In the United States Court of Federal Claims

No. 07-889V

(Filed: April 18, 2012)

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DOUG PALUCK and RHONDA PALUCK, as parents and natural guardians on behalf of their minor son, KARL PALUCK,	Vaccine case; off-Table claim stemming from neurological damage allegedly caused or aggravated by administration of MMR, varicella, and Prevnar vaccines to a child with a genetic mitochrondrial defect; differentiation of claims asserting an aggravation of a pre-existing condition from claims asserting the manifestation of a new injury; *Althen* causation framework; propriety of admitting trial testimony from an unrelated vaccine case
Petitioners,	
v.	
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	

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Chrysovalantis P. Kefalas, Trial Attorney, Torts Branch, Civil Division, United States Department of Justice, Washington, D.C., for respondent. With him on the briefs were Tony West, Assistant Attorney General, Civil Division, and Mark W. Rogers, Acting Director, Vincent J. Matanoski, Acting Deputy Director, and Catharine E. Reeves, Assistant Director, Torts Branch, Civil Division, United States Department of Justice, Washington, D.C.

OPINION AND ORDER[1]

LETTOW, Judge.

Petitioners Doug and Rhonda Paluck, on behalf of their son, Karl Paluck, seek review of a decision by a special master issued December 14, 2011, which denied them compensation under the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, § 311, 100 Stat. 3743, 3755-84 (1986) (codified as amended at 42 U.S.C. §§ 300aa-1 to -34) ("Vaccine Act"). The Palucks allege that Karl's receipt of the mumps-measles-rubella ("MMR"), varicella, and Prevnar vaccines on January 19, 2005 caused him to develop, or exacerbated a preexisting

[1]In accord with the Rules of the Court of Federal Claims ("RCFC"), App. B ("Vaccine Rules"), Rule 18(b), this opinion and order is initially filed under seal. By rule, the parties are afforded fourteen days in which to propose redactions.

condition resulting in, severe neurological damage. The Secretary of Health and Human Services ("the government") acknowledges Karl's injury but contends that its cause is unrelated to the vaccines.

The special master considered that the Palucks' claim regarding Karl's condition involved a so-called "off-Table injury," requiring the Palucks to prove causation in fact. *Paluck ex rel. Paluck v. Secretary of Health & Human Servs.*, No. 07-889V, 2011 WL 6949326, at *6 (Fed. Cl. Spec. Mstr. Dec. 14, 2011) ("*Entitlement Decision*"); *see* 42 U.S.C. §§ 300aa-11(c)(1)(C)(ii)(I), -13(a)(1), -14. After collecting documentary evidence and hearing expert testimony, the special master denied the Palucks compensation on the ground that they had failed to prove causation in fact under the framework set out in *Althen v. Secretary of Health & Human Services*, 418 F.3d 1274 (Fed. Cir. 2005). On review, the Palucks argue that the special master's opinion was arbitrary and capricious and misapplied the relevant legal standards. The government responds that the special master's decision complied with law.

BACKGROUND

A. *Facts*[2]

Karl Paluck's medical history is complex. Overall, it documents Karl's decline from normal health to severe neurological disability. The parties agree that Karl's development was unremarkable from his birth on January 20, 2004 through his first six months of life. They disagree sharply, however, as to Karl's condition thereafter and the cause or causes of his eventual neurodegeneration. Petitioners contend that Karl continued to develop normally through his first year, until he received vaccinations on January 19, 2005. Post-vaccination, they aver, Karl suffered a devastating regression through the months of February, March, and April 2005, and ultimately a severe loss of normal neurological function by July 2005. Pet'rs' Mot. for Review ("Pet'rs' Mot.") at 7-9, 11; *see Entitlement Decision* at *20 (citing Tr. 657:13-19 (Test. of Dr. Richard Frye)); *see also* Tr. 659:25 to 660:10 (Frye).[3] Contrastingly, the government argues that Karl showed symptoms of neurological dysfunction prior to the vaccinations, that Karl's condition actually improved from January to March 2005, and that Karl's regression only

[2]The transcript of the entitlement hearing before the special master is cited as "Tr. __:__." Documentary materials made part of the record are cited as "R. Ex. __, at __."

[3]To support their contentions, the Palucks rely upon the testimony and reports submitted to the special master by their expert, Dr. Richard Frye. Dr. Frye is an assistant professor of pediatrics and neurology at the University of Texas Houston Health Science Center. *See* R. Ex. 16; Tr. 37:10-14. He received a bachelor's degree in psychobiology from C.W. Post of Long Island University, a master's degree in biomedical science/biostatistics from Drexel University, and both a Ph.D. in physiology and biophysics and an M.D. from Georgetown University. Dr. Frye is board-certified in general pediatrics and in neurology with special competence in child neurology. He has published numerous articles and has held residencies or professorships affiliated with Harvard University, Boston University, the University of Miami, and the University of Texas. *See* R. Ex. 17.

began again in April 2005, far too late for vaccines to have been the cause. *See* Resp't's Mem. in Resp. to Pet'rs' Mot. for Review ("Resp't's Opp'n") at 18-22.[4] The special master in essence adopted the government's position.

Karl received well-child examinations at two, four, and six months of age, each of which was uneventful. *Entitlement Decision* at *18 (citing R. Ex. 3, at 1-2; R. Ex. 5, at 59-61). However, on September 27, 2004, when Karl was eight months old, a pediatrician, Dr. Heather Ernst, examined Karl and observed delays in his gross motor skills. She recommended that he be referred to an infant development service, K.I.D.S. *See id.*; R. Ex. 5, at 111; R. Ex. 15, at 1. The K.I.D.S. evaluation was conducted on October 21, 2004, when Karl was nine months old. The evaluators found that "Karl presents with a mixed picture" and that "Karl's gross motor delays are impacting his ability to achieve age-level skills in other areas of development." R. Ex. 15, at 4. The evaluators recommended that he receive therapy "targeting his speech/language, gross motor, and the delays in fine motor related to low muscle tone." *Entitlement Decision* at *18 (quoting R. Ex. 15, at 5).[5]

During this same time period, Karl began manifesting two medical problems that would appear repeatedly from approximately October 2004 to July 2005: otitis media[6] and erythema multiforme.[7] *Entitlement Decision* at *18; *see* R. Ex. 3 at 57-71. The experts of both parties agreed that the erythema multiforme, when present, was evidence that Karl's immune system was activated. *Entitlement Decision* at *18. The experts also agreed that Karl was born with a

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[4]For its arguments, the government relies upon the testimony and reports submitted to the special master by its expert, Dr. Robert Snodgrass. Dr. Snodgrass is a professor of pediatrics and neurology at the University of California, Los Angeles School of Medicine. He received a bachelor's degree in social relations from Harvard College and an M.D., magna cum laude, from Harvard Medical School. Like Dr. Frye, Dr. Snodgrass is board-certified in neurology, with special competence in child neurology. He has written dozens of articles and has held professorships at medical institutions associated with Harvard University, Cambridge University, the University of Southern California, Stanford University, the University of Mississippi, and the University of California, Los Angeles. *See* R. Ex. B.

[5]Tone is a measurement of the muscles' ability to maintain the body in proper posture in different positions, such as sitting, standing, or being held. Normal tone means the muscles are maintaining the body in proper posture. Low tone means the muscles do not sufficiently function to maintain the body in proper posture. *See* Tr. 109:18-25, 110:24 to 111:8 (Frye).

[6]Otitis media is "inflammation of the middle ear." *Dorland's Illustrated Medical Dictionary* 1351 (32nd ed. 2012) ("*Dorland's*").

[7]Erythema multiforme, which has rash-like symptoms, is "either of two conditions characterized by sudden eruption of erythematous papules, some of which evolve into target lesions consisting of a central papule surrounded by a discolored ring or rings. Both represent reactions of the skin and mucous membranes to factors such as viral skin infections . . . ; agents (including drugs) that are ingested or irritate the skin; [or] malignancy." *Dorland's* at 643; *see also* Tr. 261:2-12 (Test. of Dr. Robert Snodgrass).

mitochondrial defect of some kind,[8] although they disagreed as to its role in Karl's neurodegeneration. *See Entitlement Decision* at *3.

On December 27, 2004, when Karl was eleven months old, he was examined by his primary physician, Dr. Stephen McDonough. The doctor noted, the "[d]evelopmental history reveals that Karl is rolling over. He tries to crawl, he has several words that he says. . . . Neurologic examination reveals normal muscle tone. There is no ankle clonus.[9] Deep tendon reflexes appear to be symmetrical. He has good head control and fairly good truncal control but is not pulling himself to stand or crawling yet. . . . [P]ossible mild gross motor delay." R. Ex. 3, at 5-6.

On January 19, 2005, Karl was again examined by Dr. McDonough as part of his one-year well-child visit. Dr. McDonough administered the DENVER II, a common developmental screening test, by evaluating Karl's skills as listed in the test's four categories. *See* Ex. 5, at 35. First, for the "personal-social" category, Dr. McDonough marked "P" next to "initiate activities," "play ball with examiner," and "indicate wants." *Id.* He marked "F" next to "wave bye-bye" and "play pat a cake." *Id.* Second, for the "fine motor — adaptive" category, Dr. McDonough wrote a single large "P" next to the activities "bang 2 cubes held in hands" and "thumb finger grasp." *Id.* Third, for the "gross motor" category, Dr. McDonough wrote a "P" next to "stand holding on" and "pull to stand," but wrote an "F" next to "get to sitting," "stand 2 secs," and "stand alone." *Id.* Fourth, for the "language" category, Dr. McDonough marked "P" next to "dada/mama specific" and "F" next to "one word." *Id.* Dr. Frye interpreted these last marks to mean that the only words Karl could say were "mama" and "dada." *See* Tr. 700:14-24. Dr. Frye also testified that Dr. McDonough failed to score the DENVER II test correctly for Karl's age. *See Entitlement Decision* at *18; Tr. 630:9 to 638:17 (Frye).

At this appointment, Dr. McDonough made additional findings regarding Karl. On a chart labeled "physical examination," Dr. McDonough marked the category "neuromuscular" as

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[8]"Mitochondria are organelles (parts of cells) that provide energy to the cells, through a process known as oxidative phosphorylation." *Entitlement Decision* at *1 (citing *Dorland's Illustrated Medical Dictionary* 1187 (31st ed. 2007)). "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." *Id.* (quoting R. Ex. E, at 2 (Richard H. Haas et al., *Mitochondrial Disease: A Practical Approach for Primary Care Physicians*, 120 Pediatrics 1326, 1326 (2007))). While Karl's mitochondrial dysfunction was not apparent in April 2005, *see* Tr. 114:15 to 116:7 (Frye) (citing R. Ex. 5, at 29), testing done in October 2005 demonstrated specific mitochondrial abnormalities, *see* Tr. 84:17 to 88:25 (Frye).

[9]Clonus is "alternate muscular contraction and relaxation in rapid succession." *Dorland's* at 373. Ankle clonus is "a series of abnormal rhythmic reflex movements of the foot, induced by sudden dorsiflexion, which causes alternate contraction and relaxation of the . . . muscle." *Id.* Dorsiflexion is "flexion or bending toward the extensor aspect of a limb, as of the hand or foot," *i.e.*, the hand or foot bends backwards toward the arm or leg. *Id.* at 563; *see also* Tr. 538:19 to 540:1 (Snodgrass).

abnormal, noting "muscle tone [upward-pointing arrow] . . . upper . . . extremities . . . 2 beats clonus [right ankle]." R. Ex. 3, at 3; *see Entitlement Decision* at *19; Tr. 332:9-19 (Snodgrass); *see also* Tr. 467:5-13 (same).[10] Dr. McDonough also checked the category "hips" as normal and wrote next to it some word or words followed by "ROM," meaning range of motion. Dr. Frye maintained in testimony that the writing preceding "ROM" is the word "full," meaning Karl's hips showed a full range of motion. Tr. 825:9-15. In contrast, Dr. Snodgrass stated that the writing preceding "ROM" indicated decreased range of motion. Tr. 466:18-19. Dr. McDonough also wrote on the same chart that Karl "doesn't hold cup well," circled the word "babbles," and wrote beneath it "not yet no words." R. Ex. 3, at 3; *Entitlement Decision* at *18. Finally, at this same appointment, Karl was given the MMR, varicella, and Prevnar vaccines. *Entitlement Decision* at *19 (citing Ex. 4, at 18).

