

# In the United States Court of Federal Claims

No. 07-889V

(Filed: October 29, 2013)

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

**Petitioners,**

**v.**

**SECRETARY OF HEALTH AND  
HUMAN SERVICES,**

**Respondent.**

) Vaccine case; petitioners' challenge to a  
) special master's decision on remand; 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  
) mitochondrial defect; claim asserting an  
) aggravation of a pre-existing condition;  
) *Loving* causation framework; entitlement;  
) remand

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## OPINION AND ORDER<sup>1</sup>

LETTOW, Judge.

Petitioners, Rhonda and Doug Paluck, on behalf of their son Karl Paluck, seek review of  
a decision on remand by a special master dated May 10, 2013, denying them compensation under  
the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, § 311, 100 Stat. 3743,  
3755-84 (codified as amended at 42 U.S.C. §§ 300aa-1 to -34) ("Vaccine Act"). Petitioners filed

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<sup>1</sup>In accord with the Rules of the Court of Federal Claims ("RCFC"), App. B ("Vaccine  
Rules"), Rule 18(b), this opinion and order will remain sealed for fourteen days, within which  
time the parties may propose redactions.

their claim on December 21, 2007, alleging that Karl's receipt of the measles-mumps-rubella ("MMR"), varicella, and Prevnar vaccines on January 19, 2005 caused him either to develop an impairment or to exacerbate a preexisting 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.

Petitioners' claim is an off-Table injury claim, requiring proof of causation in fact by a preponderance of the evidence. The special master assigned to the case initially denied petitioners' claim for compensation on December 14, 2011, finding that the Palucks failed to meet the three-part causation test established in *Althen v. Secretary of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). See *Paluck v. Secretary of Health & Human Servs.*, No. 07-889V, 2011 WL 6949326, at \*2 (Fed. Cl. Spec. Mstr. Dec. 14, 2011) ("*Paluck I*"). In response to a motion by petitioners for review, ECF No. 103, this court rendered a decision on April 18, 2012, vacating the special master's findings under all three *Althen* prongs and remanding the case to the special master, while "ma[king] no affirmative findings of its own." *Paluck v. Secretary of Health & Human Servs.*, 104 Fed. Cl. 457, 484 (2012) ("*Paluck II*"). In its decision ordering remand, the court directed the special master and the parties first to reassess whether petitioners' claim was a significant-aggravation claim that had to be analyzed under the six-part test explicated in *Loving ex rel. Loving v. Secretary of Dep't of Health & Human Servs.*, 86 Fed. Cl. 135, 143 (2000), which the special master had not applied. See *Paluck II*, 104 Fed. Cl. at 468-69. The *Loving* test combines the three causation factors from *Althen* with three additional factors that consider a claimant's health before and after the vaccination. See *id.* at 468 n.14. The court also directed the special master to reconsider the record as a whole before making new findings regarding causation in fact. See *id.* at 475, 480, 483.

In the remanded proceedings before the special master, no new evidence was submitted by either party. Supplemental briefing regarding Karl's developmental delays before and after the vaccine was completed by September 19, 2012. *Paluck v. Secretary of Health & Human Servs.*, No. 07-889V, 2013 WL 2453747, at \*3 (Fed. Cl. Spec. Mstr. May 10, 2013) ("*Paluck IV*").<sup>2</sup> The statutory period for decision after the remand expired without a resolution, and on January 30, 2013, petitioners again moved for review by this court because of the delay. Pet'rs' Mot. for Review, ECF No. 140. On May 3, 2013, the court denied the motion, but directed the special master to issue a decision within 120 days. *Paluck v. Secretary of Health & Human Servs.*, 111 Fed. Cl. 160, 169 (2013) ("*Paluck III*"). The special master issued a decision a week thereafter, on May 10, 2013, again denying petitioners' claim. *Paluck IV* at \*1.

Petitioners renewed their motion for review of the special master's decision by this court, contending that the special master's findings of fact and conclusions of law are arbitrary and capricious, an abuse of discretion, and not in accord with the law. Pet'rs' Mot. for Review of Remand Decision ("Pet'rs' Mot.") at 2-3, ECF No. 149. The Palucks ask this court to make its own findings of fact and issue a decision on entitlement in their favor. The government argues

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<sup>2</sup>Subsequent citations to *Paluck IV* will refer to the decision as reported in Westlaw, but will omit reference to "2013 WL 2453747" and will directly designate the starred internal pages.

Similarly, citations to *Paluck I* will refer to the decision as reported in Westlaw, omitting reference to "2011 WL 6949326" and directly noting the starred internal pages.

that the special master's decision was premised on adequate findings of fact and conclusions of law and should be left undisturbed. Resp't's Mem. in Resp. to Pet'rs' Mot. for Review ("Resp't's Opp'n") at 1-2, ECF No. 151. The Palucks' motion for review, filed June 10, 2013, has been fully briefed, and a hearing was held on September 18, 2013.

## BACKGROUND

### A. Facts

Karl Paluck currently suffers from an unspecified mitochondrial disorder that was most likely present at birth. At the time of the vaccinations, that disorder had not been detected. After the vaccinations, Karl became severely disabled, but the parties disagree as to the cause.

Karl was born on January 15, 2004 and showed no apparent signs of disability from birth through about the first eight months of life. A concern about developmental delay was first recorded on September 27, 2004 by Ms. Heather Ernst during developmental screening at Karl's daycare provider, as part of the North Dakota Right Track Program. *See* R. Ex. 5, at 111.<sup>3</sup> She observed delays in his gross and fine motor skills and referred him to an infant development service, K.I.D.S. *See id.*<sup>4</sup> K.I.D.S. evaluated Karl on October 21, 2004. R. Ex. 15, at 1. The evaluation examined areas of fine motor skills, gross motor skills, speech and language skills, cognition, and adaptive behavior. *Id.* at 2. Four test protocols were used: Bayley Scales of Infant Development ("Bayley Scales"), PDMS-2 Developmental Motor Scales — gross and fine motor scales ("PDMS-2"), Preschool Language Scale-3 ("PLS-3"), and Vineland Adaptive Behavior Scales ("Vineland"). *Id.*

The Bayley Scales protocol is generally used to test a child's cognitive skills (*i.e.*, ability to remember, problem solve, use and understand language, and identify early number concepts). R. Ex. 15, at 2; Tr. 99:5-7 (Test. of Dr. Richard Frye, petitioners' expert).<sup>5</sup> Karl scored "within normal limits" and was found to have an 11% delay. R. Ex. 15, at 2.

Testing with PDMS-2's gross motor scales evaluated Karl's ability to use his large muscles, and testing with PDMS-2's fine motor scales evaluated Karl's ability to use his small muscles. R. Ex. 15, at 2. Karl showed significant delay in his gross motor skills: 44% delay in stationary skills (*i.e.*, head and trunk control, sitting), 67% delay in locomotion skills (*i.e.*, rolling/crawling and object manipulation), and 67% delay in reflexes (*i.e.*, ability to stay upright

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<sup>3</sup>Documentary materials made part of the record are cited as "R. Ex. \_\_, at \_\_."

<sup>4</sup>The special master wrongly attributed the referral to K.I.D.S. as having been prompted by a visit to Karl's pediatrician, Dr. Stephen McDonough, as a result of an examination at eight months. *Paluck IV* at \*4. In actuality, Karl was not examined at eight months of age by Dr. McDonough. Rather, he was examined at four months, six months, and one year by Dr. McDonough. *See* R. Ex. 3, at 1, 2, 3.

<sup>5</sup>The entitlement hearings took place before the special master in 2010, and the transcript of those hearings is cited as "Tr. \_\_:\_\_."

and protect against falling). *Id.* Overall, he ranked in the first percentile for gross motor skills. *Id.* He showed less delay in his fine motor skills: 11% delay in grasping and 22% delay in visual motor integration (*i.e.*, hand-eye control), ranking in the eighth percentile. *Id.* at 2-3; Tr. 99:16-17 (Frye). Karl could roll over, but he could not sit without support or crawl. R. Ex. 15, at 4-5. He could not lift his legs off of the floor while lying on his back. *Id.* at 5. He was, however, using a “wide variety” of fine motor skills. *Id.* at 4. The evaluators could not determine with certainty the reason for his gross motor delays, but ultimately believed that low muscle tone was the underlying cause of Karl’s inability to sit and crawl. *Id.* at 5.<sup>6</sup> The evaluators believed that Karl presented with elevated tone in his legs because he was using them to compensate for the instability he felt in his arms and trunk. *Id.* at 4.

PLS-3 was employed to evaluate Karl’s ability to use and understand language. Karl showed moderate delays: 33% delay in auditory comprehension and 22% delay in expressive communication, ranking in the 32d percentile. R. Ex. 15, at 3. He was able to combine sounds and produce four different consonant sounds, but he was not imitating others’ sounds or responding to “no, no, Karl.” *Id.* at 4-5.

Lastly, the Vineland protocol tested Karl’s ability to care for his needs. It looked to his communication skills, daily living skills, socialization, and motor skills. R. Ex. 15, at 3. Overall, Karl was evaluated as 14% delayed. *Id.* He was 22% behind in communication skills, 11% behind in daily living skills, 0% behind in socialization skills, and 33% behind in motor skills, ranking in the thirtieth percentile overall. *Id.* Ultimately, K.I.D.S. determined that Karl presented a “mixed picture” and recommended that he “receive infant development services from the K.I.D.S. program targeting his speech/language, gross motor, and the delays in fine motor related to low muscle tone.” *Id.* at 4, 5.

Both parties’ experts agreed that the K.I.D.S. evaluation was “good and extensive,” Tr. 99:2 (Frye); Tr. 328:24 (Test. of Dr. Robert Snodgrass, respondent’s expert), but they disagreed as to the significance of the findings relative to Karl’s neurological health.

At the time Karl underwent his first evaluation for his developmental delays, he was experiencing recurrent bouts of otitis media<sup>7</sup> and rashes that were later identified as erythema multiforme. R. Ex. 3, at 57, 83.<sup>8</sup> The erythema multiforme was first noticed on October 14,

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<sup>6</sup>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).

<sup>7</sup>Otitis media is “inflammation of the middle ear,” *Dorland’s Illustrated Medical Dictionary* 1351 (32nd ed. 2012) (“*Dorland’s*”), commonly known as an ear infection.

<sup>8</sup>Biopsy results from December 28, 2004 confirmed that the rash was consistent with erythema multiforme. R. Ex. 9, at 3.

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

2004, a week before the K.I.D.S. testing. *Id.* at 57. Thereafter, the record is replete with visits and telephone calls to the Dickinson Clinic between October 2004 and January 2005 regarding Karl's otitis media and erythema multiforme, documenting no fewer than eleven visits and telephone calls during those few months. *See* R. Ex. H, at 3-7. Dr. Robert Snodgrass, respondent's expert,<sup>9</sup> sees significance in Karl's erythema multiforme, not because children with rashes are rare, but because erythema multiforme is relatively uncommon. Tr. 261:2-12 (Snodgrass). It is a hypersensitivity reaction, and in Karl's case, it persisted for months. *Id.* Moreover, both Dr. Snodgrass and Dr. Richard Frye, petitioners' expert,<sup>10</sup> testified that it is evidence of immune activation. Tr. 294:25 to 295:3 (Snodgrass); Tr. 98:11-13 (Frye). It suggests that Karl was under some immune stress in the months leading up to the vaccinations on January 19, 2005. *See* Tr. 446:2-4 (Snodgrass). Notably, the erythema multiforme improved after a physician, Dr. Amy Oksa, prescribed Orapred, an immune suppressant drug, but recurred when Karl stopped taking it. R. Ex. 3, at 61-62.

Most of Karl's medical record in November and December 2004 centers on treating Karl's otitis media and erythema multiforme. On December 27, 2004, Karl saw Dr. McDonough for an ear check. R. Ex. 3, at 5. The record of the visit states that Karl's recent medical history, as reported by his parents, was "positive for a fever." *Id.* At that time, Dr. McDonough also

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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 (Snodgrass).

<sup>9</sup>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. 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.

<sup>10</sup>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, the University of Florida, and the University of Texas. *See* R. Ex. 17.

documented that he had normal muscle tone and no ankle clonus. *Id.*<sup>11</sup> “He has good head control and fairly good truncal control but is not pulling himself to stand or crawling yet.” *Id.* Dr. McDonough noted “possible mild gross motor delay,” but also noted that Karl was rolling over, trying to crawl, and had several words. *Id.* at 5-6.

On January 6, 2005, the daycare noted that the K.I.D.S. Program worked with Karl for thirty minutes, that Karl cried during “tummy time,” and that he seemed very tired that day. R. Ex. 22, at 1. The next day, the daycare recorded that he was “crabby” in the afternoon. *Id.* There are no other daycare notes describing Karl before the vaccinations.

