’y of Health & Human Servs., No. 98–916V, 2009 WL 331968, at *17 (Fed. Cl. Spec. Mstr. 2009), motion for review denied, 89 Fed. Cl. 158 (2009), aff’d, 617 F.3d 1328 (Fed. Cir. 2010); Snyder ex rel. Snyder v. Sec’y of Health & Human Servs., No. 01–162V, 2009 WL 332044, at *147 (Fed. Cl. Spec. Mstr. Feb 12, 2009), motion for review denied, 88 Fed. Cl. 706 (2009); Hazlehurst v. Sec’y of Health & Human Servs., No. 03-654, 2009 WL 332306, at *83-85 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), aff’d, 88 Fed. Cl. 473 (2009), aff’d, 604 F.3d 1343 (Fed. Cir. 2010). Any petitioner who proposes that oxidative stress caused some harm would probably be well served to present a person who is knowledgeable about oxidative stress, especially because oxidative stress is naturally generated during helpful activities such as exercise.

VII. Conclusion

Karl suffers from a mitochondrial disorder. He also received a set of vaccinations in January 2005. The Palucks seek compensation in the Vaccine Program because they contend that the administration of vaccinations to a person

with a mitochondrial disorder can cause a person, such as Karl, to suffer neurodevelopmental regression.

The evidentiary support for the Palucks' argument is not persuasive. First, the Palucks have not established that the theory espoused by their expert involving oxidative stress is reliable. Second, the Palucks' expert assumes a set of facts about Karl (a continuous decline) that does not match what actually happened to Karl (up and down progress). Third, Karl's neurodegeneration became evident outside the time expected by medical science. For these reasons, the Palucks are not entitled to compensation.

The Clerk's office is instructed to enter judgment in accord with this decision unless a motion for review is filed.

IT IS SO ORDERED.

S/ Christian J. Moran

Christian J. Moran
Special Master