Within two days of receiving the vaccinations, Karl showed signs of irritability and fever. His daycare provider recorded that he had a temperature of 101.5 degrees on January 21, 2005, and recorded a temperature of 101.3 degrees seven days later on January 28, 2005. *See Entitlement Decision* at *19 (citing Ex. 22, at 1-2). From January 21, 2005, to February 4, 2005, according to the daycare records, Karl was often fussy, did not eat well, and was tired. *Id.* Dr. Frye asserted that the January 19 vaccinations caused Karl's fever. Tr. 197:1-3, 644:10-13. Dr. Frye also asserted that Karl's symptoms in late January and early February indicated the first signs of the biological processes that eventually led to Karl's neurological regression. *See* Tr. 103:23 to 104:3, 197:12-14, 660:1-6 (describing Karl's post-vaccination symptoms as manifesting encephalopathy); *see also* Tr. 703:19 to 704:2. Dr. Snodgrass disagreed with both assertions, stating that the fever on January 21 manifested too early to be attributed to the vaccines, that the fever on January 28 was more likely due to an outbreak of Karl's erythema multiforme, and that the fevers in any event were not related to Karl's neurological decline. *Entitlement Decision* at *19; *see* Tr. 338:22 to 339:2, 339:19-25, 346:11-25, 350:1-10 (Snodgrass).

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[10]There is some confusion over precisely what Dr. McDonough wrote on the "neuromuscular" line of the chart. Dr. Snodgrass testified as follows on cross-examination:

> Q. [I]f you look at that handwritten note of Dr. McDonough, he's noting muscle tone increase positive upper. He doesn't say upper and lower, does he?
>
> A. I think he does. It's kind of hard to read. Now I wouldn't criticize anybody who has trouble reading it, but if you look along that line it says muscle tone and there's an arrow pointing up and a plus. Then it says upper and then you go down to the next line and you see L-O-W-E-R. To the left of the L-O-W-E-R is something that I think is an ampersand, meaning upper and lower, and then I think you can clearly read extremities after you see lower.

Tr. 466:25 to 467:12.

In February 2005, the Palucks began taking Karl to a chiropractor. Karl's chiropractic record contains an entry for February 11, 2005 in which is written the word "spastic."[11] *Entitlement Decision* at *26 (citing R. Ex. 12, at 5). An entry for February 16, 2005 states "less rigid — more comfortable on all 4s," and an entry for February 18, 2005 states "less rigid — 'happier.'" R. Ex. 12, at 5. Later entries note variable, but generally worsening, degrees of "spasticity," "stiff[ness]," and "hypertonicity."[12] *See id.* at 5-9. Dr. Frye testified that the chiropractor's finding of spasticity on February 11, 2005 "suggests a very severe neurological event, and that suggests . . . that there was very rapid change in his central nervous system." Tr. 647:14-18; *see also Entitlement Decision* at *26 (quoting Tr. 659:25 to 660:10). Dr. Snodgrass differed, testifying that "[t]hey [the chiropractic clinic] often say spastic, stiff, et cetera. So they are reporting on the same general phenomenon which first became evident to Dr. McDonough in January." Tr. 337:1-4; *see also* Tr. 543:15-20 (same); Tr. 805:14-22 ("I think that a chiropractor would have some idea of what spastic means, but not necessarily the same that a physician would. And I think when you're talking about a 13 or 14-month-old child, I don't think chiropractors are in a position to make any nuanced statements about them. . . . I don't believe they are trained to evaluate infants.").

Karl's difficulties continued into March 2005. A note from Dr. McDonough's office dated March 22, 2005 recorded that Karl has "some brief crawling" and is "babbling more," but is "not sitting on his own" and "leans to one side." *Entitlement Decision* at *20 (quoting R. Ex. 5, at 72). The special master found that the notations of Karl's "brief crawling" and "babbling more" were signs of progress since Karl's December 27, 2004 visit with Dr. McDonough. *See id.*; *see also* Tr. 545:18 to 546:24 (Snodgrass). This conclusion appears not to have been shared by Karl's treating physician, Dr. McDonough, who on March 24, 2005, referred Karl to Dr. Siriwan Kriengkrairut, a neurologist, because of Karl's "gross motor delay, global developmental delay, and hypertonicity." R. Ex. 3, at 7. Dr. McDonough wrote that he "would appreciate [Dr. Kreingkrairut's] evaluation and medical investigations into the etiology of [Karl's] developmental delay and hypertonicity." *Id.* An entry on Karl's chiropractic record for March 30, 2005, contains the notation, "discussed poss. adverse Rx/vaccine, C[erebral]P[alsy], cerebellar tumor." R. Ex. 12, at 7; Tr. 649:4-19 (Frye).

Karl's health had declined by April 2005. Dr. McDonough saw Karl on April 13, 2005 and noted "global developmental delay," including problems with "speech and fine and gross motor development." *Entitlement Decision* at *21 (quoting R. Ex. 3, at 9-10). Dr. McDonough wrote that Karl's "hips are tight with decreased hip flexion to about 70 degrees bilaterally with increased [sic, a word appears to be absent] the lower extremities. This is a change of hip movement over the last couple of months." *Id.* (alteration in original) (quoting R. Ex. 3, at 10).

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[11]Spastic means "of the nature or characterized by spasms[;] hypertonic, so that the muscles are stiff and the movements awkward." *Dorland's* at 1741.

[12]Hypertonicity is "the state or quality of being hypertonic," *Dorland's* at 897, and hypertonic refers to "exhibiting hypertonia," *id*. Hypertonia denotes "excessive tone of the skeletal muscles, so they have increased resistance to passive stretching and reflexes are often exaggerated; this usually indicates upper motor neuron injury." *Id*.

The neurologist, Dr. Kriengkrairut, examined Karl on April 19, 2005 and noted "truncal hypotonia with marked spasticity of the extremities. The baby has tendency to do cortical thumb bilaterally,[13] worse on the right compared to the left. . . . [D]elayed development as well as hypotonia of the extremities may be secondary to central nervous system pathology." R. Ex. 3, at 84-85; *see Entitlement Decision* at *21-22. Dr. Kriengkrairut also ordered an MRI of Karl's brain. R. Ex. 3, at 84. The MRI was initially interpreted as normal, but a later reexamination found signs of brain abnormality. R. Ex. 11, at 277. Dr. McDonough saw Karl again on April 26, 2005, when Karl was slightly over 15 months old, and wrote that Karl "rolls over but does not sit without support. He does not crawl and does not say any words. . . . Hips are tight on range of motion." R. Ex. 3, at 12-13. Dr. McDonough again described Karl as suffering from global developmental delay. *Id*. at 12.

Karl declined further in the ensuing months. While the special master found isolated instances of slight improvement, *see Entitlement Decision* at *22 (quoting Ex. 6, at 33), these events contrast with a general trend of deterioration from April 2005 to July 2005, *see* Tr. 476:2-17, 523:16-22 (Snodgrass). Karl suffered a seizure on July 12, 2005, and additional seizures over the next two days. *Entitlement Decision* at *22; R. Ex. 3, at 17. Dr. McDonough examined Karl on July 16, 2005 and assessed him as having "[g]lobal developmental delay with seizure disorder, possible deteriorating neurologic status in that he is unable to do some things that he was able to do previously." R. Ex. 4, at 15. Since July 2005, Karl has lived in a state of severe neurological disability.

B. *The Special Master's Decision*

The Palucks filed their petition for compensation on December 21, 2007, alleging that Karl "sustained a permanent injury to his brain and central nervous system as a result of receipt of his childhood vaccines . . . [and] that the exposure to childhood vaccines caused and/or aggravated a mitochondrial disorder in Karl." Pet. at 1. Three hearings in the case were held over the course of 2010. At the hearings, the parties disagreed as to whether Karl's vaccines caused or aggravated his neurodegenerative course. Dr. Frye testified that the vaccines either caused Karl's injury, or aggravated his condition, according to the following 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

[13]The word "cortical" means "pertaining to or of the nature of a cortex," *Dorland's* at 421, in this case, the cerebral cortex. *See* Tr. 584:4-6 (Snodgrass). Thumbing is the action of maintaining one's hand in a fist with the thumb held inside the fist. *See* Tr. 583:6-14 (Snodgrass). Dr. Frye testified that Karl's thumbing was indeed cortical and a sign of damage to the brain. Tr. 112:7-8. Dr. Snodgrass disagreed, testifying that Karl's thumbing was not necessarily cortical and only showed "dysfunction somewhere in the central nervous system above the level that controls the hand." Tr. 584:1-2.

> 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.

Entitlement Decision at *8 (quoting Pet'rs' Post-Trial Br. at 25-26); *see also* Tr. 54:25 to 81:17 (Frye); *see also* R. Ex. 16, at 2; R. Ex. 26; R. Ex. 30, at 1. Applying the theory to Karl's case, Dr. Frye testified that Karl had an underlying mitochondrial disorder that prevented him from coping with the oxidative stress of the vaccines. This led to "decompensation" within his cells and eventually cellular death, resulting in neurodegeneration. *See* Tr. 80:4 to 81:18 (Frye).

Dr. Snodgrass disagreed. He testified that "there are problems with [Dr. Frye's] theory in general and there are problems with its specific application to the case of Karl Paluck." Tr. 278:12-15; *see also* Tr. 294:17 to 295:18 (same). The problem with Dr. Frye's theory generally, according to Dr. Snodgrass, was the lack of published literature demonstrating that vaccines cause oxidative stress in humans. *See* Tr. 282:13-17, 294:17-20; *see also* R. Ex. BB. Dr. Snodgrass also disagreed with the theory's application to Karl, testifying that Karl's medical history did not support the idea that vaccines caused or aggravated his condition. Dr. Snodgrass stated that Karl manifested developmental delays before his vaccinations on January 19, 2005. *See* Tr. 326:25 to 331:14, 338:6-7. Dr. Snodgrass also stated that between January 2005 and April 2005, Karl's condition fluctuated, but did not worsen, as would be expected had the vaccines caused Karl's injury. Tr. 349:24 to 350:4, 358:9 to 359:24, 367:15-23.

The special master issued a decision denying compensation on December 14, 2011. The special master held that petitioners had failed to prove that the vaccines administered to Karl on January 19, 2005 caused his injury or significantly aggravated a preexisting condition. In so holding, the special master applied the three-prong causation framework set out in *Althen*, 418 F.3d 1274, which requires a petitioner

> 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.