On January 19, 2005, Karl saw Dr. McDonough for his one year well-child checkup. *See* R. Ex. 3, at 3, 7. Dr. McDonough administered DENVER II, a common developmental screening test. *See* R. Ex. 5, at 35. The evaluation is recorded on a standardized form on which the doctor notes whether a child “passes” or “fails” certain developmental skills appropriate for his or her chronological age. On January 19, Karl passed “imitate activities,” “play ball with examiner,” “indicate wants,” “bang 2 cubes held by hands,” “thumb finger grasp,” “jabber,” say “dada/mama specific,” say “single syllables,” “pull to stand,” and “stand holding on.” *Id.* Karl failed “get to sitting,” “stand 2 [seconds],” “stand alone,” say “one word,” “wave bye-bye,” and “play pat a cake.” *Id.*

Dr. Frye testified that Dr. McDonough incorrectly scored the DENVER II screening for some skills. Petitioners provided a standard DENVER II chart, which shows that there is a shaded box behind each skill listed on the form. R. Ex. 38. Dr. Frye explained that only when that shaded box ends before reaching the child’s chronological age should the child be considered to have “failed” the skill. Tr. 638:7-11 (Frye). The shaded box indicates what percentage of children have developed a skill at a certain chronological age. For example, the skill of saying “one word” is accompanied by a shaded box that extends from about ten months to fifteen months. *See* R. Ex. 38. Only when a child turns 15 months and still cannot speak one word, should a child be noted as having “failed” the skill. Tr. 638:7-11 (Frye). Thus, according to Dr. Frye’s testimony, Karl’s only true failed skills should have been “get to sitting,” “stand 2 [seconds],” and “play pat-a-cake.” *See id.*<sup>12</sup> Dr. Frye also noted that some of the skills Karl passed were fairly advanced for his age, such as “imitate activities,” which less than 75% of

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<sup>11</sup>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). Ordinarily, when a doctor forces someone’s foot upward, it stretches the tendon behind the ankle, which causes the calf muscle to contract. The movement should only cause one muscle contraction, and if there are a series of contractions that is what is termed clonus. A “beat” of clonus is one up-and-down cycle of the foot caused by the extra muscle contractions. Tr. 539:25 to 540:1 (Snodgrass).

<sup>12</sup>Although Dr. Frye testified that the pat-a-cake box continues through 12 months, and so Karl should not have failed the skill, *see* Tr. 638:7-11 (Frye), the box does not extend that far.

children can do at that age. Tr. 633:1-7 (Frye). Dr. Frye testified that Karl showed less of a delay at twelve months than he did at nine months. Tr. 638:20-24 (Frye). He estimated that Karl was about four or five months delayed in October based on the results of the K.I.D.S. evaluation, and about three months delayed in January based on the DENVER II evaluation. *Id.*

At this same appointment, Dr. McDonough made additional findings regarding Karl. On a chart labeled “physical examination,” Dr. McDonough marked the category “neuromuscular” as abnormal, noting “muscle tone ↑ . . . upper . . . extremities . . . 2 beats clonus [right ankle].” R. Ex. 3, at 3.<sup>13</sup> Dr. McDonough checked the category “hips” as normal and wrote next to it some word or words followed by “ROM,” meaning range of motion.<sup>14</sup> Dr. McDonough also wrote on the same chart that Karl “doesn’t hold cup well,” circled the word “babbling,” and next to “1-3 words,” he wrote “no words.” *Id.* He also circled the word “crawl” and wrote next to it “4 point” (*i.e.*, hands and knees).<sup>15</sup> Finally, at this same appointment, Karl was given the MMR, varicella, and Prevnar vaccines. *Id.*; R. Ex. 5, at 62.

Within two days of receiving the vaccinations, Karl showed signs of irritability, fever, and fatigue. His daycare 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* R. Ex. 22, at 1-2. Dr. Frye and Dr. Snodgrass disagree over whether the vaccinations caused Karl’s subsequent and persistent fever. *See* Tr. 197:1-3 (Frye), Tr. 339:1-2 (Snodgrass).

The daycare records in the two weeks following the vaccination reveal that Karl was often fussy, did not eat or nap well, and was tired. R. Ex. 22, at 1-2. The only positive note occurred on February 3, 2005 when the daycare recorded that “Shiela [from the K.I.D.S.

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<sup>13</sup>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 sign, meaning upper and lower, and then I think you can clearly read extremities after you see lower.

Tr. 466:25 to 467:12 (Snodgrass); *see also* Tr. 332:9-19 (Snodgrass).

<sup>14</sup>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 (Frye). In contrast, Dr. Snodgrass stated that the writing preceding “ROM” indicated decreased range of motion. Tr. 466:18-19 (Snodgrass). The word could also possibly be “good.”

<sup>15</sup>Based on other medical records, Dr. McDonough’s notation likely does not mean that Karl could successfully complete full cross-crawl movements.

program] said Karl did very [well] today.” *Id.* at 2. On February 8, 2005, the daycare noted that Karl was trying to crawl by “pulling his body.” *Id.*

On February 7, 2005, the Palucks first took Karl to a chiropractor to address his problems sitting, crawling, and walking. R. Ex. 12, at 2.<sup>16</sup> On February 9, 2005, the chiropractor recorded some abnormalities with Karl’s hips on cross crawl. *Id.* at 5. Karl’s chiropractic record contains an entry for February 11, 2005 in which is written the word “spastic.” *Id.*<sup>17</sup> There is significant disagreement between the parties over whether the chiropractic records suggest decline or improvement through February and March 2005. The subjective assessments noted in later entries are variable:

- February 14 – “better mood,”
- February 16 – “less rigid — more comfortable on all 4s”
- February 18 – “less rigid — ‘happier””
- February 20 – “stiff Mid + T – ‘happy – moving around – til last nite & today””
- February 21 – “Mid T tite & SOP – irritable”
- February 24 – “Spastic Mid T’s & ↓ Ts”
- March 1 – “No BM yesterday”
- March 4 – “BM’s better – less fussy”
- March 8 – “less hypertonicity – [illegible] ↑ on all fours/BMs more regular”
- March 10 – “Not sleeping last night/2AM-5AM/irritable/good day yesterday”
- March 17 – “Upper [illegible] skin blotches – back pain.” On this day the chiropractor also noted, “palpation of spine [painful] baby cries loud when touched.”
- March 27 – “rigid lower extreme. Palp. [illegible] – ‘doing well ‘til yesterday’ ‘took a few crawl steps””
- March 30 (record of a phone conversation) – “Phone convers. w/ Brenda [Erie] SCSS Re. poss. abuse alleg. I responded – No – discussed poss. Adverse Rx/vaccine, CP [cerebral palsy], Cerebellar Tumor.”

R. Ex. 12, at 5-7. Although these entries are variable, they do not show any significant improvement. Many of the comments in the records are written in quotes or describe Karl’s behavior outside his appointment, suggesting that they are descriptions of his mood and behavior at home, given to the chiropractor by the Karl’s parents. *See, e.g.*, February 18: “happier,” February 20: “happy,” March 27: “doing well ‘til yesterday,” “took a few crawl steps,” April 2: “good mood this week” “seeing improvement.” *Id.*

A telephone conversation record with Dr. McDonough’s office dated March 22, 2005 documents the Palucks’ report that Karl had “some brief crawling” and is “babbling more,” but is “not sitting on his own,” “leans to one side,” and continues to have intermittent outbreaks of

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<sup>16</sup>On January 19, 2005, Dr. McDonough had referred Karl to physical and occupational therapy. *See* R. Ex. 3, at 3.

<sup>17</sup>Spastic means “of the nature of or characterized by spasms[;] hypertonic, so that the muscles are stiff and the movements awkward.” *Dorland’s* at 1741. Dr. Frye described spasticity as “being the extreme for increased tone.” Tr. 725:22-24 (Frye).



erythema multiforme. R. Ex. 5, at 72. Dr. Snodgrass 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 by the government's expert was contrary to that reached contemporaneously by Karl's treating physician, Dr. McDonough, who noted on the same telephone record that he would make a referral to Dr. Siriwan Kriengkairut, a pediatric neurologist. R. Ex. 5, at 72. On March 24, 2005, Dr. McDonough wrote the consultation request, citing Karl's "gross motor delay, global developmental delay, and hypertonicity" as the reasons. R. Ex. 3, at 7. Global developmental delay is broader than isolated gross motor delay. "Global developmental delay is when you're affected in several areas." Tr. 651:17-19 (Frye). Dr. McDonough wrote that he "would appreciate [Dr. Kriengkairut's] evaluation and medical investigations into the etiology of [Karl's] developmental delay and hypertonicity." R. Ex. 3, at 7.<sup>18</sup>

In mid to late March, Karl developed a cold. On March 28, 2005, he saw Dr. Gary Peterson at the Dickinson Clinic for "four days of [a] wheezy cough" and a "runny nose for two weeks." R. Ex. 3, at 64. The doctor noted early bilateral otitis media and bronchiolitis. *Id.* He provided a SVN (nebulizer) treatment in the office and also prescribed one for use at home. *Id.* He noted that Mrs. Paluck preferred "no antibiotics be written as yet since he has had the trouble with erythema multiforme in the past." *Id.*

By mid-April, Karl's health was significantly worse than it was in January 2005. He continued to suffer from recurrences of otitis media. R. Ex. 3, at 9. Karl saw Dr. McDonough on April 13, 2005 for a Pre-Anesthesia Evaluation for a magnetic resonance imaging ("MRI") test that was to be performed on Karl. *Id.* He noted "global developmental delay," including problems with "speech and fine and gross motor development." *Id.* at 9-10. Dr. McDonough also 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, probably "tone"] in the lower extremities. This is a change of hip movement over the last couple of months." *Id.* at 10. Karl had not had any evidence of erythema within the past three weeks. *Id.* at 9.

The neurologist, Dr. Kriengkairut, examined Karl on April 19, 2005. She documented a brief history of the onset of Karl's problems. "According to the father since [the onset of erythema multiforme in October 2004] the child has regressed. . . . In December of 2004 his condition got worse. His hands and feet were swelled up. He was given medications. This has markedly improved from a month ago when he seemed back to his normal. Father reported that since he has been improving with the skin lesions, he also made progress in terms of development, but overall he is still behind." R. Ex. 3, at 83. Following the physical examination, she reported "truncal hypotonia with marked spasticity of the extremities. The baby has

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<sup>18</sup>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 skeletal muscles, so they have increased resistance to passive stretching and reflexes are often exaggerated; this usually indicates upper motor neuron injury." *Id.*

tendency to do cortical thumb bilaterally<sup>19</sup>], worse on the right compared to the left. . . . [B]aby does not babble. . . . [D]elayed development as well as hypotonia of the extremities may be secondary to central nervous system pathology.” *Id.* at 84-85. Overall, she labeled Karl as having “[g]lobal delayed development.” *Id.* at 84.

Dr. Frye testified that this report by Dr. Kriengkrairut suggests a substantial neurological regression in Karl since January 2005. Tr. 654:6-25 (Frye). Dr. Snodgrass disagreed that the problems observed by Dr. Kriengkrairut differed substantially from the problems observed by Dr. McDonough in January. Tr. 350:1-4 (Snodgrass).

A chiropractic record entry from April 25, 2005, reports decreased range of motion. R. Ex. 12, at 8. Dr. McDonough saw Karl the next day, on April 26, 2005, 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 13.

Dr. Kriengkrairut had recommended an MRI of Karl’s brain, R. Ex. 3, at 84, which was performed on April 27, 2005, R. Ex. 11, at 276. The results were initially interpreted as normal, but a reexamination of the results from April 2005 following a more apparently abnormal MRI in July 2005 discerned evidence of a then-existing brain abnormality – thinning of the corporal callosum. *Id.* at 276-77, 280. The parties’ experts disagreed as to when the thinning most likely began. Dr. Frye opined that it occurred “recent to the [MRI,] after January [2005],” Tr. 109:16 (Frye), whereas Dr. Snodgrass testified that he has “seen similar scans in people who had prenatal infections,” Tr. 485:2-3 (Snodgrass).

Karl declined further in the ensuing months. While the special master found isolated instances of slight improvement, *see Paluck IV* at \*43-45 (discussing chiropractic records), these events contrasted with a general trend of deterioration from April 2005 to July 2005, *see* Tr. 476:2-17, 523:16-22 (Snodgrass). On May 4, 2005, Karl was evaluated by a speech therapist, Ms. Trisha Getz. R. Ex. 6, at 5. At that time, Karl had fewer language skills than he had in October 2004, and his total language score was in the first percentile. *See* Tr. 114:1-3 (Frye). In October 2004, he could produce at least four consonant sounds, but by May 2005, he could no longer produce any consonant sounds, although he could still produce a couple vowel sounds. By May, Karl’s only gesture was reaching for objects. R. Ex. 6, at 5. Ms. Getz noted, “Karl’s parents report he had an MRI last week, which has ‘wiped him out’ and they report a decrease in many skills since undergoing the anesthesia. . . . Mom reports he has had a decrease in speech production in the last few months.” *Id.* Her reports through September 8, 2005 indicate little to

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<sup>19</sup>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 (Frye). 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 (Snodgrass).

no improvement. *Id.* at 7 (“very little progress” and “no goals met”). Karl continued to be unable to approximate sounds or produce any consonants.

