United States Court of Appeals for the Federal Circuit

HEIDI SHARPE, AS THE LEGAL REPRESENTATIVE OF HER MINOR CHILD, L.M.,
Petitioner-Appellant

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,
Respondent-Appellee

2019-1951

Appeal from the United States Court of Federal Claims in No. 1:14-vv-00065-NBF, Senior Judge Nancy B. Firestone.

Decided: July 1, 2020

CURTIS RANDAL WEBB, Twin Falls, ID, argued for petitioner-appellant.

VORIS EDWARD JOHNSON, JR., Vaccine/Torts Branch, Civil Division, United States Department of Justice, Washington, DC, argued for respondent-appellee. Also represented by JOSEPH H. HUNT, C. SALVATORE D'ALESSIO, HEATHER LYNN PEARLMAN, CATHARINE E. REEVES.

Before MOORE, REYNA, and TARANTO, *Circuit Judges*.

REYNA, *Circuit Judge*.

Heidi Sharpe, on behalf of her minor daughter, L.M., appeals from a judgment of the United States Court of Federal Claims upholding the Special Master's dismissal of L.M.'s petition for compensation under the National Childhood Vaccine Injury Act of 1986. For the reasons set forth below, we affirm the Special Master's denial of Petitioner's on-table claim and vacate and remand the Special Master's denial of Petitioner's off-table claim for further proceedings.

BACKGROUND

I

On July 26, 2010, L.M. was born at full-term and developed normally for the first six months of her life. By six months, L.M. could roll over, push herself up, play, giggle, interact with others, and maintain good head control. L.M.'s father testified that L.M. "loved to play in [his] lap, grab her daddy's hat and nose, shirt, anything she could get her hands on." J.A. 173. On the afternoon of February 10, 2011, at her six-month check-up, L.M. received several childhood vaccines, including the diphtheria-tetanus-acellular pertussis ("DTaP") vaccination. By 7:00 pm that evening, L.M. had a fever, was lethargic, had poor muscle tone, and would not eat. Concerned, L.M.'s mother, Heidi Sharpe ("Petitioner"), called the local hospital's emergency room department twice in the early morning hours of February 11, 2011, and then called her daughter's pediatrician later that morning. Petitioner was instructed to administer ibuprofen and Tylenol to L.M. and to bring L.M. in for a doctor's visit on February 14, 2011, if L.M. did not appear to improve.

Petitioner testified that from February 11 to February 14, 2011, L.M. continued to have a fever, remained lethargic, had poor head control, did not interact with her

surroundings, and could not focus on her mother while feeding. Petitioner also testified that any disturbance caused L.M. to scream.

On the morning of February 15, 2011, L.M. experienced a seizure. Petitioner rushed L.M. to the emergency room department at a local hospital. The medical records reveal that upon arrival, L.M. was "fairly floppy in her motor skills," that she could not sit by herself, and that she had "fairly poor head control." J.A. 144. The medical records also note that one month prior, Petitioner had observed L.M. having a few episodes of "spacing out," where L.M. had a "strange look in her eye and was not responsive for several seconds." J.A. 143.

L.M. had a second and third seizure on February 15, 2011, and was then transferred to a second hospital—St. Vincent's. The St. Vincent's medical records show that L.M. had poor head control and diminished responsiveness.

On February 16, 2011, L.M. was diagnosed with infantile spasms. L.M. was discharged the following day. L.M.'s medical records indicate that, on February 21, 2011, she continued to have poor head control, and by March 21, 2011, L.M. was experiencing about five to six seizures a day. By April 11, 2011, L.M.'s doctors reported that L.M.'s eyes "don't really seem to focus on anything," that L.M. did not have an "interactive smile," and that L.M. "didn't have good head control at all." J.A. 130.

Since April 2011, L.M. continues to experience seizures and has experienced profound physical and cognitive developmental delays. At the time of the Special Master's compensation hearing in this case, L.M. was about 7 years and 5 months of age. At this age, L.M. could crawl and walk with the assistance of a walker. She had a poorly coordinated grasp, suffered cortical visual impairments, and was nonverbal, though she could use a few signs to express ideas such as "hungry," "thirsty," "I want," "yes," and "no." *See* J.A. 8, J.A. 346–51.