Entitlement Decision at *6 (alteration in original) (quoting *Althen*, 418 F.3d at 1278). The special master found that the Palucks had failed to carry their burden as to any of the three prongs. Regarding *Althen*'s first prong, the special master was not convinced by the evidence presented that vaccines produce oxidative stress generally, *see id.* at *11-13, or oxidative damage particularly in persons with mitochondrial disorders, *see id.* at *14-16. Regarding *Althen*'s second prong, *i.e.*, that relating to a logical sequence of cause and effect, the special master found that Karl's history did not demonstrate that the vaccinations were the cause of his injury or aggravated condition. *See id.* at *23. According to the special master, Dr. Frye's testimony that Karl's course "looked like . . . a progressive hill downward for about six months [from January to July 2005]," *id.* at *22 (omission in original) (quoting Tr. 231:13-14), "d[id] not match what actually happened to Karl," *id.* Instead, the special master credited Dr. Snodgrass's testimony

that Karl's development fluctuated between September 2004 and April 2005, with Karl actually improving between the time of his January 2005 vaccinations and late March 2005. *See id.* at *20, *22. Regarding *Althen*'s third prong, the special master concluded that Karl's symptoms emerged too late for a proximate temporal sequence to indicate that the vaccines were the cause of Karl's injuries or a significant aggravation of them. *Id.* at *26. Discounting Dr. Frye's testimony that damage from oxidative stress can emerge within "days or weeks or months," *id.* at *24 (quoting Tr. 129:14), the special master found instead that oxidative damage would have occurred in Karl within fourteen days. *See id.* at *24-26. The special master also found that Karl's immediate post-vaccination symptoms — fever, irritability, and, according to his chiropractor, spasticity and hypertonicity — did not evidence progressing neurodegeneration. *Id.* at *26. Finding that Karl did not manifest neurological problems until April 2005, the special master held that Karl's injury fell outside the medically expected timeframe for vaccine injury. *Id.* at *27.

The Palucks filed their motion for review on January 13, 2012, arguing that the special master's conclusions on all three *Althen* prongs were "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 42 U.S.C. § 300aa-12(e)(2)(B). The government responded with a memorandum urging affirmance. Oral argument was held on March 21, 2012, and the case is now ready for disposition.

STANDARDS FOR REVIEW

In conducting the court's review, the special master's determinations of law are reviewed *de novo*. *Andreu ex rel. Andreu v. Secretary of Health & Human Servs.*, 569 F.3d 1367, 1373 (Fed. Cir. 2009) (quoting *Althen*, 418 F.3d at 1278). The special master's findings of fact are reviewed for clear error. *Id.*; *see Broekelschen v. Secretary of Health & Human Servs.*, 618 F.3d 1339, 1345 (Fed. Cir. 2010) ("We uphold the special master's findings of fact unless they are arbitrary or capricious." (citing *Capizzano v. Secretary of Health & Human Servs.*, 440 F.3d 1317, 1324 (Fed. Cir. 2006))). This court does not "reweigh the factual evidence, assess whether the special master correctly evaluated the evidence, or examine the probative value of the evidence or the credibility of the witnesses — these are all matters within the purview of the fact finder." *Porter v. Secretary of Health & Human Servs.*, 663 F.3d 1242, 1249 (Fed. Cir. 2011) (citing *Broekelschen*, 618 F.3d at 1349). So long as those findings are "based on evidence in the record that [is] not wholly implausible," they will be accepted by the court. *Lampe v. Secretary of Health & Human Servs.*, 219 F.3d 1357, 1363 (Fed. Cir. 2000). This "level of deference is especially apt in a case in which the medical evidence of causation is in dispute." *Hodges v. Secretary of Dep't of Health & Human Servs.*, 9 F.3d 958, 961 (Fed. Cir. 1993); *see also Cedillo v. Secretary of Health & Human Servs.*, 617 F.3d 1328, 1338 (Fed. Cir. 2010).

Nonetheless, a deferential standard of review "is not a rubber stamp." *Porter*, 663 F.3d at 1256 (O'Malley, J., concurring in part and dissenting in part). The special master must "consider[] the relevant evidence of record, draw[] plausible inferences and articulate[] a rational basis for the decision." *Hines ex rel. Sevier v. Secretary of the Dep't of Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991); *see* 42 U.S.C. § 300aa-13(b)(1). The special master's findings of fact must be "supported by substantial evidence." *Doe v. Secretary of Health & Human Servs.*, 601 F.3d 1349, 1355 (Fed. Cir. 2010) (citing *Whitecotton ex rel. Whitecotton v.*

Secretary of Health & Human Servs., 81 F.3d 1099, 1105 (Fed. Cir. 1996), *on remand from Shalala v. Whitecotton*, 514 U.S. 268 (1995)). And, while the special master need not address every snippet of evidence adduced in the case, *see id.*, he cannot dismiss so much contrary evidence that it appears that he "simply failed to consider genuinely the evidentiary record before him," *Campbell v. Secretary of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011).

An overarching question arises regarding the standards for review to be applied in this case. The Vaccine Act establishes two methods of proving causation. For so-called "Table injuries," causation is presumed if a petitioner's vaccine and subsequent injury, or significantly aggravated condition, are listed on the Vaccine Injury Table set out at 42 U.S.C. § 300aa-14(a). *See* 42 U.S.C. § 300aa-11(c)(1)(C)(i). However, for so-called "off-Table injuries" — that is, for injuries or significantly aggravated conditions not listed on the Vaccine Injury Table — the petitioner must prove causation in fact. 42 U.S.C. §§ 300aa-11(c)(1)(C)(ii)(I), -13(a)(1); *see Broekelschen*, 618 F.3d at 1341-42; *Andreu*, 569 F.3d at 1374. Here, the parties agree that Karl's neurodegeneration is not listed on the Vaccine Injury Table. Correlatively, the parties also agree that the three *Althen* factors for establishing causation apply. The parties' agreement on legal issues ends there, however.

A significant question arises whether to classify Karl's neurodegeneration as a significant aggravation of his preexisting mitochondrial disorder or, instead, as an altogether new injury. The distinction matters because additional elements of required proof would be triggered by a significant-aggravation claim. The Vaccine Act defines "significant aggravation" as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." 42 U.S.C. § 300aa-33(4). Thus, for claimants alleging significant aggravation, "the statute implicitly requires a comparison of the person's pre-vaccination condition with the person's current, post-vaccination condition. Indeed, such a comparison is inherent in the plain meaning of the word 'aggravation' itself." *Loving ex rel. Loving v. Secretary of Dep't of Health & Human Servs.*, 86 Fed. Cl. 135, 143 (2009) (quoting *Whitecotton*, 81 F.3d at 1107).[14] Conversely, "a claimant . . . not alleging significant aggravation" must instead show that the onset of his or her condition occurred after receipt of a

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[14]The *Loving* test requires preponderant proof of

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

Loving, 86 Fed. Cl. at 144. Elements four through six of the *Loving* test reflect the causation elements of *Althen*.

vaccine. *Whitecotton*, 514 U.S. at 274.[15]

The Palucks contend that Karl's neurological regression is a new injury. According to the Palucks, although Karl suffered from an underlying mitochondrial disorder, Karl was still making progress until his vaccinations. Only then did he begin to regress. Thus, it is their position that while the underlying mitochondrial disorder may have made Karl more susceptible to neurological regression, the resulting neurological damage is nonetheless a different injury. *See* Tr. 564:1-8 (petitioners' counsel); Hr'g Tr. 7:17 to 8:2, 15:5-16 (Mar. 21, 2012). The government disagrees, contending that Karl demonstrated signs of neurological regression prior to his vaccinations. *See* Hr'g Tr. 38:18 to 39:16 (Mar. 21, 2012). Thus the government posits that Karl's injury, if attributable to the vaccines at all, is a case of significant aggravation. *Id*.

This dispute by the parties over classification requires the resolution of two sequential issues. The first is the precise definition of Karl's injury, which is a precondition to identifying the timing of its symptoms. *Cf. Veryzer v. Secretary of Health & Human Servs.*, 100 Fed. Cl. 344, 357 (2011) ("[T]he 'etiology' of the disorder determines the appropriate temporal relationship." (citing *de Bazan v. Secretary of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008))). On the facts of this case, one question is whether Karl's neurodegeneration followed the typical course of a person that suffers from his type of mitochondrial defect. *See* 42 U.S.C. § 300aa-33(4). A related second issue is whether indicia of Karl's neurodegeneration manifested themselves prior to the vaccinations that occurred January 19, 2005. The parties have framed these issues in simplified terms, *i.e.*, whether Karl was progressing or regressing developmentally prior to his vaccinations. With a genetic abnormality of the type inhering in Karl, this may not be the proper focus for determination. Rather, based on the record as it stands, voluminous as it may be, it is medically and scientifically uncertain whether developmental progress or regress is a valid measure to assess the pre-vaccination condition of a very young child with Karl's type of mitochondrial defect, or whether another indicator should be employed. If Karl's neurological, not mitochondrial, symptoms, however defined, were manifested pre-vaccination, then Karl's case involves a significant-aggravation claim. *See Whitecotton*, 514 U.S. at 274. If not, then Karl's case concerns a new-injury claim.

The special master conducted his analysis under the *Althen* rubric, reasoning that the Palucks, regardless of the nature of Karl's injury, would be required to satisfy the three prongs set out by *Althen* and adopted equally by *Loving*. *See Entitlement Decision* at *6 n.9. That

[15]Unlike the Palucks, the petitioners in *Whitecotton* asserted an on-Table claim. Even so, the logic of *Whitecotton*'s holding extends to off-Table claims. In *Whitecotton*, the Supreme Court set out a requirement of "one injury, one onset" for a non-aggravation on-Table claim. That requirement, though, was based on the text of the Vaccine Act: "a claimant relying on the table (and not alleging significant aggravation) must show that 'the first symptom or manifestation of the onset . . . of [her table illness] . . . occurred within the time period after vaccine administration set forth in the Vaccine Injury Table.'" *Whitecotton*, 514 U.S. at 274 (alteration in original) (quoting 42 U.S.C. § 300aa-11(c)(1)(C)(i)). That operative phrase — "the first symptom or manifestation of the onset" — appears throughout the Vaccine Act to describe non-aggravation vaccine injury without any distinction between on-Table and off-Table types. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C)(ii)(II), -13(b)(2), -16(a).

preliminary conclusion of law is correct, and the court accordingly will focus on the special master's findings related to causation under the shared *Althen-Loving* framework. If Karl's claim fails under the causation standards, it would be unnecessary to consider whether the *Whitecotton-Loving* additional elements pertinent to significant-aggravation claims also apply.

Causation in off-Table cases, like the present one, must be proved by a preponderance of the evidence. The Federal Circuit has repeatedly emphasized that preponderant proof of causation does not require scientific certainty, but rather only a showing that the vaccine more likely than not caused the injury.[16] *See Althen*, 418 F.3d at 1280 ("While this case involves . . . a sequence hitherto unproven in medicine, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body."); *see also Moberly ex rel. Moberly v. Secretary of Health & Human Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010) ("A petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'" (quoting *Knudsen ex rel. Knudsen v. Secretary of Dep't of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994))); *Andreu*, 569 F.3d at 1378-79 ("Requiring 'epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act,'" *id.* at 1378 (omissions in original) (quoting *Capizzano*, 440 F.3d at 1325-26)). Even so, the preponderance standard for causation is not to be confused with a standard requiring only "possible" or "plausible" causation. *See Moberly*, 592 F.3d at 1322.

As set out in Vaccine Rule 8(b)(1), the special master must "consider all relevant and reliable evidence." *See also* 42 U.S.C. § 300aa-13(b)(1). "By inclusion of the terms 'relevant and reliable,' [the rule] necessarily contemplates an inquiry into the soundness of scientific evidence to be considered by special masters." *Cedillo*, 617 F.3d at 1339. Thus, regarding expert testimony related to causation, "the special master is entitled to require some indicia of reliability." *Moberly*, 592 F.3d at 1324 (citing *Terran v. Secretary of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999) (in turn citing *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993))); *see also Cedillo*, 617 F.3d at 1338-39 & n.3; *Hazlehurst v. Secretary of Health & Human Servs.*, 604 F.3d 1343, 1353-54 (Fed. Cir. 2010) (upholding special master's finding that theory of causation should not be credited when supported only by unreliable studies). And even a reliable theory of causation must be shown to be applicable to the facts of the particular case at hand. *See Doe*, 601 F.3d at 1355.