Karl suffered a seizure on July 12, 2005, followed by additional seizures over the next two days. 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. On July 19, 2005, Karl was admitted to Children’s Hospital in St. Paul, Minnesota by Dr. Michael Frost. R. Ex. 11, at 5. While there, MRI results showed furthering thinning of the corporal callosum, *id.* at 91, strongly suggesting that Karl was suffering from neurodegeneration, *id.* at 56. On October 27, 2005, Karl had another MRI, which showed no significant change in Karl’s brain since the July 2005 MRI. “[T]he progression of signal changes between [4/27/05 and 7/22/05] may have represented evolution of one toxic/metabolic or hypotoxic ischemic event.” *Id.* at 248.

Since July 2005, Karl has lived in a state of severe neurological disability. Earlier in 2013, he was in dire health. “There is a ‘do not resuscitate order now in place’ for him, and ‘[h]e is bedridden or wheelchair-ridden[,] has a tracheotomy tube[,] and is on a ventilator to breathe for him.’” *Paluck III*, 111 Fed. Cl. at 168 (quoting Hr’g Tr. 34:20-22, 35:12-14 (Apr. 10, 2013)).

## B. Prior Decisions

### 1. *Paluck I*.

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.” Amended Pet. at 1, ECF No. 18. 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 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.

*Paluck I* at \*8 (quoting Pet’rs’ Post-Hearing Br. at 25-26, ECF No. 90); *see also* Tr. 54:25 to 81:17 (Frye); *see also* R. Ex. 16; 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. R. Ex. 16. 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, testifying 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 (Snodgrass); *see also* Tr. 294:17 to 295:21 (Snodgrass). He criticized Dr. Frye’s theory generally on the ground of lack of published peer-reviewed literature demonstrating that vaccines cause oxidative stress in humans, although he acknowledged supporting animal-model data. *See* Tr. 282:13 to 283:12, 294:17-20 (Snodgrass); *see also* R. Ex. BB. In his view also, 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, 338:5-9 (Snodgrass). Dr. Snodgrass additionally stated that between January 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, 367:13-23 (Snodgrass).

The special master issued a decision denying compensation on December 14, 2011, concluding that petitioners had failed to prove by a preponderance of the evidence that the vaccines administered to Karl on January 19, 2005 caused his injury or significantly aggravated a preexisting condition. *Paluck I* at \*2. 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.

*Paluck I* 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. *Id.* at \*2.

Regarding *Althen*’s first prong, the special master was not convinced by the evidence presented that vaccines produce oxidative stress generally, *see Paluck I* at \*11-13, or oxidative damage particularly in persons with mitochondrial disorders, *see id.* at \*14-16. Regarding *Althen*’s second prong, the special master found that Karl’s history did not demonstrate a logical sequence of cause and effect between the vaccinations and Karl’s injury. *See id.* at \*23. According to the special master, Dr. Frye’s theory required that Karl’s medical history evidence a continuous downward trajectory, which “d[id] not match what actually happened to Karl.” *Id.* at \*22. 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. *Id.* at \*20, \*22. Regarding *Althen*’s third prong, the special master concluded that oxidative damage would have occurred in Karl within fourteen days, and that Karl’s immediate post-vaccination symptoms — fever, irritability,

and, according to his chiropractor, spasticity and hypertonicity — did not evidence such damage. *See id.* at \*24-26. Finding that Karl did not manifest further neurological regression until April 2005, the special master determined that Karl's injury fell outside the medically acceptable timeframe for vaccine injury. *Id.* at \*27.

## 2. *Paluck II*.

Petitioners filed a motion for review of the special master's decision in *Paluck I* on January 13, 2012, arguing that the special master's conclusions on all three *Althen* prongs were "arbitrary and capricious, an abuse of discretion, or not otherwise in accord with the law." Pet'rs' Mot. for Review, ECF No. 103, at 2-3; *see also* 42 U.S.C. § 300aa-12(e)(2)(B). The government urged affirmance. *See* Resp't's Mem. in Resp. to Pet'rs' Mot. for Review, ECF No. 109, at 11. Oral argument was held on March 21, 2012. *Paluck II*, 104 Fed. Cl. at 467. On April 18, 2012, this court vacated the special master's findings of fact and conclusions of law, and remanded the case to the special master for further proceedings. *Id.* at 484. The court expressly did not make any affirmative findings of fact of its own. *Id.* The court reviewed the special master's determinations of law *de novo*, and his findings of fact for clear error. *Id.* at 467 (citing *Andreu ex rel. Andreu v. Secretary of Health & Human Servs.*, 569 F.3d 1367, 1373 (Fed. Cir. 2009)).

First, the court directed the special master to reconsider whether petitioners' claim should be analyzed as a significant aggravation claim or a new injury claim. The special master had analyzed it using the standards applicable to a new injury claim without discussion of whether those standards were most appropriate. *Paluck II*, 104 Fed. Cl. at 468-69; *see Paluck I* at \*5-6; *see also Paluck IV* at \*1.

Second, the court addressed the special master's findings under each of the three *Althen* prongs. Regarding *Althen's* first prong, a medical theory causally connecting the vaccination and the injury, the court held that the special master required a higher level of proof, *i.e.*, a higher level of scientific certainty, than is demanded by the Vaccine Act. The Vaccine Act does not require that "evidence be medically or scientifically certain." *Paluck II*, 104 Fed. Cl. at 473 (quoting *Knudsen ex rel. Knudsen v. Secretary of Dep't of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994)) (internal quotation marks omitted). To support his theory, Dr. Frye relied on a peer-reviewed study published in a well-respected medical journal, various studies showing oxidative stress in animals as a result of vaccines, and a case study. *Id.* While the special master correctly determined that none of the evidence was definitive proof of the medical validity of Dr. Frye's theory, it was arbitrary and capricious for him to discard it as completely as he did. *See id.* at 474. The court also noted that Dr. Snodgrass did not dispute the reputability of the theory but only noted the dearth of human studies establishing it as fact. *Id.* The court vacated the special master's finding that petitioners failed to show by a preponderance of the evidence that vaccines can cause oxidative stress and that children with mitochondrial disorders are particularly vulnerable to oxidative stress and directed the special master to reconsider the evidence in the record under the correct legal standard. *Id.* at 476.

The court also vacated the special master's finding under *Althen's* second prong that petitioners failed to demonstrate, by a preponderance of the evidence, a logical sequence of cause

and effect showing that the vaccinations caused Karl's injury. *Paluck II*, 104 Fed. Cl. at 480. The special master had given considerable weight to unexplained notations throughout the record that Karl was progressing in his ability to prepare to crawl through the months of February, March, and April, which was something he could not do at the critical appointment on January 19, 2005 with Dr. McDonough, when he was vaccinated. *See Paluck I* at \*20. Karl was never formally evaluated as being able to crawl. *See* Tr. 546:14-21 (Snodgrass). At most, there was evidence that he was making some preparatory crawl motions at times. *See Paluck II*, 104 Fed. Cl. at 477. Similarly, the special master concluded that notations of babbling suggested development throughout the same months, *Paluck I* at \*20, despite evidence that Karl actually lost language abilities, *Paluck II*, 104 Fed. Cl. at 478. Moreover, the court opined that the special master failed fully to consider the chiropractor's records from February and March and Dr. McDonough's referral to a pediatric neurologist in March. *Id.* at 480. The court held that the special master's finding that Karl's efforts to crawl and babbling signaled improvement, therefore negating a logical sequence of cause and effect between Karl's vaccines and injury, should be vacated due to a failure to consider all of the salient evidence. *Id.*

Lastly, the court vacated the special master's finding regarding *Althen*'s third prong, a proximate temporal relationship between the vaccination and injury. *Paluck II*, 104 Fed. Cl. at 483. According to the special master, the medical literature suggested that the medically acceptable interval between vaccination and the onset of symptoms of neurological injury would be two weeks. *Paluck I* at \*26. The court rejected this conclusion. Given the medical literature relied upon by Dr. Frye, including a case study demonstrating neurodegeneration occurring post-vaccination over a period of several months, R. Ex. 21q, and a published study showing neurodegeneration occurring following infection in patients with mitochondrial disorders over a period extending to nineteen days, R. Ex. 21d, it was arbitrary and capricious for the special master to set a "hard and fast limit of two weeks." *Paluck II*, 104 Fed. Cl. at 482. The court also held that the special master's finding that Karl did not manifest any symptoms of neurologic injury within a medically acceptable interval after the vaccination was arbitrary and capricious because it failed to consider the record as a whole. *Id.* at 483.

### 3. *Paluck IV*.

Before deciding the case on remand, the special master requested supplemental briefing and any additional evidence from the parties regarding the classification of Karl's injury as a new injury or a significant aggravation claim. If the claim were found to be a significant aggravation claim, then the *Loving* factors would apply, which combine the three *Althen* causation factors with three additional factors that inquire into the claimant's condition before and after the vaccination. *See Loving*, 86 Fed. Cl. at 143 (citing *Althen*, 418 F.3d at 1278; *Whitecotton v. Secretary of Health & Human Servs.*, 81 F.3d 1099, 1107 (Fed. Cir. 1996), *on remand from Shalala v. Whitecotton*, 514 U.S. 268 (1995)); *see W.C. v. Secretary of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (approving the *Loving* test). Both parties submitted supplemental briefs, but neither submitted additional evidence. *Paluck IV* at \*3. The special master determined that Karl's claim is one of significant aggravation and must be analyzed under the six *Loving* factors because Karl's developmental delays in the autumn of 2005 strongly suggested pre-existing problems with his central nervous system. *Id.* at \*9.

The first prong of *Loving* requires addressing Karl's condition prior to vaccination. The parties agreed that Karl's mitochondrial defect was likely affecting his health before the vaccinations. *Paluck IV* at \*12. The parties disagreed over the extent of delay in Karl's language skills and the cause of Karl's gross motor delays. *Id.* at \*14. The special master found that the "preponderant weight of the evidence favors finding that Karl's language development was delayed prior to his vaccination." *Id.* at \*15. He also found that Karl's gross motor delays and language delays, in existence before the vaccinations, were caused by abnormalities in his central nervous system. *See id.* at \*63. He further determined that Karl's gross motor skill delays had worsened between December 27, 2004 and January 19, 2005. *Id.* at \*20.

The second prong concerns Karl's condition following the vaccination. The special master extensively summarized Karl's records in the months following the vaccination. *See Paluck IV* at \*20-42. He looked to Karl's daycare records, Karl's chiropractic record, Dr. McDonough's referral to the pediatric neurologist, Dr. Kriengkrairut's neurological exam, Karl's MRI in April 2005, Karl's speech therapy records, the seizures and hospitalization in July 2005, and Karl's other medical visits and mitochondrial testing. *Id.*

The third prong of *Loving* asks whether Karl's current condition constitutes a significant aggravation of his condition prior to the vaccine. Without elaboration, the special master found that "by virtually any metric, Karl was worse" after receiving the vaccines. *Paluck IV* at \*42.

The fourth prong of *Loving*, which correlates to the first prong of *Althen*, addresses whether there is a medical theory causally connecting the worsened condition to the vaccine. In response to this court's opinion in *Paluck II*, "[both] parties essentially agreed that the Palucks' evidence met the standard [for medical plausibility] as defined by the [c]ourt." *Paluck IV* at \*42. The special master accepted this apparent concession by the government without discussion, noting only that this concession does not lessen the petitioners' burden of proof under *Loving* prongs five and six. *Id.* at \*43.

The fifth prong of *Loving* requires petitioners to establish, by a preponderance of the evidence, a logical sequence of cause and effect showing that the vaccination significantly aggravated Karl's condition. The special master determined that Dr. Frye's theory "was predicated on a downhill trajectory." *Paluck IV* at \*43. Thus, the special master looked for evidence that Karl's health declined without any improvement from one day to the next following the vaccinations on January 19, 2005. In accordance with this court's order on remand, the special master considered in detail "[Karl's chiropractic] records, [Karl's] treating doctors' statements regarding the cause of Karl's decline, and Dr. McDonough's referral to a pediatric neurologist." *Id.* (internal quotation marks omitted). In considering the chiropractor's notations from February and March, the special master found that it was "difficult to glean much significance from [them]." *Paluck IV* at \*44. Ultimately, he found that the evidence of decline was too variable to suggest a linear decline, as he considered Dr. Frye's theory to require. *Id.* at \*49.