Over the years, L.M. has seen various doctors and has undergone various therapies and testing. Key here, genetic testing revealed that L.M. was born with a genetic mutation in the stem region of the dynein cytoplasmic 1 heavy chain 1 gene ("DYNC1H1 gene").

II

On January 27, 2014, Petitioner filed a petition for compensation under the National Vaccine Injury Compensation Program on behalf of L.M. Petitioner alleged that the vaccinations administered to L.M. on February 10, 2011, significantly aggravated L.M.'s pre-existing condition under two alternative theories. According to Petitioner's first theory, L.M. had a pre-existing "encephalopathy" as defined in the Vaccine Act and that the DTaP vaccination significantly aggravated L.M.'s encephalopathy within 72 hours of administration, resulting in a compensable "on-table" injury. According to Petitioner's second theory, L.M. had a pre-existing "seizure disorder" and the February 10th vaccinations, as opposed to just the DTaP vaccination, significantly aggravated L.M.'s seizure disorder, resulting in a compensable "off-table" injury.

The Special Master denied the petition for compensation. The Special Master found that Petitioner's on-table significant aggravation claim failed "because it relied on a legally untenable construction" of the Vaccine Act's definition of "encephalopathy." J.A. 3. The Special Master also found that Petitioner's off-table significant aggravation claim failed because "Petitioner did not successfully establish that the vaccines did so (or that they *could* specifically worsen the expected course of an individual with the precise mutation possessed by L.M.)." *Id.* (emphasis in original). Specifically, the Special Master denied Petitioner's off-table significant aggravation claim because L.M.'s genetic mutation was "the most compelling explanation for her predisposition to develop a seizure disorder." J.A. 56.

The United States Court of Federal Claims affirmed the Special Master's denial of both claims. Petitioner timely appeals. We have jurisdiction under 42 U.S.C. § 300aa–12(f).

DISCUSSION

This court reviews *de novo* a ruling by the Court of Federal Claims on a special master's decision to grant or deny entitlement to compensation under the Vaccine Act. *See Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000). This court thus performs the same task as the Court of Federal Claims and reviews the special master's legal determinations *de novo*, fact findings under an arbitrary and capricious standard, and discretionary rulings for an abuse of discretion. *See Munn v. Sec'y of the Dep't of Health & Human Servs.*, 970 F.2d 863, 870–73, 870 n.10 (Fed. Cir. 1992).

Before turning to Petitioner's claims, we review two aspects of the Vaccine Injury Program. First, a petitioner can allege that the vaccine caused the onset of her injuries (an onset claim) or that the vaccine significantly aggravated her pre-existing condition (a significant aggravation claim). *See* 42 U.S.C. § 300aa–11(c)(1)(C); *see also Whitecotton ex rel. Whitecotton v. Sec'y of Health & Human Servs.*, 81 F.3d 1099, 1102–03 (Fed. Cir. 1996).

Second, the Vaccine Act includes a "Vaccine Injury Table" ("Vaccine Table" or "Table"), which lists various injuries associated with various vaccines, and provides a time period with respect to each injury associated with each vaccine. 42 U.S.C. § 300aa–14(a). Included with the statutory table is a list of definitions for various Table injuries, known as the Qualifications and Aids to Interpretation ("QAI"). *See id.*, § 300aa–14(b). The Vaccine Act provides that the Secretary of the Department of Health and Human Services ("HHS") may modify the Vaccine Table, as well as the QAIs, through duly promulgated regulations. *Id.*, § 300aa–14(c); *see also Terran ex rel. Terran v. Sec'y of*

Health & Human Servs., 195 F.3d 1302, 1308 (Fed. Cir. 1999). The Secretary of HHS has promulgated a revised Vaccine Table and QAI. *See* 42 C.F.R. § 100.3.

If a petitioner can show that she experienced the first "symptom or manifestation" of a Table injury or a significant aggravation of a Table injury within the prescribed time period in the Vaccine Table, causation is presumed, and the petitioner has made her prima facie case of entitlement to compensation. *See* 42 U.S.C. §§ 300aa–11(c)(1)(C)(i), 300aa–13(a)(1)(A). These claims are known as "on-table" claims.