ANALYSIS

As stated earlier, the special master concluded that the Palucks were unable to satisfy any of the three elements of causation required by *Althen*. Consequently, the Palucks' three primary objections correspond to the special master's conclusions on each of those three elements.

[16] As noted in *Althen*, 418 F.3d at 1279 & n.6, this requirement comes from the Vaccine Act itself: "Compensation shall be awarded . . . to a petitioner . . . [who] has demonstrated by a preponderance of the evidence the matters required in the petition by [42 U.S.C. § 300aa-11(c)(1)]." 42 U.S.C. § 300aa-13(a)(1).

I. *Althen*'s First Prong: A Theory Connecting Vaccine and Injury

A. *A Biologically Plausible Theory*

As an initial step, a petitioner must establish by a preponderance of the evidence "a medical theory causally connecting the vaccination and the injury." *Althen*, 418 F.3d at 1278. The Federal Circuit has issued a number of decisions bearing on what constitutes a "reputable medical or scientific explanation" of a theory sufficient to satisfy this requirement. *Id.* In essence, a petitioner who provides a theory that is conceded as plausible by the government, or that has indicia of reliability, will satisfy *Althen*'s first prong. *See Dobrydnev v. Secretary of Health & Human Servs.*, 98 Fed. Cl. 190, 206 (2011) ("[A] medical theory propounded by medical experts with highly relevant academic credentials and specific field expertise . . . is *prima facie* evidence of biologic plausibility, unless their lack of [reliability] or bias is established or current scientific evidence is proffered to the contrary."); *Campbell*, 97 Fed. Cl. at 658 n.18 (defning a theory for the purposes of *Althen's* first prong as "a hypothesis that is offered, propounded, or accepted as accounting for the known facts"). In *Althen*, for example, the court upheld the trial court's finding of causation where the petitioner's theory was uncontradicted by the government's expert. *See Althen*, 418 F.3d at 1281-82; *Althen v. Secretary of Health & Human Servs.*, 58 Fed. Cl. 270, 285 (2003), *aff'd*, 418 F.3d 1274; *cf. Jay v. Secretary of Dep't of Health & Human Servs.*, 998 F.2d 979, 984 (Fed. Cir. 1993) (a reputable and uncontradicted medical explanation connecting facts to an on-Table injury demonstrates causation as a matter of law). In *Capizzano*, the court similarly held that "the first prong of the *Althen* . . . test was satisfied by the finding that the hepatitis B vaccine can cause [rheumatoid arthritis]." 440 F.3d at 1326 (citing *Capizzano v. Secretary of Dep't of Health & Human Servs.*, No. 00-759V, 2004 WL 1399178, at *16 (Fed. Cl. Spec. Mstr. June 8, 2004), *aff'd*, 63 Fed. Cl. 227 (2004), *vacated & remanded on other grounds*, 440 F.3d 1317). Likewise, in *Andreu*, the court held that petitioners had satisfied *Althen*'s first prong when the government "did not dispute the biologic plausibility of [the petitioner's expert's] medical theory, [even though] numerous medical studies . . . failed to find a relationship between" the petitioner's symptoms and vaccination. *Andreu*, 569 F.3d at 1377-78 (internal quotation marks omitted).

In contrast, where basic indicia of reliability do not exist, the special master may reject a petitioner's medical theory. *See Porter*, 663 F.3d at 1253-54; *Moberly*, 592 F.3d at 1322. Thus, a theory relying upon "a literature review based on two papers from the early 1950s, which in turn considered vaccine cases between 1929 and 1952" was found insufficient to satisfy *Althen*'s first prong. *Broekelschen*, 618 F.3d at 1350-51. Likewise, a theory linking a pertussis vaccine to brain damage was rejected by a special master when the theory had never been tested and was criticized by the government's expert as biologically implausible. *Moberly*, 592 F.3d at 1325; *see also id.* at 1321 (testimony of petitioner's expert was "contradictory and confusing" and "shockingly poor" (quoting *Moberly ex rel. Moberly v. Secretary of Health & Human Servs.*, 85 Fed. Cl. 571, 605 (2009), *aff'd*, 592 F.3d 1315)). Similarly, the Federal Circuit has approved of a special master's rejection of medical literature that had no relation to the question of causation. *See Cedillo*, 617 F.3d at 1349 (quoting *Cedillo v. Secretary of Health & Human Servs.*, No. 98-916V, 2009 WL 996299, at *1 (Fed. Cl. Spec. Mstr. Mar. 16, 2009), *aff'd*, 89 Fed. Cl. 158

(2009), *aff'd*, 617 F.3d 1328); *see also Porter*, 663 F.3d at 1252-53.[17]

In this instance, the theory in dispute turns on a recent spate of research studies generated over the past four or five years exploring whether some adverse neurological conditions are linked to genetic defects in mitochondria.

B. *Dr. Frye's Theory*

To meet their burden under *Althen*'s first prong, the Palucks proffered the reports and testimony of Dr. Frye, accompanied by several dozen medical articles. Dr. Frye's theory begins with the process of immune activation. Foreign agents, such as vaccines, activate the body's immune system. Tr. 55:5-21 (Frye). The activated immune system produces reactive oxygen species and reactive nitrogen species. Tr. 63:6-8. Reactive oxygen species are "molecules that contain an oxygen atom with an unpaired electron." Tr. 58:21-22. Likewise, reactive nitrogen species are "molecule[s] with nitrogen in [them] and an unpaired electron," Tr. 60:23-24, which can, through an interaction between nitric oxide and a superoxide reactive oxygen species, "make a very toxic reactive nitrogen species which has a tendency to react with proteins and also cellular DNA." Tr. 61:11-12. When the amount of reactive oxygen species within the cell is high, the cell is in a state of oxidative stress. Tr. 61:16-17. To counterbalance oxidative stress, the body uses its antioxidant defenses to "convert these reactive oxygen species to harmless compounds." Tr. 65:21-22. If, however, the body's antioxidant defenses fail, oxidative stress can cause damage both to the body's cells generally and, specifically, to the cell organelles known as mitochondria. Tr. 66:12-14.[18] Damage to mitochondria or cells increases oxidative

[17]Instructive is the treatment of proffered causal theories in a series of cases in which claimants alleged their autism was caused by vaccines. The claimants' theories in those cases relied primarily upon the work of Dr. Andrew Wakefield and data from the Unigenetics laboratory, a for-profit, non-accredited institution established to support similar vaccine-related litigation in the United Kingdom. *See Hazlehurst*, 604 F.3d at 1346. In each case, the government introduced evidence that the Unigenetics testing was scientifically unreliable, methodologically flawed, could not be replicated, and was possibly fraudulent, and that Dr. Wakefield's work had been dismissed by the scientific community. *See id.* at 1347-48; *Cedillo*, 617 F.3d at 1340; *Snyder ex rel. Snyder v. Secretary of Health & Human Servs.*, 88 Fed. Cl. 706, 744 (2009). The government's experts in those cases rejected the plausibility of petitioners' theories. *See Hazlehurst ex rel. Hazlehurst v. Secretary, Dep't of Health & Human Servs.*, 88 Fed. Cl. 473, 489 n.33 (2009), *aff'd*, 604 F.3d 1343 ("[R]espondent's expert Dr. MacDonald, when asked about the plausibility of petitioners' medical theory, testified that it was 'fantastic, improbable and . . . most importantly not based on any data.'" (omission in original)). In each case, the court affirmed the special master's findings that the petitioner's theory was insufficient because it "depended on evidence that was discredited, unreliable, or inapposite." *Hazlehurst*, 604 F.3d at 1348; *see id.* at 1351; *Cedillo*, 617 F.3d at 1345-47; *Snyder*, 88 Fed. Cl. at 744-45.

[18]Mitochondria are "small spherical to rod-shaped cytoplasmic organelles. . . . Mitochondria generate energy (in the form of adenosine triphosphate [ATP] synthesis) by the oxidation of nutrients, and they contain the enzymes . . . [for] oxidative phosphorylation. In response to toxic insults they release enzymes that cause apoptosis." *Dorland's* at 1169 (first

stress, leading to a "vicious cycle" of damage and, eventually, cell death. Tr. 66:14-23; *see* R. Ex. 26, at 2. This cell death can occur through direct damage to the cell or through the activation of any of multiple intracellular pathways, some of which involve the mitochondria, that result in apoptosis. Tr. 70:15 to 71:23, 80:17-23; *see* R. Ex. 26, at 3; *see also* R. Exs. 21ee, 21ff. Oxidative stress occurs over the entire body, but certain cells, especially brain cells, are more vulnerable than others to oxidative damage and death. Tr. 61:24 to 62:18, 69:4-8. Cell death in the brain leads to neurodegeneration. *See* Tr. 111:13-17, 127:6-9.

According to Dr. Frye's theory, individuals with defective mitochondria are more vulnerable than others to oxidative stress. This is because mitochondria are responsible for the creation of the energy-carrying molecule adenosine triphosphate ("ATP"). ATP, in turn, is required for the synthesis of a primary antioxidant, glutathione. Tr. 73:23 to 74:6 (Frye).[19] Cells with defective mitochondria cannot efficiently create ATP, so they struggle to produce and recycle enough glutathione to neutralize reactive oxygen species. Tr. 74:25 to 75:4; *see also* R. Ex. 21qq. Additionally, defective mitochondria themselves produce abnormally high amounts of reactive oxygen species, which also can cause damage. Tr. 78:15-25, 79:7-25; *see* R. Ex. 26, at 5.[20]

Turning to Karl's case, the parties agree that Karl suffers from a mitochondrial defect. Hr'g Tr. 8:3-9 (Mar. 21, 2012). Dr. Frye testified that this mitochondrial defect rendered Karl particularly susceptible to "environmental stressors" that can cause "metabolic decompensation," *i.e.*, progressive dysfunction of the mitochondria leading to cellular death. Tr. 81:9-17, 89:19; *see also* R. Ex. 16, at 1; R. Ex. 30, at 1 (citing Ex. 21a (Bruce A. Barshop & Marshall L. Summar, *Attitudes Regarding Vaccination Among Practitioners of Clinical Biochemical*

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alteration in original); *see also supra*, at 4 n.8. Apoptosis is "a morphologic pattern of cell death affecting single cells." *Dorland's* at 118.

[19]Glutathione is "a tripeptide . . . [that] functions in various redox reactions, such as the destruction of peroxides and free radicals, the detoxification of harmful compounds, and activity as a cofactor for enzymes. . . . [T]hese reactions prevent oxidative damage by reduction of methemoglobin and peroxides." *Dorland's* at 791.

[20]The special master simplified Dr. Frye's theory thusly:

> 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 accumulate[,] leading to oxidative stress;
> 4. Oxidative stress causes cells to die;
> 5. The killed cells include brains cells[,] and the death of brain cells causes developmental regression.

Entitlement Decision at *8.

Genetics, 95 Molecular Genetics & Metabolism 1 (2008) ("Barshop, *Practitioners of Clinical Biochemical Genetics*"))). Environmental stressors include bacterial or viral illnesses and vaccines. Tr. 90:13-22. When Karl received his vaccinations on January 19, 2005, those vaccines activated an immune response from Karl. That response was manifested by Karl's fever, lethargy, and irritability in the days after the vaccination, Tr. 103:23 to 104:1, and indicated the beginning of Karl's "cascade of metabolic decompensation." Tr. 104:1-3; *see* R. Ex. 30, at 12.[21] The damage from this metabolic decompensation was evident from Dr. McDonough's and Dr. Kriengkrairut's examinations of Karl in April 2005, during which both doctors noted several symptoms of neurological dysfunction. *See* Tr. 108:15-19, 110:13-21; *see also* R. Ex. 11, at 277 (noting an MRI dated April 27, 2005 that showed brain abnormality). The damage continued to progress from April to July 2005, as Karl began to manifest more severe symptoms. Tr. 117:20 to 118:6; *see* R. Ex. 16, at 1-2.