The final prong of *Loving* requires the special master to determine a medically acceptable temporal relationship between the vaccine and the significant aggravation and then determine whether the claimant's injuries occurred within that time frame. Upon reconsideration of an

article by Dr. Joseph L. Edmonds, the special master lengthened the medically acceptable temporal interval from two weeks, which he had specified in *Paluck I*, to three weeks. *See Paluck IV*, at \*55; *see also*, R. 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 (2002). Accordingly, the special master looked for evidence of neurodegeneration, defined as the loss of a skill, within three weeks following January 19, 2005, which extended to February 10, 2005. *Paluck IV* at \*56. Karl’s daycare records and chiropractic records were the only records contemporaneously created during that period. The special master was persuaded by the government’s expert that Karl’s fevers and irritability in the ten days following the vaccinations did not constitute encephalopathy, as Dr. Frye had opined. *Id.* at \*57. Additionally, the special master was unconvinced by Dr. Frye’s testimony that the chiropractor’s notation describing Karl as “spastic” on February 11, 2005 was evidence of “a very severe neurological event [suggesting] a very rapid change in his central nervous system.” Tr. 647:14-18 (Frye); *see Paluck IV* at \*60. The special master posited three reasons for not relying on the chiropractor’s notation: in his view, (1) spasticity is closely related to hypertonia, which Dr. McDonough noticed on January 19, 2005, (2) chiropractors are not sufficiently well trained to recognize clinical spasticity in infants, and (3) the variability of the chiropractor’s records rendered them unreliable. *Paluck IV* at \*59-60. The special master also placed emphasis on the fact that Karl did not appear to stay home from daycare in February, nor did he see doctors with the same frequency he had in December, although he saw the chiropractor frequently. *Id.* at \*60. Overall, the special master concluded that Karl had not been as sick in February as he was in December. *Id.* The special master concluded that the petitioners could not show by a preponderance of the evidence that Karl manifested evidence of neurological degeneration within the three-week “bound of the appropriate temporal limit.” *Id.* at \*62.

Based upon a failure of proof respecting the fifth and sixth prongs of *Loving*, the special master denied entitlement to compensation. *Paluck IV* at \*63.

## STANDARDS FOR REVIEW

Under the Vaccine Act, the court may “set aside any findings of fact or conclusions of law of the special master found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and issue its own findings of fact and conclusions of law.” 42 U.S.C. § 300aa-12(e)(2)(B). The special master’s determinations of law are reviewed *de novo*. *Andreu*, 569 F.3d at 1373. The special master’s findings of fact are reviewed for clear error. *Id.*; *see also 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))). Under Vaccine Rule 8(b)(1), the special master must “consider all relevant and reliable evidence.” Vaccine Rule 8(b)(1); *see also* 42 U.S.C. § 300aa-13(b)(1) (“[T]he special master or court shall consider the entire record and the cause of the injury, disability, illness, or condition until the date of the judgment of the special master or court.”). A special master’s findings regarding the probative value of the evidence and the credibility of witnesses will not be disturbed so long as they are “supported by substantial evidence.” *Doe v. Secretary of Health &*



*Human Servs.*, 601 F.3d 1349, 1355 (Fed. Cir. 2010) (citing *Whitecotton*, 81 F.3d at 1105); *see also Porter v. Secretary of Health & Human Servs.*, 663 F.3d 1242, 1249 (Fed. Cir. 2011).

As this court stated previously,

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). . . . And, while the special master need not address every snippet of evidence adduced in the case, *see Doe*[], 601 F.3d at 1355], 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).

*Paluck II*, 104 Fed. Cl. at 467.

## ANALYSIS

There is no dispute that Karl’s claim involves an “off-Table” injury, *i.e.*, an injury or aggravated condition that is not 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)(ii). Accordingly, petitioners must prove causation in fact. The special master concluded that petitioners’ claim is most appropriately analyzed as a significant-aggravation claim governed by the *Loving* factors. *See Paluck II*, 104 Fed. Cl. at 408. Petitioners continue to contest classification of the claim as a significant-aggravation claim rather than a new-injury claim, notwithstanding the circumstance that the special master found that the factors related specifically to significant aggravation had been satisfied. *See Pet’rs’ Mot.* at 4. Petitioners also contest the special master’s conclusions primarily respecting *Loving* prongs five and six, *i.e.*, logical sequence of cause and effect and medically acceptable temporal interval, respectively. *See id.* at 14-23. The government urges affirmance of the special master’s findings. Resp’t’s Opp’n at 1-2.

### I. NEW INJURY OR SIGNIFICANT AGGRAVATION

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). After giving the parties an opportunity to file supplemental briefs and giving them an opportunity to present more evidence, the special master concluded that the preponderance of the evidence weighed in favor of finding that petitioners’ claim should be analyzed as a significant-aggravation claim. *Paluck IV* at \*8-11. Petitioners maintain that Karl’s neurodegeneration constitutes a new injury, distinct from any delays he might have been experiencing in the months before the vaccination. *See Pet’rs’ Mot.* at 4-8. The government avers that Karl’s neurodegeneration can only be properly analyzed as a

significant-aggravation claim because he already showed signs of developmental delay before the vaccination. Resp't's Opp'n at 7.

Whether petitioners' claim should be classified as a new injury or significant-aggravation claim rests on the "the precise definition of Karl's injury, which is a precondition to identifying the timing of its symptoms" and "whether indicia of Karl's neurodegeneration followed the typical course of a person that suffers from his type of mitochondrial defect." *Paluck II*, 104 Fed. Cl. at 468-69. In its remand opinion, this court sought elucidation of whether developmental delays were the best indicator of neurological injury in someone with a mitochondrial defect. The special master, on remand, specifically asked the parties to address Karl's "neurological, not mitochondrial, symptoms" before the vaccination. *Paluck IV* at \*7 (quoting *Paluck II*, 104 Fed. Cl. at 469). The government responded that "one cannot separate 'mitochondrial symptoms' from the symptoms related to mitochondrial disorder-affected organs, including the central nervous system." Resp't's Supplemental Br., at 3, ECF No. 125.

Petitioners, however, pointed to pieces of evidence in the record to show that Karl first exhibited neurological symptoms after the vaccinations, including the chiropractor's records from February and March 2005, the K.I.D.S. evaluation, the April 2005 MRI, and the April 2005 neurological assessment. Petr's' Supplemental Br. in Resp. to Resp't's Supplemental Br. ("Petr's' Supplemental Br."), at 4, ECF No. 127. The experts disagree about the significance each of these pieces of evidence.

Petitioners emphasized the October 2004 K.I.D.S. evaluation which found "Karl's brain to be functioning within normal limits" and attributed Karl's gross motor delay to low muscle tone. Petr's' Supplemental Br. at 2-3. Dr. Frye testified that the K.I.D.S. evaluation was significant because it showed that Karl's cognitive abilities were unimpaired in October 2004. See Tr. 101:8-11 (Frye). In his view, the concern was Karl's low muscle tone, not his central nervous system. *Id.* He further explained that this low muscle tone was most likely due to Karl's then-undiagnosed mitochondrial disorder. Tr. 636:8-12 (Frye). Dr. Frye testified that although Karl's language skills were below average according to the PLS-3 test, the delay was minimal. Tr. 100:5-8 (Frye). His combined standard score for the PLS-3 was 96, and Dr. Frye testified that the average is 100. "[Ninety-six] is very close to 100 on these scales." Tr. 100:7 (Frye). According to Dr. Frye, "[Karl's] delays were most prominently gross motor delays, maybe a little bit of fine motor delays, but cognition, language was absolutely normal." Tr. 101:9-11 (Frye). "His ability to make language sounds and to interact with others, to be attentive to what was going on in the room, this was all very important and shows that his brain and cognition [were] working." Tr. 102:12-15 (Frye). Dr. Snodgrass disagreed without elaboration. He opined that describing Karl as "right at the average" was not accurate and that the K.I.D.S. evaluation did not show Karl's cognition and language as "absolutely normal," as Dr. Frye described. See Tr. 329:3-17 (Snodgrass) ("Q: So would this statement of Dr. Frye's be true then, 'Cognition language was absolutely normal[,] transcript page 101? A: Well, I think if we refer to Exhibit 15 we'd have to say no[,] that's not correct.>").

In turning to the chiropractor's notation of spasticity in February 2005, the cortical thumbing noted in April 2005, and the MRI results from April 2005, the experts disagreed over the significance of all three of these. In short, Dr. Frye found all three to be evidence of sudden

neurological regression after the vaccinations, and Dr. Snodgrass found them to be either a continuation of the same problems that existed before the vaccinations or insignificant.

The experts disputed the value of the chiropractic records in determining Karl's neurological state in February and March. In particular, they disagreed over the significance of the chiropractor's notation of "spastic" on February 11, 2005. Dr. Frye testified that the chiropractor's finding of spasticity "suggests a very severe neurological event, and that suggests . . . that there was very rapid change in his central nervous system." Tr. 647:14-18 (Frye); *see also Paluck I* at \*26 (quoting Tr. 659:25 to 660:10 (Frye)). Dr. Snodgrass saw no special significance in that record, 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 (Snodgrass); *see also* Tr. 543:15-20, 805:14-22 (Snodgrass) ("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.").

The experts also disputed the importance of Dr. Kriengkrairut's finding of cortical thumbing in April 2005. Dr. Frye called it a "significant sign of advanced upper motor neuron lesions and something that you don't see with just some type of change in tone or even mild spasticity[;] that is a very significant finding." Tr. 654:22-25 (Frye). He considered that the cortical thumbing, in addition to being a sign of neurological change, demonstrated an impairment occurring since December 2004, when Karl was able to open his hands and grab wrapping paper at Christmas. Tr. 110:6-21 (Frye). Dr. Snodgrass disagreed that the problems observed by Dr. Kriengkrairut differed substantially from the problems observed by Dr. McDonough in January 2005. Tr. 350:1-4 (Snodgrass) ("The function recorded in January by Dr. McDonough is the same function that was recorded by Dr. [Kriengkrairut] in April and by Dr. McDonough when he again saw Karl in April."). Dr. Snodgrass testified that cortical thumbing is not a significant finding and is not one he would have expected Dr. McDonough, a pediatrician, to note. Tr. 577:17 to 578:3 (Snodgrass). Upon further questioning by the special master, Dr. Snodgrass stated that thumbing is abnormal in a one-year-old, but in the context of also seeing increased tone, it is insignificant. Tr. 583:6 to 584:6 (Snodgrass). He further stated that the thumbing was not necessarily "cortical," and thus was not necessarily representative of a brain abnormality. *Id.*

Lastly, regarding the April 2005 MRI, Dr. Snodgrass and Dr. Frye both concede that it showed evidence of thinning of the corpus callosum, but Dr. Snodgrass testified that that thinning could have been present since birth, whereas Dr. Frye testified that it most likely occurred close in time to the MRI, after the January 2005 vaccinations. Tr. 485:1-4 (Snodgrass); Tr. 109:12-16 (Frye).

Whether Karl's severe neurodegeneration would have eventually resulted from his mitochondrial defect without the vaccinations posed a vexing issue. The government and petitioners appear to agree that mitochondrial disorders are "a heterogeneous group of disorders characterized by impaired energy production due to genetically based oxidative phosphorylation dysfunction." *Paluck IV* at \*6 (quoting R. Ex. E, at 2, Richard H. Haas et al., *Mitochondrial*

*Disease: A Practical Approach for Primary Care Physicians*, 120 Pediatrics: Official J. Am. Acad. Pediatrics 1326, 1326 (2007)). They also agree that manifestations of mitochondrial diseases are variable. Tr. 286:11-13 (Snodgrass); Tr. 128:22-23 (Frye). The government maintains that “the aggravation of symptoms as Karl aged stemmed from the natural progression of the disease.” Resp’t’s Opp’n at 14.

The special master asked Dr. Frye what he would think if a hypothetical child, with Karl’s same genetic makeup and medical history, experienced the same neurodegeneration as Karl, without having received any vaccinations. Tr. 241:6 to 242:2. Dr. Frye responded that he would immediately look for some other trigger, such as a bad infection or a bad viral illness because it would be very puzzling to see such a regression with no identifiable cause. Tr. 242:6-11 (Frye). Dr. Snodgrass stated that “[m]itochondrial problems are heterogeneous. . . . [T]hey vary enormously.” Tr. 286:11-15 (Snodgrass). The evidentiary record is bereft of any basis for a natural progression of a mitochondrial condition to the severely debilitating point Karl experienced.

The special master acknowledged that it was possible that Karl’s gross motor delays were purely related to low muscle tone and not his central nervous system, but he believed three reasons supported finding that Karl had preexisting neurodegeneration allegedly significantly aggravated by the vaccines. *See Paluck IV* at \*9-10. First, it is generally accepted that there is a connection between muscle tone and the nervous system. *Id.* at \*9. Second, Karl showed delay in his expressive language according to the K.I.D.S. evaluation in October 2004. Third, the special master pointed to the Palucks’ Amended Petition, filed October 17, 2008, stating that they allege that the vaccines “caused a ‘significant aggravation’ of Karl’s underlying mitochondrial disorder, leading to . . . subsequent neurodevelopmental regression.” *Paluck IV* at \*10 (quoting Amended Pet. at 2).