If a petitioner cannot show that she experienced a Table injury or that such injury occurred within the prescribed time frame in the Vaccine Table, a petitioner will not be afforded a presumption of causation. Instead, the petitioner must prove that the vaccine in fact caused her injuries by a preponderance of the evidence. 42 U.S.C. §§ 300aa–11(c)(1)(C)(ii), 300aa–13(a)(1)(A). These claims are known as "off-table" claims. *See Whitecotton*, 81 F.3d at 1102. Notably, the preponderance of the evidence standard for off-table claims does not require a petitioner to prove causation with scientific certainty. *See Knudsen ex rel. Knudsen v. Sec'y of Dep't of Health & Human Servs.,* 35 F.3d 543, 548–49 (Fed. Cir. 1994). Rather, "[c]ausation in fact under the Vaccine Act is . . . based on the circumstances of the particular case . . . [and] involves ascertaining whether a sequence of cause and effect is 'logical' and legally probable." *Id.* With this backdrop, we now turn to Petitioner's on-table claim, followed by Petitioner's off-table claim.

I. On-Table Claim

Petitioner argues that the Special Master legally erred in denying her on-table significant aggravation claim, which alleges that the DTaP vaccination L.M. received on February 10, 2011, significantly aggravated her Table-

injury of "encephalopathy" within 72 hours. For the below reasons, we disagree with Petitioner.

For her on-table significant aggravation claim, Petitioner had to demonstrate that: (a) pre-vaccination, L.M. experienced an "encephalopathy," as defined in the QAI promulgated by HHS; (b) L.M. suffered a significant aggravation of that encephalopathy post-vaccination; and (c) the first symptom or manifestation of the significant aggravation of L.M.'s encephalopathy occurred within 72 hours post-vaccination. *See Whitecotton*, 81 F.3d at 1107. At issue here is whether L.M. experienced a QAI-defined "encephalopathy" pre-vaccination.

Pursuant to the QAI issued by HHS, an individual suffers an "encephalopathy" only if "such recipient manifests, within the applicable period," an "acute encephalopathy" followed by "a chronic encephalopathy [which] persists in such person for more than 6 months beyond the date of vaccination." 42 C.F.R. § 100.3(b)(2)(2014). For children less than 18 months of age, "[a]n acute encephalopathy is indicated by a significantly decreased level of consciousness lasting for at least 24 hours." *Id.*, § 100.3(b)(2)(i)(A).

In *DeRoche v. Secretary of the Department of Health & Human Services*, the special master recognized that under the QAI's definition of an encephalopathy—an acute encephalopathy followed by a chronic encephalopathy for six months—petitioners face the "infeasible" task of showing a significant aggravation of such a serious, chronic injury. No. 97-643V, 2002 WL 603087, *27 (Fed. Cl. Spec. Mstr. Mar. 28, 2002). The special master also explained that given the short timetable for childhood vaccines, a child petitioner would have received an immunization before six months had elapsed, rendering it difficult to establish an aggravation of an encephalopathy. *Id.* Thus, the special master construed the QAI's definition of encephalopathy to require only an acute encephalopathy when applied to on-table, significant aggravation claims. *Id.* at *29.

In this case, the Special Master followed the *DeRoche* approach. Specifically, the Special Master narrowed the QAI's definition of encephalopathy to an acute encephalopathy only. Here, there is no real dispute that pre-vaccination, L.M. did not experience an acute encephalopathy. At most, L.M. experienced a few episodes of "spacing out" one month prior to her February 10, 2011 vaccinations, which fall short of a decreased level of consciousness for a 24-hour period. Accordingly, the Special Master found that L.M. did not experience an acute encephalopathy and denied L.M.'s on-table significant aggravation claim.

We see no error in the Special Master's determination. "All statutes must be construed in the light of their purpose. A literal reading of them which would lead to absurd results is to be avoided when they can be given a reasonable application consistent with their words and with the legislative purpose." *Haggar Co. v. Helvering*, 308 U.S. 389, 394 (1940). This principle of statutory interpretation applies to the interpretation of regulations. *See Trustees of Indiana Univ. v. United States*, 618 F.2d 736, 739 (Ct. Cl. 1980). Here, the QAI definition of encephalopathy, i.e., an acute encephalopathy followed by a chronic encephalopathy, would lead to an absurd result if literally applied to on-table significant aggravation claims. Rather, the dual requirement for acute and chronic encephalopathies is better suited for on-table onset claims. Thus, as in *DeRoche*, it was reasonable for the Special Master to construe "encephalopathy" to mean only an acute encephalopathy for Petitioner's on-table significant aggravation claim. Additionally, the record is clear that L.M. did not experience an acute encephalopathy pre-vaccination.