Dr. Snodgrass's view of Dr. Frye's theory was mixed. On direct examination, Dr. Snodgrass testified that Dr. Frye's theory as a general proposition was not reliably supported because Dr. Snodgrass was unable to find published articles demonstrating that vaccines cause oxidative stress in humans. Tr. 282:12-17, 294:17-20; *see also* Tr. 756:20 to 757:4. Dr. Snodgrass also stated that persons with certain mitochondrial disorders may in fact improve when exposed to exercise-induced oxidative stress. *See* Tr. 348:4-20 (citing R. Ex. S (Julie L. Murphy et al., *Resistance Training in Patients with Single, Large-Scale Deletions of Mitochondrial DNA*, 131 Brain 2832 (2008) ("Murphy, *Patients with Single, Large-Scale Deletions of Mitochondrial DNA*"))). On cross examination, however, Dr. Snodgrass conceded that Karl's mitochondrial disorder was different from those in the exercise study. Tr. 451:8-11. Likewise, when pressed, Dr. Snodgrass conceded the major points of Dr. Frye's theory. *See* Tr. 448:18 to 449:7 (a person with a mitochondrial disorder, compared to a person with normal mitochondria, would have a lesser ability to recover from an excessive amount of reactive oxygen and nitrogen species); Tr. 482:7 to 484:15 (vaccines could cause persons with mitochondrial disorders to worsen).

C. *The Biological Plausibility of Petitioners' Theory*

The special master determined the Palucks' theory to be unreliable for two reasons. First, the special master found that the theory relied upon an unsubstantiated link between vaccines and oxidative stress. *See Entitlement Decision* at *12-13, *17. Second, the special master found that the Palucks had failed to prove that children with mitochondrial disorders were particularly vulnerable to oxidative stress. *See id.* at *13, *17.

As to the link between vaccines and oxidative stress, Dr. Frye's theory relied upon several medical articles. *Entitlement Decision* at *10. Of primary importance was a recent

[21] While not always explicit, the parties' experts appeared to have also addressed the possibility that Karl was especially susceptible to vaccine-induced metabolic decompensation because of the added immune system stress caused by his otitis media and, especially, his repeated bouts of erythema multiforme. *See* Tr. 625:1-8, 704:8-17 (Frye); Tr. 445:1-13, 483:14-22, 490:19 to 491:4 (Snodgrass).

article by Dr. Michael Phillips and others reporting an increase in purported markers of oxidative stress in persons given a flu vaccine. *See* R. Ex. 37a (Michael Phillips et al., *Effect of Influenza Vaccination on Oxidative Stress Products in Breath*, 4 J. Breath Res. 026001 (2010) ("Phillips, *Effect of Influenza Vaccination on Oxidative Stress Products in Breath*")). The special master found the Phillips article to be of little value, concluding that the biological markers measured in the study were not reliable measures of oxidative stress. *See Entitlement Decision* at *11-12.[22] The special master gave two reasons for this conclusion. First, the special master found that an earlier study conducted by Dr. Phillips used a different set of biological markers to measure oxidative stress. *See id.* at *11 (citing R. Ex. AA (Michael Phillips et al., *Effect of Oxygen on Breath Markers of Oxidative Stress*, 21 Eur. Respiratory J. 48 (2003))). Second, the special master found that "[t]he best way to detect oxidative stress is to measure the level of a substance known as F2-isoprostane." *Id.* at *12 (citing Tr. 280:3-7, 435:2 to 437:17, 579:1-13 (Snodgrass); Tr. 608:1-9, 697:11-19 (Frye)).

As to Dr. Frye's position that persons with mitochondrial disorders are particularly vulnerable to oxidative stress, the special master was again unpersuaded. First, the special master reasoned that mitochondrial problems are heterogeneous and, therefore, "[w]hat happens in one mitochondrial disorder may not happen in the next person with a mitochondrial disorder." *Entitlement Decision* at *13 (citing Tr. 286:5-19; R. Ex. 21z (John Shoffner et al., *Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression*, 25 J. Child Neurology, 429, 429 (2010) ("Shoffner, *Fever Plus Mitochondrial Disease*")), at 4). Second, the special master credited an article reporting that exercise, which causes oxidative stress, nonetheless benefited certain patients with mitochondrial DNA deletions. *See id.* (citing R. Ex. S (Murphy, *Patients with Simple, Large-Scale Deletions of Mitochondrial DNA*)). On this basis, the special master concluded that "[t]o 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." *Id*.

On review of these findings, it is plain that the special master required a higher level of proof from the Palucks than the Vaccine Act demands. This is true of the special master's treatment of both the link between vaccines and oxidative stress and the evidence related to mitochondrial disorders. Regarding oxidative stress, the special master rejected the Phillips article simply because the biomarkers used were different from those used in other studies. The Vaccine Act does not require that evidence be "medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49. While the best way to detect oxidative stress may, or may not, be to use the biomarker F2-isoprostane,[23] the burden to prove causation is not perfection or scientific

[22]The biological markers used were "volatile organic compounds," "including alkanes and methylated alkanes." R. Ex. 37a (Phillips, *Effect of Influenza Vaccination on Oxidative Stress Products in Breath*), at 2; *see also id.* at 6.

[23]Understandably, Dr. Phillips did not try to detect F2-isoprostane, because F2-isoprostane is found in *urine*, *see Entitlement Decision* at *12 (citing Tr. 436:14-18), while Dr. Phillips was searching particularly for biomarkers in patients' *breath*, *see* Ex. 37a (Phillips, *Effect of Influenza Vaccination on Oxidative Stress Products in Breath*), at 2 ("Breath testing for volatile organic compounds (VOCs) offers a potentially useful new approach to early diagnosis

certainty, but a preponderance of the evidence. The fact that the research investigating a link between vaccinations and oxidative stress is of quite recent origin is not fatal to the theory. Inquiry into the subject is just beginning, as the very recent dates of the articles show. "'[I]n a field bereft of complete and direct proof of how vaccines affect the human body,' a paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery." *Andreu*, 569 F.3d at 1379 (alteration in original) (quoting *Althen*, 418 F.3d at 1280). Tellingly, Dr. Snodgrass did not dispute the theory. Rather than rejecting the concept that vaccines could cause oxidative stress, he stated only that he could not find any studies establishing it as fact. *See* Tr. 282:13-17, 294:17-20 (Snodgrass). This is far from the emphatic denunciations that have doomed petitioners' theories in other cases. *See Moberly*, 592 F.3d at 1320 (government expert testifying that "people in the field d[o] not consider those aspects of the theory to be biologically plausible" (internal quotation marks omitted)); *Hazlehurst*, 88 Fed. Cl. at 489 n.33. The special master's rejection of the Palucks' oxidative-stress theory, on this record, was arbitrary and capricious.

Likewise, the special master was mistaken to reject the Palucks' evidence related to mitochondrial disorders. Here, the special master was "wrong as a matter of logic." *Campbell*, 97 Fed. Cl. at 669; *see Burlington Truck Lines v. United States*, 371 U.S. 156, 168 (1962) (an agency rationale lacking a logical basis is arbitrary and capricious). The special master wrote in full:

> 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 disorder may not happen in the next person with a mitochondrial disorder. Second, exercise, which causes oxidative stress, produced beneficial effects in people with mitochondrial DNA mutations. [R. Ex. S (Murphy, *Patients with Single, Large-Scale Deletions of Mitochondrial DNA*)]. Based upon this article, the [government] argues that "Dr. Frye's contention has no objective support and is objectively contradicted." 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.

Entitlement Decision at *13 (citations omitted). The special master's first postulate (that mitochondrial disorders are variegated) effectively abrogates any conclusions that can be drawn from the second (that oxidative-stress-inducing exercise benefited certain patients with specific mitochondrial disorders). Indeed, when questioned about the Murphy article, Dr. Snodgrass stated that the patients involved were unlike Karl. *See* Tr. 450:14 to 451:11. For the special master to dismiss the mitochondrial aspect of the Palucks' theory on this line of reasoning was

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of viral infections."). Notably, Dr. Phillips has published several articles on breath-based biomarkers. *See id.* at 7-8.

arbitrary and capricious.[24]

Finally, the special master erroneously rejected additional evidence to discount Dr. Frye's theory. The Palucks submitted four articles purportedly demonstrating that vaccines cause oxidative stress and oxidative damage in animals. *See Entitlement Decision* at *13 & n.17.[25] Dr. Snodgrass testified that the animal studies were not particularly helpful because the intent of the studies was "to make these animals sick," which would cause oxidative stress. Tr. 763:15-16. The special master translated Dr. Snodgrass's testimony as indicating that "these animal studies provide[d] little basis for opining that vaccines lead to the production of oxidative stress in humans." *Entitlement Decision* at *13. The Palucks also submitted a case study of a young girl with mitochondrial dysfunction, Hannah Poling, who suffered developmental regression after receiving vaccinations. *See Entitlement Decision* at *14 (citing R. Ex. 21q (Jon S. Poling, Richard E. Frye, John Shoffner & Andrew W. Zimmerman, *Developmental Regression and Mitochondrial Dysfunction in a Child with Autism*, 21 J. Child Neurology 170 (2006) ("Poling, *Developmental Regression and Mitochondrial Dysfunction*"))). The special master gave little weight to the Poling article, noting that case reports such as the Poling article shed little light on causation. *Id.* at *15.

It is axiomatic that animal studies are only "indirect evidence that may establish biologic plausibility [in humans]." *Kelly v. Secretary of Health & Human Servs.*, 68 Fed. Cl. 84, 93 (2005) (internal quotation marks omitted) (citing *Kelly v. Secretary of Health & Human Servs.*, No. 02-223V, 2005 WL 1125671, at *5 (Fed. Cl. Spec. Mstr. Mar. 17, 2005), *rev'd on other grounds*, 68 Fed. Cl. 84). It is also true that case reports "do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value." *Campbell*, 97 Fed. Cl. at 668. "Nonetheless, the fact that case reports can by their nature only present indicia of

[24]The special master similarly made a logical error in his treatment of an article reporting an e-mail survey of metabolic disorder experts for their views on vaccination. *See* R. Ex. 21a (Barshop, *Practitioners of Clinical Biochemical Genetics*). The special master concluded from the article that "[i]t appears that the consensus view of the respondents was that vaccines do not affect metabolic diseases." *Entitlement Decision* at *14. The article, however, says no such thing. Rather, as the special master recited in his decision, the article only reports that "[t]he overwhelming majority . . . feel that the benefits of the current schedule outweigh the risks to individuals with undiagnosed metabolic disease." *Id.* (quoting Ex. 21a (Barshop, *Practitioners of Clinical Biochemical Genetics*), at 2).