The special master’s reasoning in finding evident neurodegeneration prior to the vaccinations is partially but not fully supported by the record. The parties accepted that the central nervous system helps maintain muscle tone, Tr. 111:19-22, 647:12-24 (Frye); Tr. 333:4-6 (Snodgrass), but the experts did not agree that low muscle tone is necessarily a result of a problem in the central nervous system. Dr. Frye testified that Karl’s gross motor delays were attributable to “problems with muscle development, and energy that the muscle needs, because of his [then-undiagnosed] mitochondrial disorder.” Tr. 636:5-12 (Frye). This testimony is corroborated by the contemporaneous finding by the K.I.D.S. evaluators that Karl’s delays were likely a result of low muscle tone. *See R. Ex. 15*, at 4. It is also corroborated by the fact that Dr. McDonough did not recommend that Karl see a neurologist until late March. *See R. Ex. 5*, at 45. If low muscle tone was necessarily caused by a problem in the central nervous system, that would have been evidence that the K.I.D.S. evaluators and Dr. McDonough should have been and actually were concerned about neurological causes from October 2004 onwards. Contrastingly, Dr. Snodgrass nonetheless opined that Karl’s gross motor delays and observed low muscle tone were secondary to undiagnosed problems in his central nervous system. Tr. 420:7-10 (Snodgrass). Although Dr. Snodgrass’s opinion is plausible, it is supported by the

contemporaneous medical records only insofar as Dr. McDonough's examination of Karl on January 19, 2005 indicated "two beats clonus [right ankle]." *See* R. Ex. 3, at 3.<sup>20</sup>

The special master's emphasis on Karl's language delay as evidence of pre-vaccination neurodegeneration is minimally supported by the record. There is evidence of delay, but the delay is moderate at most. Petitioners assert there was absolutely no cognitive or language delay. Pet'rs' Mot. at 8. Karl tested within normal limits on the Bayley Scales and tested slightly below average on the PLS-3 scales. *See* R. Ex. 15, at 2-3. Karl was, however, referred to speech therapy by the K.I.D.S. program evaluators. *Id.* at 5. There is room for debate over whether Karl's language skills were actually "delayed," and the special master could have reasonably concluded that being below average, even just slightly, constitutes delay, but to label that delay as evidence of then-existing problems in the central nervous system stretches inference from the evidence too far. In stating that "expressive language tends, at least in the absence of other identified causes, to be considered a C[entral] N[ervous] S[y]stem problem," the special master only cites Dr. Snodgrass's testimony that "alludes" to such a connection between expressive language and CNS. *Paluck IV* at \*10. Any cognitive and language delays that Karl had were mild prior to the vaccination and were not of strong concern. *See* Tr. 636:20-22 (Frye) (testifying that Karl was one month above his chronological age for the social domain according to the Vineland test). To find that these delays definitively represented a "CNS problem" is not supported by substantial evidence.

The special master commented that "special masters 'can always rule on a factual issue no matter how scanty the evidence is,'" *Paluck IV*, at \*8 (quoting *King v. Secretary of Health & Human Servs.*, No. 03-584V, 2008 WL 1994968, at \*3 (Fed. Cl. Spec. Mstr. Feb. 7, 2008)), but that recitation is not a license to ignore the record. In this instance, substantial contemporaneous medical records exist. The four-month and six-month evaluations by Dr. McDonough, the records of illness with otitis media and erythema multiforme, and especially the K.I.D.S. evaluative results provide significant information about Karl's condition pre-vaccination. These records suggest that no one believed or even suspected Karl's problems were neurological in nature until after the vaccinations. The special master is not free to decide otherwise in the face of this evidence.

Despite these flaws, the special master's conclusion that petitioners' claim is one of significant aggravation and not new injury will not be disturbed. It is evident that Karl faced a multitude of setbacks in the fall. He was not a completely healthy child when he received the vaccinations. He had an undiagnosed mitochondrial disorder that was causing developmental delays in some areas, and he was experiencing repeated stresses to his immune system in the form of persistent otitis media and erythema multiforme. *See* R. Ex. 3, at 57, 61. Given this

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<sup>20</sup>Ankle clonus might, but does not necessarily, represent neurological injury. On cross-examination, Dr. Snodgrass explained that a severely agitated child "who is screaming [his] head off" might have clonus. Tr. 469:8-11 (Snodgrass). Petitioners' counsel asked Dr. Snodgrass whether two beats of clonus is "mild clonus." Dr. Snodgrass replied, "I think that depends on the circumstance. I think the basic issue is it's clonus, which was not present before." Tr. 468:16-19 (Snodgrass). Upon further questioning, Dr. Snodgrass responded, "Well, it's — two beats of clonus is less than say five. But it's still not normal." Tr. 468:20-23 (Snodgrass).

evidence that Karl's immune system was not functioning optimally, the court concurs that petitioners' claim is more appropriately analyzed as one of significant aggravation. It is not necessary to find with specificity that Karl's gross motor delays were neurological rather than musculoskeletal in nature prior to the vaccinations. If Karl's problems prior to the vaccinations on January 19, 2005, were neurological, the impairment was small and not evident to the treating physicians. Given petitioners' claim that the vaccine overwhelmed Karl's immune system causing cell death, it is enough to find that Karl's body was under immune stress in the months leading up to the vaccinations and that his underlying mitochondrial defect made his body less able to respond to immune stressors. Thus, petitioners' claim is properly analyzed as one of significant aggravation and not new injury.

## **II. LOVING FACTORS**

After determining that petitioners' claim is more properly analyzed as a significant aggravation claim, the special master applied the *Loving* test. The court concurs that the *Loving* test applies and 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.

### ***A. Loving Prong 1: Condition Prior to the Vaccinations***

The special master found that "[o]verall, by January 19, 2005, Karl had problems in his CNS. His pediatrician diagnosed him with gross motor delays, which had worsened in the preceding three weeks. Karl was also having problems with his language. Finally, Karl was recovering from the most recent episode of erythema multiforme." *Paluck IV* at \*20.

Petitioners contest the special master's findings regarding Karl's condition before the vaccinations as arbitrary and capricious and not in accord with the law. First, they challenge the special master's interpretation of Dr. Snodgrass's testimony as meaning that the erythema multiforme was another possible cause of the neurodegeneration. Pet'rs' Mot. at 10. Second, they dispute the special master's finding that Karl had expressive language delay that, "in the absence of other identified causes, [is] to be considered a CNS problem." *Paluck IV* at \*10. Third, petitioners question the special master's finding that Karl's developmental delays worsened between December 2004 and January 2005, contending that the special master ignored Dr. Frye's testimony to the contrary. Pet'rs' Mot. at 11. The government asserts that the special

master's conclusions of fact, including his conclusion that Karl's delays prior to January 2005 represented a problem with his central nervous system, are supported by appropriate evidence. Resp't's Opp'n at 1-2.

The special master recounted the evidentiary record in his analysis of Karl's condition prior to the vaccinations. He considered both the contemporaneous medical records and the expert testimony regarding Karl's recurrent erythema multiforme, finding that it was evidence of chronic activation of Karl's immune system. Tr. 294:24 to 295:14 (Snodgrass); Tr. 98:8-13 (Frye).<sup>21</sup>

The dispute over whether Karl's language abilities were delayed poses a different type of issue. As discussed *supra*, reasonable minds could differ over whether Karl could or should be classified as having had a speech delay before the vaccinations.<sup>22</sup> Consequently, the special master could properly conclude that Karl had speech delays. On the other hand, there is no evidence that those speech delays were necessarily a result of neurological problems. As discussed *supra* regarding the propriety of a significant-aggravation analysis, the contemporaneous records do not suggest that Karl's treating physicians and therapists believed that any extant pre-vaccination speech delay was neurological in nature.

Regarding Karl's gross motor delays, the special master found that they represented problems in his central nervous system before the January 19, 2005 vaccinations. In support, the special master compares Dr. McDonough's findings in December 2004, that Karl had normal muscle tone and no ankle clonus, to his findings in January 2005, that Karl had increased tone and two beats of clonus in his right ankle. *Paluck IV* at \*18-19. This evidence supports the special master's conclusion that Karl's physical condition had worsened between December 2004 and January 2005. A report by the same doctor that Karl went from normal muscle tone to increased muscle tone and from no ankle clonus to two beats of ankle clonus is compelling. Again, however, the special master's conclusion that this worsening is necessarily a result of problems with Karl's central nervous system steps beyond the inferences that can permissibly be drawn from the medical evidence. Although Karl's medical problems make this case a significant-aggravation claim rather than a new-injury claim, there is very little direct evidence

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<sup>21</sup>The special master questioned whether the erythema multiforme could have caused Karl's eventual neurodegeneration but determined that "[r]esolution of this question is not necessary because . . . Karl did not significantly decline in the weeks immediately following January 19, 2005, when he both received a set of vaccinations and suffered another bout of erythema multiforme." *Paluck IV* at \*13. This latter observation foreshadows the special master's analysis of *Loving* prong six, addressed *infra*.

<sup>22</sup>On December 27, 2004, Dr. McDonough saw Karl when his parents brought him into the clinic for otitis media and possible erythema multiforme. R. Ex. 3, at 5. Under "Developmental History" Dr. McDonough recorded, possibly based upon discussion with Karl's parents, that "he has several words that he says." *Id.* On January 19, 2005, however, he recorded that Karl had no words, except for "mama" and "dada". *Id.* at 3; R. Ex. 5, at 35. No other evidence suggests that Karl ever had any words beyond "mama" and "dada", and as such, the descriptive statement in Dr. McDonough's report of December 27, 2004 is uncorroborated.

that Karl's condition before the vaccinations had a neurological foundation. Certainly his treating medical providers did not think it was neurological at the time.<sup>23</sup> Thus, the evidence shows that Karl had gross motor delays and speech delays, but it does not support finding that those delays were caused by a significant impairment of his central nervous system. If his central nervous system was adversely affected, any such disability was not a major one.

### ***B. Loving Prong 2: Condition Following the Vaccinations***

*Loving* prong two inquires into the claimant's current condition or condition following the vaccinations. As the special master noted, because Karl's current condition is not at issue, the focus turns to his condition in the six months following receipt of the vaccines. *Paluck IV* at \*20. Two days after the vaccinations, Karl's daycare recorded that he had a temperature of 101.5 degrees. R. Ex. 22, at 1. For the next week, Karl reportedly acted tired and fussy. *Id.* On January 28, nine days after the vaccinations, Karl still had a fever of 101.3, as recorded by his daycare. *Id.* at 2. The experts disagree as to the cause of the fever. Dr. Frye testified that the fever was a symptom of immune activation caused by the vaccinations on January 19, 2005. Tr. 197:1-3, 644:10-13 (Frye). Dr. Frye also opined 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, 659:25 to 660:10 (Frye) (describing Karl's post-vaccination symptoms as manifesting encephalopathy); *see also* Tr. 703:22 to 704:2 (Frye). Dr. Snodgrass disagreed, stating that the fever on January 21 manifested too quickly to be attributed to the vaccines,<sup>24</sup> that the continued fever on January 28 was more likely due to an outbreak of Karl's erythema multiforme,<sup>25</sup> and that the fevers in any event were not related to Karl's neurological decline. *See Paluck I* at \*21; *see also* Tr. 338:22 to 339:2, 339:19-25, 346:11-25, 350:1-10 (Snodgrass). Karl's daycare records, which extend through February 8th, largely describe him as being tired, irritable, and fussy. *See* R. Ex. 22, at 1-2.

Karl's chiropractic records, which begin on February 7, 2005, describe Karl as "irritable" on February 9th and then "spastic" on February 11, 2005. R. Ex. 12, at 5. The next three visits suggest some slight progress, but the chiropractor's assessment of Karl's condition remained the same. *Id.* The following visits noted increased stiffening and spasticity, with the assessment of Karl's condition remaining the same. *Id.* at 6. The first visits of March again indicated some slight progress, but the remaining three visits in March showed a decline and decreased range of motion. *Id.* at 5-7. In April, Karl's condition continued to be variable. *Id.* at 7-8. Taken as a

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<sup>23</sup>The K.I.D.S. evaluation pointed specifically to low muscle tone, R. Ex. 15, at 4, and Dr. McDonough did not refer Karl to a neurologist until late March 2005, two months after the vaccination, following reports that Karl was deteriorating further, R. Ex. 3, at 7.

<sup>24</sup>Dr. Snodgrass testified that the MMR vaccine introduces a virus into the body that grows with time. Those viruses "will present a larger stimulus at seven to ten days than they do on day 1, 2, or 3." This is unlike a killed bacteria vaccine, which does not multiply in the body and causes reactions more quickly. Tr. 513:10-17 (Snodgrass).

<sup>25</sup>Karl's daycare noted the reappearance of spots on his arms and legs on January 31, 2005. R. Ex. 22, at 2.



whole, the chiropractor's records document a decline, albeit not a linear one. The observation by the chiropractor that he was "spastic" is significant. That Karl was a little less spastic or stiff some days than others does not mean that Karl's condition improved beyond his initial appointments in early February. This is consistent with Dr. Frye's theory that Karl was likely experiencing changes at the cellular level that would take time to appear at the clinical observation level.