Petitioner argues, however, that the Special Master did not go far enough in correcting the QAI's definition of encephalopathy for on-table significant aggravation claims. Appellant's Br. at 26. Specifically, Petitioner argues that even the more limited definition of encephalopathy articulated in *DeRoche*, i.e., an acute encephalopathy, should not

apply here. *Id.* at 23. This is because, according to Petitioner, most encephalopathies are not acute until after vaccination, and, thus, it would be nearly impossible to prove a significant aggravation of a pre-existing acute encephalopathy. *Id.* at 28. Rather, Petitioner argues, the Special Master should have applied the "common, ordinary, and accepted meaning" of an encephalopathy, which is "a disease of the brain." *Id.* at 23, 25.

Petitioner, however, provides no support that most encephalopathies do not become acute until after vaccination. In the absence of such evidence, Petitioner's conclusory argument is not a sufficient ground for excising the acute requirement from the QAI's definition of encephalopathy.

For the above reasons, we affirm the Special Master's denial of Petitioner's on-table claim.

II. Off-Table Claim

Petitioner also challenges the Special Master's denial of her off-table claim. According to Petitioner, L.M.'s receipt of vaccinations on February 10, 2011, significantly aggravated L.M.'s pre-existing "seizure disorder." J.A. 18, J.A. 55. To prevail on an off-table significant aggravation claim, a petitioner must satisfy the six-prong inquiry announced in *Loving ex rel. Loving v. Secretary of Health & Human Services*, 86 Fed. Cl. 135 (2009). Under the *Loving* framework, a petitioner must establish:

> (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.

Id. at 144; *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (holding that "the *Loving* case provides the correct framework for evaluating off-table significant aggravation claims").

If a petitioner successfully satisfies the *Loving* inquiry, the burden shifts to the government to prove by a preponderance of the evidence that a "factor unrelated" to the vaccine caused the petitioner's injuries. 42 U.S.C. § 300aa–13(a)(1)(A)–(B); *see also Hines v. Sec'y of the Dep't of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991). If the government fails to carry its burden, the petitioner is entitled to compensation.

Here, the Special Master determined that Petitioner satisfied *Loving* prongs 1, 2, and 6. The Special Master, however, determined that Petitioner failed to satisfy *Loving* prongs 3, 4, and 5 and, thus, did not make out her prima facie case of causation-in-fact. The Special Master also determined that even if Petitioner had proven causation-in-fact, she still was not entitled to compensation because the government sufficiently satisfied the "factor unrelated" inquiry. Specifically, the Special Master determined that L.M.'s DYNC1H1 gene mutation, and not the vaccination, was the sole, substantial cause of L.M.'s significantly aggravated seizure disorder. On appeal, Petitioner challenges the Special Master's determinations under *Loving* prongs 3, 4, and 5, and the "factor unrelated" inquiry. We discuss each of these factors below.

A. *Loving* prong 3

Petitioner argues that the Special Master legally erred in applying *Loving* prong 3. We agree with Petitioner. The Special Master's *Loving* prong 3 analysis makes clear he required Petitioner to prove the expected outcome for a

child with a DYNC1H1 gene mutation and to show that L.M.'s current, post-vaccination condition was worse than that expected outcome. Specifically, the Special Master explained that "[s]ubsumed within the *Loving* analysis is the requirement to evaluate the likely natural course of an injured party's preexisting disease, in order to determine whether the vaccine made the petitioner worse than he would have been but for the vaccination." J.A. 36; *see also* J.A. 51 (noting that *Loving* prong 3 required "an evaluation of what is known about the preexisting mutation and *its likely impact* on an affected individual's life" (emphasis added)). *Loving* prong 3, however, does not require a petitioner to demonstrate an expected outcome and that her current-post vaccination condition was worse than such expected outcome. To understand why this is not required, we believe it necessary to review this court's development of the significant aggravation claim framework.