[25]The four articles are: R. Ex. 37b (Sindhu Saraswathy & Narsing A. Rao, *Photoreceptor Mitochondrial Oxidative Stress in Experimental Autoimmune Uveitis*, 40 Ophthalmic Res. 160 (2008) ("Saraswathy, *Photoreceptor Mitochondrial Oxidative Stress*")); R. Ex. 37c (Guey-Shuang Wu et al., *Photoreceptor Mitochondrial Tyrosine Nitration in Experimental Uveitis*, 46 Investigative Ophthalmology & Visual Sci. 2271 (2005) ("Wu, *Photoreceptor Mitochondrial Tyrosine Nitration*")); R. Ex. 37d (E. Philip Jesudason et al., *Anti-Inflammatory Effect of Melatonin on Aβ Vaccination in Mice*, 298 Molecular & Cellular Biochem. 69 (2007)); R. Ex. 37e (Asunción 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)).

causation does not deprive them of all evidentiary weight." *Id.* Further, the animal studies and the Poling article demonstrate that the relationship between vaccination, oxidative stress, and oxidative damage is the subject of active scientific investigation, albeit with, perhaps, inchoate results thus far for humans. *See Andreu*, 569 F.3d at 1379 ("[I]n some instances well-grounded but innovative theories will not have been published . . . . Some propositions, moreover, are too particular, *too new*, or of too limited interest to be published." (alterations in original) (emphasis added) (quoting *Daubert*, 509 U.S. at 593)). It was error for the special master to discount this additional evidence when it suggests that Dr. Frye's theory is, while not scientifically certain, under active, continuing scientific investigation by a range of researchers, showing that it is sufficiently worthy and reliable to merit that extensive scientific inquiry. The Vaccine Act requires no more.

D. *Synopsis*

The special master's treatment of the Paluck's medical theory reflects a failure to consider "the record as a whole." 42 U.S.C. § 300aa-13(a)(1).[26] As set out *supra*, a petitioner satisfies *Althen*'s first prong if he or she posits a medical theory that either is not contested by the government or is accompanied by indicia of reliability. Here, the only objection to the Palucks' general theory presented by the government's expert was that oxidative stress from vaccines has not been established in humans. *See* Tr. 282:13-17, 294:17-20 (Snodgrass). The Palucks' response to this criticism in the form of the Phillips article was improperly discounted by the special master. Putting aside that objection, then, Dr. Snodgrass otherwise conceded that Dr. Frye's general theory was plausible. *See* Tr. 449:6-7 ("I would say that if you have a mitochondrial abnormality, you[r] ability to recover [from oxidative stress] may be less."); Tr. 449:24 to 450:1 (same); Tr. 482:14-17 ("[O]f the many patients I've seen over my lifetime with mitochondrial disorders, none of them have gotten worse with immunization. That doesn't mean it couldn't happen in other cases."); *cf.* Tr. 795:3-7 (Q. "Based on all the evidence that you reviewed and the evidence you've heard today, have you heard anything that convinces you that vaccine causation or aggravation was even possible *in Karl's case*?" A. "*In Karl's case*, no." (emphasis added)). The special master's finding that the Palucks failed to put forward a plausible medical theory is vacated.

[26]In purporting to regard the record as a whole, the special master stated that "[t]he overall impression is that Dr. Frye's theory was not well thought-out." *Entitlement Decision* at *17. The special master based this conclusion on the organization of Dr. Frye's supplemental report and his delayed submissions of medical literature. The very recent nature of that literature may have been a factor in that regard. In all events, to the extent the special master penalized the Palucks for the staccato nature of Dr. Frye's presentation, such action was erroneous. The standard is whether the Palucks, through Dr. Frye, presented a medical theory of sufficient reliability, not whether Dr. Frye's litigation performance was sufficiently crisp. *Cf. Broekelschen*, 618 F.3d at 1349 ("In general, when two expert witnesses, both highly qualified, dispute an issue of medical fact with supporting and contradictory evidence, it is immaterial whether one witness makes a better appearance on the stand.").

II. *Althen*'s Second Prong: A Logical Sequence of Cause and Effect

A. *Karl's Medical History*

The second prong of the *Althen* framework requires a petitioner to demonstrate, by a preponderance of the evidence, "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. The Palucks contend that Karl's medical history demonstrates that the vaccines caused Karl's regression. They aver that, prior to the vaccinations on January 19, 2005, Karl's development was within normal limits for all areas except gross motor skills, and that even in the area of gross motor skills, Karl was "a little bit less delayed" in January than in earlier months. Pet'rs' Mot. at 7 (quoting Tr. 638:24 (Frye)). But within two days of his vaccination, the Palucks continue, Karl developed a fever and irritability. Within weeks, Karl's chiropractor reported that Karl was suffering spasticity and hypertonicity, which is evidence of "a very severe neurologic event" and a continuing metabolic decompensation. *Id.* at 8 (quoting Tr. 647:14-15 (Frye)). Finally, the Palucks contend, the special master's finding that Karl was worse in April 2005 than in January 2005 demonstrates that Karl's regression constituted a "continuous downward slope." *Id.* at 10 (quoting *Entitlement Decision* at *22).

The special master characterized Karl's history differently. Regarding Karl's symptoms in the days after vaccination, the special master wrote that "[a] finding that the January [19], 2005 vaccinations caused Karl to have a fever on January 21, 2005, and on January 28, 2005 does not mean that either fever had any lasting consequence on Karl. The record shows that Karl attended daycare [regularly from January 21, 2005 to February 8, 2005]. These records do not show any consistent problem with Karl's health." *Entitlement Decision* at *19 (citation and footnote omitted). These findings reflect the government's position that the "very detailed" daycare records show that Karl suffered a fever on only two days and thus did not fit the symptoms expected for vaccine-induced neurodegeneration. Hr'g Tr. 61:10 to 62:8 (Mar. 21, 2012).[27]

[27]The daycare records, which prominently feature a cartoon-style drawing of a lion and contain one to three hand-written, point-form notes for each date about Karl's condition, are not detailed, contrary to the government's contention. Nonetheless, they repeatedly mention that between January 21, 2005 and February 8, 2005, Karl was "very tired," "very fussy," and "didn't eat very good [sic]." R. Ex. 22, at 1-2. Such statements suggest that there was indeed a consistent problem with Karl's health. As for Karl's fever, entries mentioning fever are only recorded for two dates. Nonetheless, "[r]easoning from . . . omissions to a positive postulate is always questionable." *Campbell*, 97 Fed. Cl. at 669; *see also Loving*, 86 Fed. Cl. at 151-52. Simply because fevers were not recorded on other dates does not mean that Karl did not have a fever on those dates. *See Shapiro v. Secretary of Health & Human Servs.*, 101 Fed. Cl. 532, 538 (2011) (quoting *Murphy v. Secretary of Dep't of Health & Human Servs.*, 23 Cl. Ct. 726, 733 (1991)). This is especially so given that the fevers reported on the two days were more than 101 degrees; whether daycare staff potentially failed to report or were unable to detect a lesser fever probably will never be resolved.

The special master also found that Karl improved, rather than regressed, during February and March 2005. *See Entitlement Decision* at *20-22. Specifically, the special master found that Karl improved in the areas of crawling and babbling. Regarding crawling, the special master wrote:

> At the December 27, 2004 visit, Dr. McDonough stated that Karl "tries to crawl." The chiropractor's February 7, 2005 record says that Karl is not crawling. Similarly, the February 8, 2005 entry from daycare says that Karl "tries to crawl [by] pulling his body." Thus, when the parents communicate [on March 22, 2005] that Karl is doing "some brief crawling," 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." Another telephone record, this one from April 11, 2005, shows that Mr. Paluck reported that "Karl is crawling about 2 wks ago."

Id. at *20 (first alteration in original) (citations omitted). The special master characterized Karl's progress in babbling in this manner:

> The March 22, 2005 record from a phone call also states that Karl is "babbling more." 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. Thus, Karl improved, at least a little bit, between January 19, 2005 and March 22, 2005. *See* [Tr. 793:5 to 794:16] (Dr. Snodgrass's discussion of fluctuations in Karl's progress, providing babbling as an example of how Karl got better).

Id. (citations omitted).

As to Karl's crawling, the special master pieced together disparate items of evidence, drawing upon the phrases "tries to crawl," "tries to crawl pulling his body," "some brief crawling," "taking few crawling steps," and "crawling about 2 wks ago." None of Karl's healthcare providers, whether daycare or parents, provided any context for these statements, nor, during February and March, did any healthcare provider suggest Karl's crawling ability was improving. Indeed, when Karl's crawling was formally evaluated by Dr. McDonough on April 26, 2005, and July 12, 2005, Karl was found unable to crawl. *Entitlement Decision* at *20 n.28. Likewise, the expert testimony did not support the special master's determination. Dr. Snodgrass stated, "[w]hat we know from Dr. McDonough in January was that Karl . . . couldn't really crawl in a proper way . . . . Now that continues to be true. Dr. Siriwan [Kriengkrairut] tells us that same thing and we have other reports saying that he's crawling a bit more. But we don't ever have a health person saying that he crawls or sits properly. So I think what happened there was there were small areas of improvement but not major improvements." Tr. 546:14-24. Dr. Frye also found that Karl's crawling did not prove progress:

> Q. So here there's a telephone conversation record, Mr. Paluck is calling and he says that Karl is crawling about two weeks ago. How does Karl's crawling fit within your theory of the case?
>
> A. . . . [S]ometimes kiddos that have increased tone may find it easier to crawl because if you have normal tone you actually have to push off with your muscles. If you have actually stiff legs sometimes it's . . . easier to actually crawl. So I don't know that it necessarily negates the fact that he had these neurologic abnormalities. . . .
>
> Q. Would crawling be evidence of a new achievement I guess?
>
> A. I think it's hard to say because we know that neurologically he's so abnormal at this point, I don't know that we could really interpret it within the same context of normal development.

Tr. 826:18 to 827:15. The special master's inference that Karl's crawling improved has some support in the record but that support is limited.

The special master's assessment of Karl's babbling has a similarly limited grounding in the record. The special master noted that Karl babbled at his January 19, 2005 appointment with Dr. McDonough, and compared that observation to the record of a telephone call on March 22, 2005, stating that Karl is "babbling more." *Entitlement Decision* at *20 (quoting R. Ex. 5, at 72). There is no logical basis for the special master's determination that the "more" of "babbling more" on March 22 was meant as a comparison to some baseline set out by the January 19 appointment. *Cf.* Tr. 793:19-23 (Snodgrass). These were two separate records written by different persons in different contexts. The special master's conclusion is also cast into doubt by Karl's mother, who reported to Dr. McDonough on May 4, 2005 that Karl "has had a decrease in speech production *in the last few months*." R. Ex. 6, at 5 (emphasis added).

The special master's findings regarding Karl's health in February and March were based on thin evidence. Contemporaneous medical records were available, and those records pointed to a contrary finding. Between February 7, 2005 and March 30, 2005, Karl's chiropractor recorded observations of Karl's health on sixteen occasions.[28] Among other things, the

[28]On February 11, 2005, the chiropractor noted "spastic." R. Ex. 12, at 5. Entries on February 16 and February 18 note "less rigid," and a box titled "progress" contains an upward arrow that extends about a halfway up the inside of the box. *Id.* An entry on February 20, 2005, however, states "stiff." *Id*. at 6. The "progress" box contains two upward pointing arrows, followed by a downward pointing arrow. *Id*. Another box, titled "R[ange]O[f]M[otion] C/S," contains a downward pointing arrow on this date. *Id*. All the arrows extend to the full lengths of their boxes. *Id*. The next several entries, from late February to early March, note "spastic," "less hypertonicity," with small upward arrows in the "progress" box. *Id.* However, entries on March 10, 17, 27, and 30, 2005, suggest decline. *Id*. at 7. The entries on March 10 and March 27 contain large, downward-pointing arrows in the "progress" and "Range Of Motion" boxes, the March 17 entry notes "palpation at spine painful[;] baby cries loud when touched," and the

chiropractor referred to both "spasticity" and "hypertonicity," both of which can denote neuron injury. *See supra*, at 6 & nn.10-11. Apart from the notes taken during a visit to Dr. Kamille Sherman to treat Karl's cough on March 3, 2005, these are the only reports of a percipient medical witness to Karl's condition between February 9, 2005 and March 21, 2005. *See* R. Ex. H, at 7-8. Inexplicably, the special master omitted all discussion of these records when analyzing Karl's history. *See Entitlement Decision* at *19-20. This, despite the fact that "[t]here is little doubt that the decisional law in the vaccine area favors medical records created contemporaneously with the events they describe." *Shapiro*, 101 Fed. Cl. at 537 (citing *Cucuras v. Secretary of Dep't of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993)); *see Andreu*, 569 F.3d at 1375 ("[T]reating physicians are likely to be in the best position to determine whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury." (second alteration in original) (quoting *Capizzano*, 440 F.3d at 1326)). Such omission runs afoul of the Vaccine Act's instruction to consider "any diagnosis, conclusion, [or] medical judgment . . . contained in the record," 42 U.S.C. § 300aa-13(b)(1)(A), and indicates that the special master "ignore[d] entirely significant evidence that contradicts a finding." *Shapiro*, 101 Fed. Cl. at 541; *see also Hines*, 940 F.2d at 1528; *Campbell*, 97 Fed. Cl. at 668. Such omission was arbitrary and capricious.