Moreover, there was a phone conversation between Brenda Erie of Stark County Social Services and the chiropractor on March 30, 2005, reproduced below, where the chiropractor discussed possible causes for Karl's condition, including abuse, adverse reaction to medication or a vaccine, cerebral palsy, or a cerebellar tumor:

Date	3/30												
S:	Phone convers w/ Brenda Erie SCSS Re: pos. diag w/ Karl												
O:	PROGRESS	NCM	PALP	IMP	ANTALGIA	SBACH	REFLEX	TAINTENDER	ROMCS	ROMUS	GRADE	ORTH	EVAL
											1 2 3 4 5		
A:	I Responded - NO - discussed pos. Adverse Rx/Vaccine CP, Cerebellar tumor												
P:	P.T./D.T. in contact w/ Chiro care												
											THERAPY	PATIENT RECORD	Next Visit

See R. Ex. 12, at 7. The special master read this record as indicating that "[t]he chiropractor answered 'No'" to the possibility that an adverse reaction to the vaccination might have caused Karl's deteriorating condition. *Paluck IV* at \*46. In the hearing held by the court on September 18, 2013, the government acknowledged that the special master misread this record. The chiropractor said "No" to child abuse allegations, not to the possibility of an adverse reaction to a medication, cerebral palsy, or a cerebellar tumor. See Hr'g Tr. 40:23 (respondent's counsel).

On March 24, 2005, Dr. McDonough referred Karl to a neurologist. This occurred two days after a phone call between Dr. McDonough and the Palucks, during which the Palucks reported that Karl had some brief crawling, was not sitting on his own, leans to one side, is babbling more, and has an intermittent rash. R. Ex. 5, at 72. This is the first time in the record, that anyone recommended Karl see a neurologist. At that point, Dr. McDonough could not have thought Karl had improved since the January vaccinations.

On March 28, 2005, Karl had a bout of otitis media and bronchiolitis, documented by Dr. Gary Peterson. R. Ex. 3, at 64. A week later, Karl's symptoms were improving in that regard, and the doctor recommended weaning him off the nebulizer that he had been using to treat the bronchiolitis. *Id.* at 66. On April 13, Karl saw Dr. McDonough for a pre-anesthesia appointment in preparation for his planned MRI. *Id.* at 9. At that point, Dr. McDonough noted "increased [tone] in the upper and lower extremities," no clonus, "decreased hip flexion to about 70 degrees bilaterally," no speech, and "[g]lobal developmental delay with resolving otitis media." *Id.* at 10. Dr. McDonough described the decreased hip flexion as "a change [in] hip movement over the last couple months." *Id.* He also documented his hope that "the parents w[ould] agree to evaluation for congenital infections, metabolic disorders, and other tests requested by Dr. [Kriengkrairut] for his global developmental delay." *Id.*

Dr. Frye testified that this examination represented a neurological decline in Karl "because now he has increased tone in the upper and lower extremities, so – and he says, 'Global

developmental delay with resolving otitis media.’ So here his concerns are that his neurological exam has gotten worse” since January 2005. Tr. 108:15-22 (Frye). Dr. Frye further opined that Dr. McDonough’s suspicion of a metabolic disorder was consistent with a finding of increased tone. Tr. 109:5-7 (Frye). Increased tone suggested damage to the cortex of the brain, which can be seen in white-matter abnormalities in an MRI. *Id.* Dr. Snodgrass disagreed that the examination on April 13th evidenced significant change, stating that while the hip flexion is more severely limited, it was present in January in any case. Tr. 792:11-12 (Snodgrass).

On April 19, 2005, Karl saw the pediatric neurologist, Dr. Kriengkrairut. She reported “truncal hypotonia with marked spasticity of the extremities. The baby has tendency to do cortical thumb bilaterally, worse on the right compared to the left. . . . [B]aby does not babble. . . . [D]elayed development as well as hypotonia of the extremities may be secondary to central nervous system pathology.” R. Ex. 3, at 84-85.

Dr. Frye testified that this report by Dr. Kriengkrairut suggests substantial worsening in Karl. “[This is] a third medical provider talking about spasticity, not just some subtle increases in tone. [She] actually says on the motor exam[ ‘]marked spasticity.[’] This is very[, ]very different than just a subtle change in tone.” Tr. 654:6-25 (Frye). Dr. Frye also explained that hypotonia, cortical thumbing, and cessation of babbling all represent neurological regression. Tr. 110:6-21, 112:17 to 113:2 (Frye). Dr. Snodgrass disagreed. He considered that Dr. Kriengkrairut’s exam revealed no new neurological problems in Karl. Tr. 350:1-4 (Snodgrass). In his view, cortical thumbing was not a significant finding. Tr. 577:17 to 578:3 (Snodgrass). He also stated that the thumbing was not necessarily “cortical” and thus was not necessarily representative of a brain abnormality. Tr. 583:6 to 584:6 (Snodgrass).

Dr. Snodgrass’s critical commentary on Dr. Kriengkrairut’s findings appears to have had two objectives, first, to suggest that Karl’s neurological condition in April 2005 was not substantially different from his condition before the vaccinations, and, second, to suggest that Karl’s neurological condition was not deteriorating. Both implications have no support in the contemporaneous medical records. Karl’s pediatrician, Dr. McDonough, in March had referred Karl to Dr. Kriengkrairut for a detailed neurological examination because of perceived neurological abnormalities. Dr. Kriengkrairut found multiple indicia of “central nervous system pathology.” R. Ex. 3, at 85. What Dr. McDonough had suspected was in fact borne out by Dr. Kriengkrairut. The spasticity first observed by the chiropractor in early mid-February, shortly after the vaccinations, was still evident, along with other neurological abnormalities. By April, Karl was regressing markedly.

In summary, the court finds that Karl had significant signs of neurodegeneration by the end of April, as evidenced by the marked spasticity, cortical thumbing, and lack of babbling observed by Dr. Kriengkrairut, the decreased hip flexion and “global developmental delay” noted by Dr. McDonough, and the belatedly diagnosed abnormal MRI exam from April 27, 2005.

In May 2005, Karl saw a speech therapist. R. Ex. 6, at 5. Karl made no progress throughout May regarding his speech, and the therapist’s records show that Karl had lost skills since October 2004. *See id.* at 5, 25-36. He could no longer produce consonant sounds, but

continued to be able to reach for desired toys. *Id.* at 5-6. Karl's evaluation in September 2005 stated, "No goals met." *Id.* at 7.

On July 12, 2005, Karl experienced his first seizure. R. Ex. 6, at 68. Upon discharge from the MedCenter One Hospital in Bismarck, Dr. McDonough noted that he had "[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. 3, at 18. On July 19, 2005, Karl saw Dr. Michael Frost at St. Paul Children's Hospital in Minnesota. R. Ex. 11, at 5. His medical history from that appointment notes that Karl "has been receiving therapies with some intermittent [decreased] tone but overall [he is] declining in all areas." *Id.* It also notes that by fourteen months, *i.e.*, March 15, 2005, Karl showed no signs of significant developmental progress. *Id.* Dr. Frost noted that Karl was being admitted for a determination of what the etiology might be for his deteriorating neurological status. Dr. Frost believed, after a second MRI in July, that Karl was experiencing neurodegeneration. *Id.* at 56. A third MRI performed in October 2005 showed that the thinning of Karl's corporal callosum had stabilized, suggesting that there may have been a toxic or metabolic event he experienced that had also stabilized. R. Ex. 11, at 280. In short, Karl's condition following the vaccinations reflected marked neurodegeneration.

***C. Loving Prong 3: Whether the post-vaccination condition constitutes a significant aggravation of the pre-vaccination condition***

By October 2005, Karl had "no purposeful movements. He had increased tone throughout and increased deep tendon reflexes throughout with multiple beats of clonus at the [ankles]." R. Ex. 11, at 279. He had no specific smiling or distinctive eye contact. *Id.* This condition starkly contrasts to the previously "very happy" child, R. Ex. 3, at 9, that was "aware and tuned into faces" and who "enjoy[ed] interactive play," R. Ex. 15, at 3. The special master properly concluded that substantial evidence showed that Karl was indisputably worse in the months following his vaccination. *Paluck IV* at \*42. The parties do not dispute this finding, and the court concurs that substantial evidence supports the special master's conclusion.

***D. Loving Prong 4 (Althen Prong 1): Whether there is a medical theory causally connecting the significantly worsened condition to the vaccination***

The special master found that petitioners satisfied their burden of proof as to *Loving* prong four (Althen prong one), *i.e.*, in showing that a medical theory causally connected Karl's worsened condition to the vaccination. The special master succinctly stated that "[i]n briefing after the [c]ourt's Opinion and Order, the parties essentially agreed that the Palucks' evidence met the standard as defined by the [c]ourt." *Paluck IV* at \*42. In that connection, the special master quoted the government's interpretation of *Paluck II* as having "hamstrung the special master from denying compensation under prong one of *Althen*." *Id.* (quoting Resp't's Resp. to Pet'trs' Status Report Following Remand at 4, ECF No. 120).

On this second review, the government contends that the court in *Paluck II* "inappropriately relaxe[d] the Vaccine Act's requirements." Resp't's Opp'n at 15 (referring to the court's observation in *Paluck II*, 104 Fed. Cl. at 475, "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 government’s criticism is misplaced. The Federal Circuit has repeatedly emphasized that preponderant proof of causation does not require scientific certainty, but rather a showing that the vaccine more likely than not caused the injury.<sup>26</sup> 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*, 35 F.3d at 548-49)); *Andreu*, 569 F.3d at 1378 (“Requiring ‘epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant’s burden under the Vaccine Act,’” (omissions in original) (quoting *Capizzano*, 440 F.3d at 1325)). 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.

Mitochondrial disorders are only incompletely understood in biomedical science, although basic mechanisms are known. Those with normally functioning mitochondria have better antioxidant defenses that allow them to “convert . . . reactive oxygen species to harmless compounds.” Tr. 65:21-22 (Frye). This is because mitochondria are responsible for the creation of the energy-carrying molecule, adenosine triphosphate (“ATP”), which is required for the synthesis of the primary antioxidant, glutathione. Tr. 73:23 to 74:6 (Frye). Contrastingly, defective mitochondria can have an opposite effect, themselves producing abnormally high amounts of reactive oxygen species, which can cause damage. Tr. 78:15-25, 79:7-25 (Frye), see R. Ex. 26, at 5. Thus, people with mitochondrial defects are more vulnerable to oxidative stress. Tr. 89:18-24 (Frye); Tr. 448:18 to 449:7 (Snodgrass).

Dr. Snodgrass did not disagree with the basic premises behind Dr. Frye’s theory, but he disagreed that there was evidence, *i.e.*, published peer-reviewed studies, that normal vaccines given to humans cause oxidative stress. See Tr. 448:18 to 449:7 (“I would say that if you have a mitochondrial abnormality, you[r] ability to recover [from excessive reactive oxygen species or reactive nitrogen species] may be less.”), Tr. 482:7 to 484:15 (Snodgrass) (vaccines can affect children with mitochondrial disorders). Dr. Snodgrass stated that of his about twenty patients with a mitochondrial disorder, none of them have worsened with immunization, but he admitted that because mitochondrial disorders are heterogeneous, it is difficult to predict how the same stressor would affect different people. Tr. 482:9 to 483:1 (Snodgrass). On cross-examination, Dr. Snodgrass conceded that, in theory, Karl’s otitis media, erythema multiforme, and the vaccines

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<sup>26</sup>As noted in *Althen*, 418 F.3d at 1279 n.6, this criterion 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).

administered in January 2005 could have “all worked together and been a substantial factor in bringing about his neurodegeneration.” Tr. 483:14-25 (Snodgrass). He maintained, however, that the theoretical postulate was not established in this case because Karl did not get worse in January and February after the immunizations. *Id.* Nonetheless, whether Karl got worse in January and February after the vaccinations does not relate to the legal acceptability of Dr. Frye’s theory under *Loving* prong four, but instead bears on *Loving* prongs five and six, *i.e.*, the logical sequence of cause and effect and a medically acceptable approximate temporal relationship.

Contrary to the government’s reading of this court’s articulation of a standard for *Loving* prong four (*Althen* prong one) in *Paluck II*, it is not solely because a theory is under active scientific investigation that it is reputable, worthy, and reliable. The court instead was stating that the special master could not wholly discount animal studies showing oxidative stress resulting from vaccinations *plus* ongoing, continuing scientific investigation into whether humans also can experience similar oxidative stress resulting from vaccinations. *See Paluck II*, 104 Fed. Cl. at 475. Nor could the special master discredit a peer-reviewed study that suggested oxidative stress in humans resulted from receipt of the flu vaccine, solely because the researcher used a different biomarker than he did in a prior study. *See id.* at 473 (discussing R. Ex. 37a, at 1, Michael Phillips et al., *Effect of Influenza Vaccination on Oxidative Stress Products in Breath*, J. Breath Research (June 2010), at 1). The court was not relaxing the standard for reliability, but rather was applying the pertinent and appropriate standard where research was underway testing reputable theories that were supported by basic knowledge.

***E. Loving Prong 5 (Althen Prong 2): Whether there is a logical sequence of cause and effect showing that the vaccination caused the significant aggravation***

Accepting Dr. Frye’s theory of causation that vaccines can activate an overwhelming immune response in children with mitochondrial defects and lead to neurodegeneration, the next inquiry is whether, in Karl’s particular case, that process occurred. Similar to the level of proof required in establishing a medical theory, the sequence of cause and effect must be “logical and legally probable, not medically or scientifically certain.” *Knudsen*, 35 F. 3d. at 548-49.