The Court of Federal Claims announced the first framework for analyzing on-table significant aggravation claims in *Misasi v. Secretary of the Department of Health & Human Services*, 23 Cl. Ct. 322 (1991). The *Misasi* inquiry required a special master to compare "the actual condition of the child after the vaccination with the child's predicted condition had the vaccine not been administered." *Whitecotton*, 81 F.3d at 1105 (discussing the *Misasi* framework). "If the child's current condition represent[ed] a significant aggravation of the child's expected condition, then the child [was] entitled to the presumption" of causation for on-table claims. *Id.* The reasoning underlying the *Misasi* inquiry was to "distinguish cases in which the vaccination caused the significant aggravation from cases in which the vaccination had no detrimental effect." *Id.*

In *Whitecotton*, in discussing an on-table significant aggravation claim, we squarely rejected the *Misasi* inquiry as "improperly requir[ing] a petitioner to prove, as part of her *prima facie* case, that petitioner's significant aggravation was not caused by a pre-existing injury." *Id.* at 1106

(emphasis in original). We instead explained that the Vaccine Act only requires a "comparison of the person's pre-vaccination condition with the person's current, post-vaccination condition." *Id.* at 1107 (citing 42 U.S.C. § 300aa–33(4)). This comparison is now known as prong 3 of the *Whitecotton* inquiry for on-table significant aggravation claims. *Id.*[1]

The Court of Federal Claims then announced the *Loving* inquiry for off-table significant aggravation claims. We subsequently approved the *Loving* approach for such claims, *W.C.*, 704 F.3d at 1357, and the government accepts that approach. Key here, the *Loving* court incorporated prongs 1, 2, and 3 of the *Whitecotton* inquiry into its analysis. *Loving*, 86 Fed. Cl. at 144. The last three prongs of the *Loving* inquiry correspond to the three-part inquiry articulated in *Althen v. Secretary of Health & Human Services*, 418 F.3d 1274 (Fed. Cir. 2005). *Id.*

Thus, *Loving* prong 3, like *Whitecotton* prong 3, only requires a comparison of a petitioner's current, post-

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[1] The *Whitecotton* inquiry for on-table significant aggravation claims requires a court to:

> (1) assess the person's condition prior to administration of the vaccine,
> (2) assess the person's current condition, . . .
> (3) determine if the person's current condition constitutes a "significant aggravation" of the person's condition prior to vaccination within the meaning of the statute . . . . and[]
> (4) determine whether the first symptom or manifestation of the significant aggravation occurred within the time period prescribed by the Table.

Whitecotton, 81 F.3d at 1107.

vaccination condition with her pre-vaccination condition. To require a petitioner to prove her expected outcome and that her post-vaccination condition is worse than this expected outcome, as the Special Master required here, revives the defunct *Misasi* test and is improper under our precedent.

The impropriety of the *Misasi* test is readily apparent in gene mutation cases, in which a clinical outcome is nearly impossible to predict. As the government's own expert, Dr. Descartes, testified:

> The dream of the geneticist is to find genotype-phenotype correlation, because when a parent comes to talk to me, the first thing they want to know, is my child going to be able to do this and that? How long my child is going to live? Do you have any answer to these questions? The mutation that you found, what do you know? And the answer, unfortunately, to all these questions that parents ask all the time is **we don't know.**

J.A. 389: 5–12 (emphasis added).

The Special Master reasoned that a comparison of L.M.'s current, post-vaccination condition with the expected course of a DYNC1H1 gene mutation is consistent with *Stone ex rel. Stone v. Secretary of Health & Human Services*, 676 F.3d 1373 (Fed. Cir. 2012). The Special Master misread *Stone*. In *Stone*, we explained that "evidence of other possible sources of injury can be relevant not only to the 'factors unrelated' [inquiry], but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question." 676 F.3d at 1379. We also explained that "no evidence should be embargoed from the special master's consideration simply because it is also relevant to another inquiry under the statute." *Id.* at 1380. We agree with *Stone* that a court should consider all evidence in the record, including evidence of other possible sources of injury. There is, however,

a fine line between a court properly considering evidence in the record, *Stone*, 676 F.3d at 1380, and improperly placing the burden on the petitioner to prove that her significantly aggravated condition was not caused by her gene mutation. *See Whitecotton*, 81 F.3d at 1106. Here, the Special Master unequivocally engaged in the latter. *See* J.A. 36, 51.