B. *Statements of Treating Healthcare Providers*

Later in his analysis, the special master notes that both the chiropractor and another doctor suggested vaccines as a possible etiology of Karl's condition. According to the chiropractor's entry of March 30, 2005, he or she "discussed poss. [a]dverse rx [reaction] / vaccine." *Entitlement Decision* at *23 (alterations in original) (quoting R. Ex. 12, at 7). Similarly, a doctor who examined an MRI of Karl reported that the "[f]indings are consistent with a progressing leukodystrophy (consider hereditary, toxic or metabolic etiologies)." ***Id.*** (quoting R. Ex. 11, at 91).[29] The special master discounted both statements, writing that "[n]either document . . . presents a probative statement from a treating doctor that the medical professional considered the vaccines as the cause of Karl's problems." ***Id.*** The special master did not explain why he considered the statements to be non-probative. Such summary rejection of these statements by treating healthcare providers was arbitrary and capricious. *See Hines*, 940 F.2d at 1528 (The special master must "consider[] the relevant evidence of record . . . and articulate[] a rational basis for the decision."); ***cf., e.g.***, ***Broekelschen v. Secretary of Health & Human Servs.***, No. 07-137V, 2009 WL 440624, at *16-18 (Fed. Cl. Spec. Mstr. Feb. 4, 2009),

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March 27 entry notes "rigid lower extrem[ities]." *Id*. Finally, the March 30 entry notes "discussed poss. adverse Rx/vaccine, C[erebral]P[alsy], cerebellar tumor." *Id*. at 7; *see* Tr. 649:4-19 (Frye).

[29]Additionally, in a report dated December 5, 2005, Dr. Michael Frost examined MRIs of Karl's brain taken April 27, 2005, July 22, 2005, and October 27, 2005. Dr. Frost noted problems with Karl's brain and wrote "[t]his could represent nonspecific leukodystrophy. Alternatively, the progression of a signal change is between 04/27/05 and 07/22/05 [sic] may have represented evolution of 1 toxic/metabolic event, which is now stable." R. Ex. 11, at 280; *see also* Tr. 119:18 to 120:24 (Frye). The special master did not address Dr. Frost's report.

(comprehensively analyzing the weight to be given various treating physicians' diagnoses), *aff'd*, 89 Fed. Cl. 336 (2009), *aff'd*, 618 F.3d 1339.

C. *Other Evidence Relevant to Karl's Post-Vaccination Status*

Other evidence in the record raises significant questions that were not addressed by the special master as to Karl's development from January 2005 through April 2005.

First is Dr. McDonough's referral of Karl to Dr. Siriwan Kriengkrairut on March 25, 2005. *See* R. Ex. 3, at 7-8. In the referral, Dr. McDonough describes Karl as suffering from "gross motor delay, global developmental delay, and hypertonicity." *Id.* at 7. No testimony was elicited regarding why Dr. McDonough referred Karl to the neurologist at this particular time, but Dr. McDonough's cryptic notes are consistent with the chiropractor's observations and indicate serious neurological concerns. Both specifically referred to "hypertonicity," which by definition "usually indicates upper motor neuron injury." *See supra*, at 6 n.12 (quoting *Dorland's* at 897).

Second, MRIs of Karl's brain taken on April 27, 2005 and July 22, 2005 suggest a decline that may have begun earlier than April 27, 2005. *See* Tr. 115:18 to 116:7, 232:5-15 (Frye). In a report comparing the two MRIs, Dr. Frost wrote that "[m]oderate cerebral atrophy has developed since the last exam with further thinning of the corpus callosum." R. Ex. 11, at 91.[30] The word "further" suggests that the corpus callosum was already thin by April 27, 2005, and thus had began to thin, or was thin, even earlier than that. Dr. Frost also wrote, "[Karl's] previous MRI . . . on 04/27/05 was reviewed and compared to an MRI done on 07/22/05. On reviewing the previous MRI, it was felt that the abnormality was apparent on the initial MRI as well." *Id.* at 277. This report suggests that the abnormality, already extent at the time of the initial MRI, had its genesis at an earlier date. *See* Tr. 232:5-15 (Frye).

Third, the special master credited two observations in May 2005 as signs of progress in Karl, which the special master used to support his general finding that Karl's development fluctuated, rather than linearly declined, between January 2005 and July 2005. *See Entitlement Decision* at *22-23. Specifically, the special master wrote:

> 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."

Id. at *22 (quoting Ex. 6, at 33). These statements, however, must be examined in context. On direct examination, Dr. Snodgrass stated that the "strength is increasing" comment is "consistent with the fact that Karl has not deteriorated compared to January. No doubt his performance will

[30]The corpus callosum is "an arched mass of white matter . . . connecting the cerebral hemispheres" of the brain. *Dorland's* at 417.

vary from one day to the next according to whether he's irritable or at his best or at his worst." Tr. 359:23 to 360:2. On examination by the special master, however, Dr. Snodgrass stated, "[W]e need to look at the totality of the evidence, all of the evidence, and not stress any individual point. . . . [I]n May[,] Trisha Getz tells us Karl is a lot worse." Tr. 523:5-7, 20-21; *see also* Tr. 582:7-11 (same).

Dr. Snodgrass's latter conclusion appears to be confirmed by the record. At the time of the beginning of therapy on May 4, 2005, Karl had apparently worsened significantly since January. *See* R. Ex. 6, at 5-6. As therapy continued, despite brief improvements recorded by comments such as the "play with a ball" notation, the general pattern appears to be no improvement but rather a decline. *See id.* at 23 (speech therapy progress note dated June 2, 2005) ("decreased oral motor strength"); *compare id.* at 6 (speech evaluation dated May 4, 2005) (setting short-term goals for Karl such as approximating sounds, formulating syllables, and responding to visual and verbal cues), *with id.* at 23 (progress note dated June 2, 2005) (setting short-term goals for Karl such as participating in oral motor stretches and reaching for a desired toy when given a choice between two objects); *compare also id.* at 34 (speech therapy record dated May 13, 2005) (Karl "was obs[e]rved eating a cheerio and small bite of toast."), *with id.* at 26 (speech therapy record dated May 27, 2005) ("Therapist placed cheerio in left cheek and watched to see if Karl would move his tongue to get cheerio. He did not move tongue but began to cry and cheerio was removed by therapist."), *and id.* at 20 (speech therapy record dated June 8, 2005) (same). *See generally* R. Ex. 6, at 5-36; R. Ex. H, at 13-19.

D. *Synopsis*

The special master discounted the chiropractor's observations which were the most comprehensive contemporaneous records of Karl's condition in the several months after the vaccinations. The special master failed to explain his rejection of treating medical providers' statements regarding the cause of Karl's decline. And, the special master failed to address the treating physician's referral of Karl to a neurologist in March because of specific concerns with Karl's post-vaccination neurological health. These errors go to the central question of this case: whether Karl suffered an injury or significant aggravation of his preexisting condition after receiving vaccinations on January 19, 2005. A proper examination of all the evidence is essential to answer that question. Because the special master failed to consider these "diagnos[e]s, conclusion[s], [and] medical judgment[s] . . . contained in the record," 42 U.S.C. § 300aa-13(b)(1)(A), his findings under *Althen*'s second prong are vacated.

III. *Althen*'s Third Prong: A Proximate Temporal Relationship

The third prong of the *Althen* framework requires a petitioner to demonstrate, by a preponderance of the evidence, "a proximate temporal relationship between vaccination and injury." *Althen*, 418 F.3d at 1278. This requirement demands "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *De Bazan*, 539 F.3d at 1352 (citing *Pafford v. Secretary of Health & Human Servs.*, 451 F.3d 1352, 1358 (Fed. Cir. 2006)). Thus, if symptoms manifest later or earlier than medically expected, it is less likely that

the vaccine is the cause. *See id.*

A. *A Medically Acceptable Interval*

Dr. Frye testified that an adverse reaction to a vaccine in a child with a mitochondrial defect would happen within a week, Tr. 127:16-22, but that the damage from an ongoing metabolic decompensation could continue for months, Tr. 128:5-12; *see also* Tr. 129:6-14. The special master, however, found that the articles 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." *Entitlement Decision* at *24. The special master found that the evidence "coalesce[d] around a finding" that the medically acceptable interval between vaccination and symptoms of neurological injury was two weeks. *Id*. at *26.

In reaching this conclusion, the special master relied on several medical articles cited by Dr. Frye. The first article, by Dr. Joseph L. Edmonds and others, studied incidences of neurodegeneration following infection in patients with mitochondrial disorders. *See Entitlement Decision* at *24 (citing Ex. 21d (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 (2009) ("Edmonds, *The Otolaryngological Manifestations of Mitochondrial Disease*"))). Dr. Edmonds reported that "[i]n most patients (10[of]13), the neurologic event occurred 3 to 7 days after the onset of infection . . . . This pattern of delayed neurodegeneration in association with infection is depicted graphically in Figure 3." R. Ex. 21d (Edmonds, *The Otolaryngological Manifestations of Mitochondrial Disease*) at 6 (emphasis omitted). Figure 3 showed a bell curve peaking at nine days and representing that the tails on either side of the peak ranged from one day at one side to nineteen days on the other side. *Id.* at 7.

The second article relied upon by the special master discussed the records of 28 patients who suffer from both autism and mitochondrial disorders. *See Entitlement Decision* at *25 (citing R. Ex. 21z (Shoffner, *Fever Plus Mitochondrial Disease*)). The authors there observed that in several instances, autistic regression occurred after a fever. However, as noted by the special master, "[t]he authors' *definition of regression was limited* to 'regression as beginning within 2 weeks of a febrile [feverous] episode." *Id.* (emphasis added) (citing R. Ex. 21z (Shoffner, *Fever Plus Mitochondrial Disease*), at 2).

The third article relied upon by the special master was a case report of Hanna Poling, a young girl with mitochondrial dysfunction. *See Entitlement Decision* at *25 (citing R. Ex. 21q (Poling, *Developmental Regression and Mitochondrial Dysfunction*)). Hannah was born with a mitochondrial defect and her vaccinations were delayed because she suffered from "frequent bouts of otitis media with fever." R. Ex. 21q (Poling, *Developmental Regression and Mitochondrial Dysfunction*), at 3. Hannah experienced a fever within 48 hours of receiving a set of vaccinations, which fever continued for twelve days. *Id.* Ten days after vaccination, she developed "a generalized erythematous macular rash." *Id.* Hannah then lost her ability to

communicate over the ensuing three months. *Id.* Some of her communication function thereafter returned. *Id.*[31]

Given Dr. Frye's testimony and the actual content of these articles, it is difficult to understand the special master's conclusion that "[t]he evidence coalesces" at fourteen days as the appropriate interval between vaccination and the onset of neurological injury. *Entitlement Decision* at *26. The Edmonds article, *Otolaryngological Manifestations of Mitochondrial Disease*, suggests an onset of neurological degeneration of up to nineteen days. *See* R. Ex. 21d, at 7. The Shoffner article, *Fever Plus Mitochondrial Disease*, defined *ex ante*, rather than found *ex post*, regression as that occurring within two weeks of fever. R. Ex. 21z, at 2. And, the Poling case study, *Developmental Regression and Mitochondrial Dysfunction*, describes a girl who suffered gradually increasing neurological problems over the course of three months. R. Ex. 21q, at 3. It was arbitrary and capricious for the special master to set a hard and fast limit of two weeks given this evidence.