Petitioners contend that the special master put aside expert testimony and contemporaneous medical records in favor of drawing his own medical conclusions from the evidence. *See Pet’rs’ Mot.* at 14-15. Specifically, petitioners challenge his reading of the chiropractic records, Dr. McDonough’s referral to the neurologist in March 2005, and testimony regarding the various MRIs. *Id.* at 14-20.

First, the special master determined that Dr. Frye’s theory requires a linear, downward decline without any periodic improvements. *See Paluck IV* at \*43. Both the government and the special master cite this court’s opinion in *Paluck II* for the proposition that this court approved of the special master’s prior conclusion that “petitioners’ medical theory predicted a steady, downward decline in health after vaccination.” Resp’t’s Opp’n at 15 (citing, *but not quoting*, *Paluck II*, 104 Fed. Cl. at 476); *see Paluck IV* at \*43 (“The [c]ourt did not disturb the finding that Dr. Frye’s theory was predicated on a downhill trajectory”). The citation provided by both the

respondent and the special master misapprehends the court's prior action. This court did not address the special master's determination in *Paluck I* that Karl's regression could only fit Dr. Frye's theory if Karl experienced a "continuous downward slope" of injury. *Paluck I* at \*22.

The decision to require a linear, downward slope is unfounded in the testimony. The special master in *Paluck I* interpreted Dr. Frye's phrase that "[Karl's progress] looked like it was just a progressive hill downward for about six months," to mean "a continuous downward slope." *Paluck I* at \*22 (quoting Tr. 231:13 (Frye)). The special master maintained this interpretation in *Paluck IV*. See *Paluck IV* at \*49 ("the special master again concludes that Karl's deterioration was non-linear"). Dr. Frye, however, never suggested that a child experiencing neurodegeneration could not have periods of remission or improvement. His use of the word "progressive" does not mean a continuous linear decline. As a general matter, when used in describing a disease, progressive means "increasing in extent or severity." *Merriam-Webster's Tenth Collegiate Dictionary* 932 (1998); see also *New Oxford American Dictionary* 1396 (2010) ("(of a disease or ailment) increasing in severity or extent."). This standard medical usage allows for a non-linear decline. To fall within Dr. Frye's theory and the applicable medical literature, it is sufficient if Karl's medical records show a decline in condition over time, notwithstanding periods of remission or modest improvement.

Second, the special master considered the chiropractic records and statements by his treating physicians regarding Karl's decline. In the remand, the court ordered the special master to reconsider the importance of these particular pieces of the record, in conjunction with other pieces of the record. See *Paluck II*, 104 Fed. Cl. at 480. Accordingly, this court will consider the entire record in determining whether petitioners have met their burden of proof under *Loving* prong five.

Karl had a fever on January 21, 2005, two days after the vaccinations, that continued to be evident on January 28, 2005, nine days after the vaccinations. R. Ex. 22, at 1-2. Daycare notes from the intervening days consistently show that Karl was tired, irritable, and not eating well. *Id.* According to Dr. Frye, these are all systemic signs of being sick, that is, signs of immune activation. Tr. 103:23 to 104:1, 105:3-5, 143:6-15 (Frye). Dr. Frye testified that a fever any time within two weeks of a vaccination could reasonably be attributed to the vaccination. Tr. 145:17-18 (Frye). Dr. Snodgrass disagreed that Karl's fever could have been caused by the vaccines. He explained that the MMR and varicella vaccines do cause fever in some children, but fever would not usually appear until the seventh or eighth day. Tr. 338:22 to 339:1, 571:4-12 (Snodgrass). On cross-examination, petitioners' counsel asked Dr. Snodgrass whether he was familiar with the packaging insert accompanying the Prevnar vaccine, which states that "15% of children who receive PCV-7 report fever of greater than 38 degrees centigrade within two days following vaccination." Tr. 575:10-17 (petitioners' counsel).<sup>27</sup> He responded that he was, but that the packaging insert does not truly prove causation as a scientific matter. Tr. 575:18-24 (Snodgrass). He referred to a study about the MMR vaccine, one of the other vaccines Karl received, which took 500 sets of identical twins, giving one twin the vaccine and the other a placebo. Tr. 576:2-10 (Snodgrass). In his view, this type of study better proves that a vaccine causes fevers. *Id.* In short, Dr. Snodgrass again looked for medical certainty where none is

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<sup>27</sup>The packaging insert is in the record as R. Ex. 33.

required. It is sufficiently logical that Karl had a reaction to the Prevnar vaccine, manifesting as a fever within two days. He additionally did not explain why the fever on day nine could not be attributed to the vaccinations, stating only that Karl's fevers could have been due to an outbreak of his erythema multiforme, which reappeared on January 31st. Tr. 339:15-25 (Snodgrass); R. Ex. 22, at 2. He testified further that fever is very common among children in daycare and may not specifically indicate oxidative stress. Tr. 291:4-9 (Snodgrass). Similarly, in his view, while irritability might be an indication of something serious, it is not specific. Tr. 291:12-14 (Snodgrass).

Several points of common ground exist. A fever is usually a symptom of immune activation; that much was acknowledged by both experts. Tr. 429:4-16 (Snodgrass); Tr. 105:3-5 (Frye). And, the daycare records contemporaneously documented that Karl had lethargy and irritability along with the fever in the days following the vaccinations. While fever, lethargy, and irritability might possibly have been caused by something besides the vaccinations, sufficient evidence exists to indicate that they were in fact caused by the vaccinations. That at least one of the five vaccines that Karl received, or a combination thereof, caused him to have a fever due to immune activation is logical and legally probable. A *prima facie* case to that effect was established. Accordingly, the burden shifted to the respondent to show another, alternative, cause. That shifted burden was not met, nor did the respondent attempt to meet it.

Dr. Frye's theory postulates that immune activation can cause the development of potentially toxic reactive oxygen species and reactive nitrogen species that, if left unchecked by the body's antioxidants, can lead to oxidative stress and cell death. *See supra*, at 11. Thus, one would look for evidence of whether Karl experienced cell death. In this case, petitioners contend that Karl's neurodegeneration is evidence of brain cell death.

Karl's health deteriorated in February 2005. The chiropractor noted he was spastic on February 11, 2005. R. Ex. 12, at 5. As detailed previously, Karl's later chiropractic records reflect varying levels of rigidity and tone. *Id.* at 5-7. Regardless of whether Karl had days in the subsequent weeks where he was more or less rigid, Karl never appeared to improve above his initial assessment, and he was still reported as spastic in April by the pediatric neurologist, Dr. Kriengkrairut. R. Ex. 3, at 84. Upon questioning by the special master regarding the chiropractic treatment Karl received, Dr. Frye testified that spasticity can be improved by "pulling the muscles and loosening the muscles so that they have full range of motion." Tr. 726:9-14 (Frye). This does not solve the upper neuron problem causing the spasticity, but it can mitigate the symptoms. "[B]y manipulating the muscles you're resetting the feedback mechanism that sets the tone of the muscle[s]. . . . When [neurons from the brain] aren't there [the] feedback loop becomes or [is] set too high and the muscles have too much tone. . . . By using physical therapy we start to stretch out the muscles and that can try to reset the feedback loop that we have in the muscles." Tr. 726:19 to 727:10 (Frye). That Karl's tone fluctuated while he was seeing the chiropractor, *see* R. Ex. 22, at 2, and the K.I.D.S. therapists, *see* R. Ex. 12, would be expected.

In asserting that Karl did not decline between January and February, Dr. Snodgrass stated that "the single most important thing is that we had a lot of calls and doctor visits in November and December. If Karl had a precipitous decline in January and February, these parents who

seem to be responsible parents would have been calling and visiting the doctor, that's number one." Tr. 790:9-14 (Snodgrass). Dr. Snodgrass's inference and the special master's reliance on it, *see Paluck IV* at \*57, are not supported by substantial evidence. Karl's parents actually *were* taking him frequently to a medical provider, *i.e.*, the chiropractor. They took him to the chiropractor nine times in a three week period in February alone, apparently believing that Karl had a pinched nerve preventing his development. *See* R. Ex. 3, at 7. Dr. Snodgrass can disagree with their course of action, implicitly being critical of treatment by a chiropractor rather than a physician, but his testimony implying that the Palucks thought medical treatment unnecessary for Karl is not supported by evidence.

Contrary to the special master's conclusion, the fact that Karl had few visible signs of injury other than fever immediately following the vaccinations is in keeping with Dr. Frye's theory. *See Paluck IV* at \*49 ("part of the Althen prong 2 analysis may consider whether the expert's 'theory accounted for [the vaccinee's] injury'" (quoting *Hibbard v. Secretary of Health & Human Servs.*, 698 F.3d 1355, 1364 (Fed. Cir. 2012))). Dr. Frye testified that changes at the cellular level would occur first and would take time to become clinically visible. Tr. 232:5-10 (Frye). That the MRI from April 2005 was initially interpreted as normal and only later reinterpreted as abnormal upon re-examination in July 2005 suggests that the changes were indeed small at first, but they had been initiated. *Id.* Because the changes were likely occurring at a cellular level at first, Karl was probably worsening in February and March even if it was not linearly progressive. Tr. 730:25 to 731:6 (Frye.). The rate at which that process would occur would depend on the type and severity of the person's mitochondrial disorder.

As an example, Dr. Frye pointed to the Hannah Poling case study. Tr. 121:25 to 123:16, 132:21-24 (Frye) (referring to 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)). Hannah was a developmentally normal nineteen-month-old girl who, within 48 hours of receiving several vaccinations, developed a high fever, inconsolable crying, irritability, and lethargy, and refused to walk. R. Ex. 21q, at 3. Four days later, she could not walk up stairs. *Id.* She had a low-grade intermittent fever during the next twelve days. *Id.* She continued to decline over the next three months, developing autistic behaviors and losing all speech. *Id.* Previously she had been able to say at least twenty words. *Id.* It was later discovered that she had a mitochondrial disorder. *Id.* In 2006, at the time of publication of the case study, Hannah was six and had greatly improved in her language functions and sociability, although she still exhibited mild autism. *Id.* This case study did not prove causation with any medical certainty, but it hypothesized that "[i]f [mitochondrial] dysfunction is present at the time of infections and immunizations in young children, the added oxidative stresses from immune activation on cellular energy metabolism are likely to be especially critical for the central nervous system, which is highly dependent on mitochondrial function." *Id.* at 4.

Dr. Frye pointed to similarities between Hannah and Karl. First, they have similar mitochondrial abnormalities. Tr. 122:20-23 (Frye). Both received MMR and varicella vaccinations, developed a fever around 48 hours later, became noticeably irritable, and eventually experienced neurological regression. Tr. 122:24 to 123:12 (Frye). Hannah's decline occurred more quickly in some ways, but her regression, like Karl's, appeared to continue over a



number of months. Her appetite remained poor for six months, but she began saying a few words again about four months after the vaccinations. R. Ex. 21q, at 3. In contrast, Karl has experienced complete neurodegeneration and is not expected to improve. Tr. 123:7-13 (Frye). Dr. Frye opined that Karl's pre-existing chronic immune activation may have impaired his ability to recover as Hannah did. Tr. 704:3-17 (Frye).

Dr. Frye also pointed to a peer-reviewed article by Dr. John Shoffner and others. The researchers found in a retrospective study that autistic regression occurred twice as often in a subset of autistic children with mitochondrial disorders after a fever than it did in the general population of autistic children. See Tr. 124:1 to 125:12 (referring to R. Ex. 21z, John Shoffner *et al.*, *Fever Plus Mitochondrial Diseases Could Be Risk Factors for Autistic Regression*, 25 J. Child Neurology 429 (2010)).<sup>28</sup> Approximately 25% of children with autism will experience autistic regression before the age of three. R. Ex. 21z, at 1. The researchers defined autistic regression to mean "a loss of developmental skills that included speech, receptive skills, eye contact, and social interests in individuals." *Id.* at 2. A relationship between fever and regression was defined as "regression beginning within [two] weeks of a febrile episode without the suggestion of infection, meningitis, or encephalitis." *Id.* In the study, 60.7% of the children experienced autistic regression, which was a "statistically significant increase" over the estimated 25% reported in the general autistic population. *Id.* at 3. A high percentage, 70.6%, of those who experienced autistic regression did so following a fever. *Id.* In 33.3% of those who experienced autistic regression following fever, the fever was associated with response to a vaccination. *Id.* The specific vaccine schedule leading to fever in the subjects was not available. The study acknowledged that "[d]ue to the complexities in mitochondrial disease pathogenesis, oxidative phosphorylation enzyme defects are highly variable even among groups of individuals who harbor identical mutations." *Id.* at 4.<sup>29</sup> According to Dr. Frye, this study, combined with the Poling case study, strongly suggested that vaccinations in children with mitochondrial diseases can cause fever followed by regressive loss of skills. See Tr. 188:11-15, 621:1-6 (Frye).

Dr. Snodgrass cited a number of differences between Karl's case and Hannah's case. First, Hannah's clinical worsening was much more dramatic than Karl's. She refused to walk within 48 hours of receiving the vaccination, a more notable loss of skill than anything Karl experienced. Tr. 344:1-21 (Snodgrass). Second, there is no evidence that Karl suffered encephalopathy, and it was agreed that Hannah did. *Id.* "In Karl's case we really don't see that.

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<sup>28</sup>In this retrospective study, researchers examined the charts of 28 children who they knew to have autism and mitochondrial disease. They used the charts to determine whether the children experienced fever followed by autistic regression.

<sup>29</sup>Phosphorylation is defined as "the metabolic process of introducing a phosphate group into an organic molecule." Oxidative phosphorylation, specifically, is defined as "the formation of high energy phosphate bonds by phosphorylation of ADP to ATP coupled to the transfer of electrons from reduced coenzymes (NADH or FADH<sub>2</sub>) to molecular oxygen via the electron transport chain. . . . Three molecules of ATP per NADH and two per FADH<sub>2</sub> are produced as a result of a proton gradient created across the mitochondrial inner membrane by the electron transport chain." *Dorland's* at 1439. Thus, "oxidative phosphorylation enzyme defects" can be understood as defects in ATP production.

Yes, he was irritable. Irritability is not encephalopathy. He was not kept home from day care, he was not taken to the doctor. So we do not see evidence that Karl had encephalopathy.” Tr. 344:16-20 (Snodgrass). As for Dr. Frye’s reliance on the Shoffner paper, Dr. Snodgrass criticized its simplicity, questioning how researchers could have known that any particular fever that a child experienced caused the regression. Tr. 345:15-25 (Snodgrass).

Dr. Snodgrass’s critiques might provide valid points of departure for further scientific study in this area of medicine, but they do not negate the evidentiary value provided by the Poling case report or the Shoffner study.<sup>30</sup> Dr. Snodgrass and Dr. Frye agreed that case studies do not prove causation. But Dr. Frye correctly pointed out that “that’s where science starts is with case reports.” Tr. 716:1-2 (Frye). Dr. Frye testified that this particular area of medicine is “emerging and evolving.” Tr. 126:1-6 (Frye). Mitochondrial diseases themselves are difficult to identify, and their courses of progression are not easily predicted. The effect of fevers on those with a mitochondrial disorder is even more difficult to assess. The Poling case report and the Shoffner study nonetheless provide indicia for this case.

In considering the opinions of Karl’s treating doctors as to the cause of Karl’s decline, the special master considered the chiropractor’s opinion, Dr. McDonough’s referral to the neurologist, and the MRI reports. First, as discussed *supra*, the special master’s statement that the chiropractor did not believe Karl had an adverse reaction to a vaccine simply misread a handwritten entry in the medical record. Rather, the chiropractor believed it *was* possible Karl had an adverse reaction to a vaccine. *See supra*, at 25. Second, in reviewing Dr. McDonough’s referral to Dr. Kriengkairut, the pediatric neurologist, the special master inquired into Dr. McDonough’s motivations. Aside from desiring more complete testing of Karl’s neurological system, the special master opined that Dr. McDonough made the referral because he was “frustrated the Palucks were not following his recommendations for physical therapy, occupational therapy, and a stimulation program for Karl.” *Paluck IV* at \*47. The special master criticized petitioners for not raising the argument that Dr. McDonough made the referral because he believed Karl was getting worse. *Id.* at \*47 n.69. The special master apparently ignored Dr. Frye’s testimony on direct examination that the referral is “the first indication that we have that the pediatrician is now concerned [to such] a level that Karl needs to see a neurologist.” Tr. 107:4-6 (Frye). There simply is no evidentiary support for the special master’s hypothesis that Dr. McDonough made the referral out of frustration with the Palucks.

Third, regarding the MRI reports, the special master concluded that “[t]he Palucks have not established that Dr. Frye’s conclusion that Karl’s corpus callosum started to thin after the vaccination is more likely than Dr. Snodgrass’s conclusion that the corpus callosum could have been thin before the vaccination.” *Paluck IV* at \*48. Accordingly, the special master used his finding that Karl had problems in his central nervous system before the vaccination as the tie breaker to determine that the thinning occurred before the vaccinations. *Id.* This court has overturned the special master’s finding that Karl definitively had neurological problems before

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<sup>30</sup>Evidence of causation need not be proven to a medical certainty; it need only be “logical and legally probable.” *Knudsen*, 35 F. 3d. at 548-49 (internal quotation marks and citations omitted).

the vaccinations. *See supra*, at 23-24. The subtlety of the thinning in April, and the clarity of the thinning in July, suggests that the thinning had only begun in April or shortly before then.

Petitioners have presented sufficient evidence to show that Karl regressed after receiving the vaccines, and they have provided medical records and medical literature to establish, by a preponderance of the evidence, that Karl's pre-existing medical problems were significantly aggravated by the vaccinations. Karl had a fever shortly after receiving the vaccinations, was described as "spastic" for the first time on February 11, was referred to a neurologist in March, and by April had a negative neurological evaluation and an abnormal MRI. Petitioners presented a peer-reviewed study showing increased regression in children with mitochondrial diseases following fever. They also presented a case study demonstrating that a young girl with an underlying mitochondrial disorder lost previously developed skills over the course of months after experiencing a fever within 48 hours of vaccinations. Petitioners have carried their burden of proof on this prong.

***F. Loving Prong 6 (Althen Prong 3): Whether a medically acceptable proximate temporal relationship exists between the vaccination and the significant aggravation***

The final prong of the *Loving* analysis requires the court to determine the time frame for which it is medically acceptable to infer causation and whether the onset of the claimant's injury occurred within that time frame.

Petitioners contend that the special master ignored the record in concluding that Karl exhibited no evidence of neurodegeneration within an acceptable time frame. Pet'rs' Mot. at 21. Specifically, they argue that he ignored Dr. Frye's testimony that evidence of neurodegeneration occurred within a medically acceptable time. *See* Tr. 127:15 to 129:14 (Frye). Respondent maintains that the special master carefully considered all of the evidence and found respondent's expert more persuasive than petitioners', an approach and result that is well within the special master's role as a finder of fact. Resp't's Opp'n at 18.

In *Paluck IV*, the special master found that the medically acceptable temporal interval is three weeks. *Paluck IV* at \*62 (concluding that "the bound of the appropriate temporal limit is three weeks"). He based this determination largely on an article by Dr. Edmonds entitled *The Otolaryngological Manifestations of Mitochondrial Disease and the Risk of Neurodegeneration with Infection* in the record as R. Ex. 21d.<sup>31</sup> The Edmonds article collected information about 40 patients with mitochondrial diseases. Of these forty patients, eighteen experienced neurodegenerative events. R. Ex. 21d, at 6. Intercurrent infection was recognized as a precipitant of neurodegenerative events in thirteen of these eighteen patients. *Id.* at 4-6. The article graphically depicts the timing of the onset of neurodegenerative events after the onset of infection as ranging until nineteen days after infection. *Id.* at 7; *see also Paluck IV* at \*55. While the Edmonds article looked for neurodegeneration after infection, not reaction to a vaccination, both experts agree that it provides a reasonable guideline for neurodegeneration following immune activation. Tr. 524:1-5 (Snodgrass); *see* Tr. 619:6-11 (Frye).

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<sup>31</sup>This article is briefly addressed *supra*, at 16.

The special master also relied on the Shoffner study, which found that a relationship between fever and autistic regression existed, *see Paluck IV* at \*53-54, but this reliance is somewhat misplaced because the Shoffner study *defined* a relationship between fever and regression as occurring within two weeks, excluding later sequelae, R. Ex. 21z, at 2. Therefore, by definition, the study could not have found a relationship between fever and regression more attenuated than two weeks. Thus, while the Shoffner article supports a statement that autistic regression following fever can occur within two weeks, it cannot equally support a statement that autistic regression following fever must occur within two weeks. The special master also relied on the Hannah Poling case study, noting that she had a fever within 48 hours, could not climb the stairs within seven days, and developed a rash within two weeks. *Paluck IV* at \*55.

The Edmonds article is the most enlightening regarding an acceptable medical time frame for the onset of neurodegenerative events following immune system activation. The Edmonds article, however, acknowledges the severe dearth of medical literature in this area: “Because of the relative novelty of mitochondrial disorders, no reports in the literature have quantified the risk for neurodegenerative events triggered by infections in patients with mitochondrial disease.” R. Ex. 21d, at 3. Dr. Bob Naviaux, Co-Director of the Mitochondrial and Metabolic Disease Center at the University of California, San Diego, expressed a similar sentiment in commenting on the Shoffner study. *See* R. Ex. 31, Bob Naviaux, “*Commentary on John Shoffner et al., Fever Plus Mitochondrial Disease Could Be Risk Factors for Autistic Regression, published in 25 J. Child Neurology 429 (2010).*” According to Dr. Naviaux, the temporal relationship between the triggering event and neurodegeneration is unsettled. There appears to be a more rapid “flare” response and a more delayed “fade” response. *Id.* at 2. He credited the Shoffner study with providing a touchstone for new questions, such as “which kinds of mitochondrial defects lead to rapid, high-grade fevers in response to infection or vaccination” and “which defects lead to a failed fever response, or to a low-grade fever, or to a reduced immune response to vaccination?” *Id.* at 3.

Dr. Frye accepted the premises of these articles, testifying that the temporal link requires much further study. He did testify, however, that an adverse reaction to a vaccine is likely to appear within a week of receiving it. Tr. 127:21-22 (Frye). He further stated that the adverse reaction can peak several days after the vaccination, and then “lead to . . . metabolic decompensation, which is an ongoing process . . . [that will] continue until it burns itself out,” if it is not interrupted. Tr. 128:5-9 (Frye). Dr. Snodgrass and Dr. Frye disagree whether Karl’s first fever, within two days of the vaccination, could have been caused by the vaccination, but they apparently agree that any fever around one week following Karl’s vaccinations could have been caused by the vaccines. *See id.*; Tr. 513:10-17 (Snodgrass). Thus, at least Karl’s continuing fever is safely within any type of medically accepted time frame for Karl’s injury.

The special master appeared determined to establish a definitive bound for neurodegeneration, but the court disagrees that such a bound can be sharply delineated in this specific area. Neither the medical literature nor the expert testimony stated with any certainty when neurodegeneration can be expected to begin in all cases. Dr. Snodgrass based his testimony that a change would have to begin “within a few weeks” on the Edmonds article. Tr. 524:1-6 (Snodgrass). As previously discussed, the Edmonds article is the first of its kind and cannot be read to suggest a definitive temporal interval for neurodegeneration in response to all

triggering events for any type of mitochondrial disorder. In response to questioning from the special master, Dr. Frye testified that the timing for neurodegenerative changes to appear clinically in a child would depend on the severity and type of mitochondrial disorder. Tr. 128:22-23 (Frye). This is consistent with Dr. Naviaux's commentary on the Shoffner study.

In this instance, Dr. Frye pinpointed the chiropractor's notation that Karl was "spastic" on February 11, 2005 as an identifiable neurodegenerative event. *See* Tr. 659:23 to 660:10 (Frye). To Dr. Frye, the neurodegenerative process must have begun by then. This event occurred within the general time frame suggested by both the special master and Dr. Snodgrass. *See* Tr. 524:5-6 (Snodgrass) ("The change should come within a few weeks."). Starting with this chiropractic notation, the record shows Karl experienced a general decline. His chiropractic assessment remained the same throughout all of February, even if the subjective descriptions of Karl's day-to-day behaviors varied. Karl was losing language throughout this period, and by late March, Dr. McDonough saw a need for him to be evaluated by a neurologist.

In conclusion, setting a hard and fast time frame in an uncertain area undergoing sustained scientific investigation is contrary to the precepts governing the Vaccine Act. Karl had a fever within 48 hours of the vaccinations, accompanied by a week of lethargy, irritability, more fever, and disrupted sleeping and eating cycles. This prompt reaction is consistent with an adverse immune reaction to the vaccines. An observation of spasticity followed within a time that all agreed would have been appropriate for a neurodegenerative event. Karl experienced total decline within six months, and he did not continue to develop in any way after the vaccinations. These facts combined with his febrile reaction to the vaccine show, by a preponderance of the evidence, that Karl's existing medical setbacks were significantly aggravated by his receipt of the vaccinations within a medically acceptable time.

## CONCLUSION

For the reasons stated, the Palucks' motion for review is GRANTED, the special master's decision of May 10, 2013 denying compensation is VACATED, and the court acts in accord with 42 U.S.C. § 300aa-12(e)(2)(B) to find that petitioners have satisfied each of the six *Loving* elements and are entitled to compensation under the Act.<sup>32</sup> The case is remanded to the special

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<sup>32</sup>The Vaccine Act provides that upon the filing of a motion for review of a special master's decision, this court

may thereafter —

- (A) uphold the findings of fact and conclusions of law of the special master and sustain the special master's decision,
- (B) set aside any findings of fact or conclusions of law of the special master found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and issue its own findings of fact and conclusions of law, or

master to determine compensation.

It is so ORDERED.

s/ Charles F. Lettow

Charles F. Lettow

Judge

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(C) remand the petition to the special master for further action  
in accordance with the court's direction.

42 U.S.C. § 300aa-12(e)(2).