B. *The Onset of Karl's Symptoms*

Applying the two-week time limit, the special master found that Karl's symptoms of neurodegeneration manifested far too late. In doing so, the special master discounted Dr. Frye's testimony regarding Karl's condition in the days and weeks following vaccination, the chiropractor's observations in February and March, and the treating physician's referral of Karl to a neurologist in March after observing neurological deficits. *See Entitlement Decision* at *26-27.

Dr. Frye addressed Karl's fever and irritability in the days following his vaccination, followed by his spasticity and hypertonicity when examined by a chiropractor three weeks later:

> What we seem to see [in] the pattern of regression is that of fever, irritability, what we call encephalopathy, and then regression . . . of cognitive abilities over weeks to months after that . . . . We see spasticity emerging at Karl on February

[31]The special master also relied upon a set of three articles involving experiments on animals, specifically rats, in which damage from oxidative stress was observed to occur within 14 days. *Entitlement Decision* at *25 & n.34 (citing R. Ex. 21j (Rahul N. Khurana et al., *Mitochondrial Oxidative DNA Damage in Experimental Autoimmune Uveitis*, 49 Investigative Ophthalmology & Visual Sci. 3299 (2008)); R. Ex. 37b (Saraswathy, *Photoreceptor Mitochondrial Oxidative Stress*); R. Ex. 37c (Wu, *Photoreceptor Mitochondrial Tyrosine Nitration*)). The studies reported in the Saraswathy and Wu articles had previously been disregarded by the special master as insufficiently probative to show a plausible or reliable biological theory under the first *Althen* prong. *See id.* at *13 & n.17. There, the special master credited Dr. Snodgrass's testimony that the studies were "not applicable" to petitioners' theory. Tr. 765:24; *see Entitlement Decision* at *13 (citing Tr. 763:12 to 770:23); *see also* Tr. 301:19-21 (Snodgrass) (Q. "And does [the Khurana article] help us understand what was at work with Karl?" A. "No."). The special master's reliance on the animal studies for his findings as to timing while disregarding them as to the plausibility or reliability of petitioners' biological theory undercuts his decision.

> 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.

Entitlement Decision at *26 (alteration in original) (quoting Tr. 659:25 to 660:10). The special master discounted this testimony thusly:

> The source of "spasticity" mentioned by Dr. Frye is the chiropractor's February 11, 2005 note. 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." 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.

Id. (citations omitted). Contrary to the special master's reasoning, Dr. Frye's testimony did not rely solely on the chiropractor's note of "spasticity." Dr. Frye's theory posited that fever, irritability, and other signs of alleged encephalopathy following vaccination were themselves manifestations of the onset of neurodegeneration. *See, e.g.*, Tr. 103:23 to 104:3, 126:14-23, 143:6-21, 232:16-21. These symptoms emerged within two days of Karl's vaccination, which is well within even the two-week frame of reference derived by the special master. Dr. Frye cited the spasticity emerging 23 days later[32] as a further event, not as the initial manifestation, in Karl's neurodegenerative course. Thus, Dr. Frye did not rest his assessment on the single word "spastic," contrary to the special master's finding.

It was also arbitrary and capricious for the special master to dismiss Dr. Frye's testimony on the basis that Karl's condition "ameliorated." Neither expert expressed an opinion that the chiropractor's later February entries suggested amelioration. Further, as discussed in Part II.A, *supra*, the chiropractor's records taken as a whole indicate, if anything, a decline in Karl's health, not an amelioration.

Finally, it was also arbitrary and capricious for the special master to dismiss the chiropractor's findings of spasticity and hypertonicity on the basis that Karl's chiropractor had not examined Karl pre-vaccination. The special master wrote that the chiropractor "did not examine Karl before the January [19], 2005 vaccinations" and therefore was not "capable of detecting and reporting changes in Karl's gross motor skills." *Entitlement Decision* at *26. The special master's inference does not accord with the record. As to the chiropractor's capability, even Dr. Snodgrass agreed that "the chiropractor can identify . . . muscle tone." Tr. 341:7-8. More importantly, however, the chiropractic records do not attempt to make a comparison of Karl's condition before and after the vaccination, nor is that necessary to determine an appropriate temporal relationship between vaccination and injury. Rather, it was Dr. Frye, using

[32]The special master incorrectly wrote that Karl's vaccinations occurred on January 15, 2005 and thus incorrectly calculated the interval between vaccination and the report of spasticity on February 11, 2005 as 27 days. *See Entitlement Decision* at *26 n.36.

the records of Dr. McDonough and the chiropractor, who compared Karl's pre- and post-vaccination condition. *See* Tr. 647:13-18 ("[C]hanges in tone sometimes are very subtle things. Spasticity though suggests a very severe neurological event . . . and [for] spasticity to actually develop within . . . a month[] suggests that there was very rapid change in [Karl's] central nervous system."). While the two sets of records are not perfectly commensurable, *i.e.*, they do not have a common measure or template, that is not what the Vaccine Act requires. "[T]he purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280. Thus, in this case, as in so many others, "a claimant must build a causal framework piece by evidentiary piece, each fragment building upon and supporting the other until the preponderant silhouette of causation is achieved." *Campbell*, 97 Fed. Cl. at 673; *see also Shapiro*, 101 Fed. Cl. at 540-41 ("[A] finder of fact generally is not required to itemize each piece of evidence on an issue and adopt or reject it," but "this principle is no license to ignore entirely significant evidence that contradicts a finding."). Dr. Frye's testimony regarding the chiropractor's observations was such an attempt to build "piece by evidentiary piece." It was arbitrary and capricious for the special master to demand a before-and-after assessment by a single medical provider as a precondition to finding a medically appropriate temporal relationship between vaccine and injury.

C. *Synopsis*

The special master found that two weeks was the appropriate interval between vaccination and injury. The evidence upon which this finding was based, however, does not support that conclusion. The special master also found that Karl did not manifest any symptoms of injury within a medically acceptable time period. The special master did so by misapprehending the testimony of Dr. Frye and ignoring salient medical-record evidence of Karl's symptoms during the relevant time period. These errors were arbitrary and capricious. Thus, the special master's findings that two weeks is the acceptable time period for manifestation, and that Karl's injury did not occur within an acceptable time period, are vacated.

IV. The Admission of Testimony from an Unrelated Proceeding

The Palucks also contend in their motion for review that the special master abused his discretion when he admitted two particular exhibits, Record Exhibits U and V. *See* Pet'rs' Mot. at 3. The exhibits are excerpts of testimony given by two experts called by the government during the Omnibus Autism Proceeding cases.[33] The Palucks contend that admission of the

[33]The Omnibus Autism Proceeding was adopted to manage procedurally the influx of approximately 5,000 petitions related to vaccines and autism filed with this court's Office of Special Masters beginning in the early 2000s. *See In re Claims for Vaccine Injuries Resulting in Autism Spectrum Disorder or a Similar Neurodevelopmental Disorder* (Autism General Order #1), 2002 WL 31696785 (Fed. Cl. Spec. Mstr. July 3, 2002). The Office of Special Masters established two sets of three test cases focusing on general causation. Each set of three cases was heard by a panel of three special masters. In the first set of cases, the petitioners advanced the theory that the combination of an MMR vaccine and a vaccine containing thimerosal (a mercury-based preservative) can cause autism. *See Snyder ex rel. Snyder v. Secretary of Dep't of*

exhibits was improper because they have no bearing on any aspect of the present case, thus violating the principles of fundamental fairness that govern admission of evidence in vaccine proceedings. Pet'rs' Mot. at 22-23; *see* Vaccine Rule 8(b)(1).

"It is axiomatic that special masters in vaccine cases have great leeway in building a record for decision [and enjoy] 'flexible and informal standards of admissibility of evidence.'" *Davis v. Secretary of Health & Human Servs.*, 94 Fed. Cl. 53, 65 (2010) (quoting 42 U.S.C. § 300aa-12(d)(2)(8)), *aff'd*, 420 Fed. Appx. 973 (Fed. Cir. 2011). However, "while special masters are given broad authority over the manner in which they conduct Vaccine Act proceedings, that authority may not be used in a way that deprives a party of procedural rights provided by the Vaccine Act and the Vaccine Rules." *Simanski v. Secretary of Health & Human Servs.*, 671 F.3d 1368, 1385 (Fed. Cir. 2012). Vaccine Rule 8(b)(1) directs the special master to consider "all *relevant* and reliable evidence." (emphasis added); *see* 42 U.S.C. § 300aa-13(b)(1) (The special master shall consider certain medical information "in addition to all other *relevant* medical and scientific evidence." (Emphasis added.)); *cf.* Fed. R. Evid. 402 ("Irrelevant evidence is not admissible."). It was an abuse of discretion for the special master to admit transcripts of testimony taken in an unrelated case, regarding an unrelated theory of causation, connected to an unrelated injury.

With that said, the special master's error was nonetheless harmless. *See Davis*, 94 Fed. Cl. at 66 (finding harmless error when substantial other evidence in the record supported the special master's findings); *Morris v. Secretary of Dep't of Health & Human Servs.*, 57 Fed. Cl. 383, 391 (2003) (same). The Palucks have suffered no prejudice from the special master's admission of the disputed transcripts. When Dr. Snodgrass was asked how much of his testimony was reliant on the transcripts, he replied, "maybe one percent." Tr. 486:7. Correlatively, in the special master's opinion, the only references to the transcripts are in connection with the controversy over their admissibility. *Entitlement Decision* at *4-5. In light of the fact that the special master's findings are being vacated *in toto* for other reasons, no additional remedy stemming from this error is necessary.

Health & Human Servs., No. 01-162V, 2009 WL 332044, at *2 & n.5 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd sub nom. Snyder ex rel. Snyder v. Secretary of Health & Human Servs.*, 88 Fed. Cl. 706. In the second set of cases, the petitioners advanced the theory that thimerosal alone can cause autism. *See King ex rel. King v. Secretary of Health & Human Servs.*, No. 03-584V, 2011 WL 5926126, at *1 (Fed. Cl. Spec. Mstr. Sept. 22, 2011). Regarding the first set of cases, the special masters found, and this court and then the Federal Circuit affirmed, that the petitioners had failed to prove causation. *See Cedillo*, 617 F.3d 1328; *Hazlehurst*, 604 F.3d 1343; *Snyder*, 88 Fed. Cl. 706. In the second set of cases, the special masters again found that the petitioners had failed to prove causation. *See Dwyer ex rel. Dwyer v. Secretary of Health & Human Servs.*, No. 03-1202V, 2010 WL 892250 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); *Mead ex rel. Mead v. Secretary of Health & Human Servs.*, No. 03-215V, 2010 WL 892248 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); *King ex rel. King v. Secretary of Health & Human Servs.*, No. 03-584V, 2010 WL 892296 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). The petitioners declined to seek review in the second set of cases.

CONCLUSION

For the reasons stated, the Palucks' motion for review is GRANTED, the special master's decision of December 14, 2011 denying compensation is VACATED, and the case is REMANDED to the special master for further proceedings. The court sets aside the findings of the special master but makes no affirmative findings of its own.

It is so ORDERED.

s/ Charles F. Lettow
Charles F. Lettow
Judge