The government argues that the Special Master's application of *Loving* prong 3 was in line with our decision in *Locane v. Secretary of Health & Human Services*, 685 F.3d 1375 (Fed. Cir. 2012). We disagree. In *Locane*, the special master did not require the petitioner to prove that her significantly aggravated condition was not caused by her preexisting condition. 685 F.3d at 1381. Instead, the special master found that the petitioner's condition "was not affected by the vaccination." *Id.* at 1378. This proposition is not new. In any vaccine case, if the evidence as a whole ultimately shows that the vaccine was not a substantial factor in causing the petitioner's injury, then compensation should be denied.[2]

For the above reasons, the Special Master legally erred in applying *Loving* prong 3.

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[2] To the extent that *Locane* could be read as requiring a comparison of a petitioner's current, post-vaccination condition with her expected outcome to establish a significant aggravation, then that portion of *Locane* conflicts with *Whitecotton*. Because *Whitecotton* pre-dates *Locane*, *Whitecotton* would govern. *See Newell Cos. v. Kenney Mfg. Co.*, 864 F.2d 757, 765 (Fed. Cir. 1988) ("Where there is direct conflict, the precedential decision is the first.").

B. *Loving* prong 4

Petitioner argues that the Special Master legally erred in applying *Loving* prong 4. For the below reasons, we agree with Petitioner.

The Special Master's *Loving* prong 4 analysis indicates that Petitioner had to eliminate L.M.'s pre-existing gene mutation as the cause of her significantly aggravated seizure disorder. Specifically, the Special Master faulted Petitioner for not sufficiently showing that L.M.'s gene mutation would have "more likely than not" resulted in a benign trajectory. J.A. 54. The Special Master also noted that:

> No doubt future research may . . . make it easier to conclude that a tail-located DYNC mutation *is unlikely to be pathogenic* [i.e., disease-causing] in the manner relevant herein. But such research does not yet exist, and on the present record I do not find that Petitioner's showing established the first "can cause" [*Loving*] prong.

Id. (emphasis added). This analysis is legally flawed.

First, a petitioner may be able to make out a prima facie case under *Loving* prong 4 without eliminating a pre-existing condition as the cause of her significantly aggravated injury. And if the petitioner does so, the burden falls on the government under the "factor unrelated" inquiry to show that the pre-existing condition caused the significantly worsened condition. *Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1151 (Fed. Cir. 2007) (noting that "the government bears the burden of establishing alternative causation . . . once the petitioner has established a prima facie case"). Under *Loving* prong 4, a petitioner need only provide a "medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination." *Loving*, 86 Fed. Cl. at 144. In other words, Petitioner was required to present a medically plausible theory

demonstrating that a vaccine "can" cause a significant worsening of L.M.'s seizure disorder. *See Pafford ex rel. Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1356–57 (Fed. Cir. 2006).

Second, the Special Master should not have been concerned with what "future research" may show but rather with the research presented in the record. *See Knudsen*, 35 F.3d at 549.

> [A court] is . . . not to be seen as a vehicle for ascertaining precisely how and why DTP and other vaccines sometimes destroy the health and lives of certain children while safely immunizing most others. This research is for scientists, engineers, and doctors working in hospitals, laboratories, medical institutes, pharmaceutical companies, and government agencies. The special masters are not "diagnosing" vaccine-related injuries. The sole issues for the special master are, based on the record evidence as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the child's injury.

Id. The Vaccine Injury Program, after all, is designed to "allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Althen*, 418 F.3d at 1280.

The Special Master separately determined that Petitioner failed under *Loving* prong 4 because the medical literature regarding the SCN1A gene mutation, a different gene mutation than at issue here, "effectively rebutted" Petitioner's medical theory. J.A. 55. The Special Master emphasized that because "the environmental impact of vaccination was not deemed significant enough to alter the course" of a SCN1A gene mutation, the same must be true for the DYNC1H1 gene mutation. *Id.* (emphasis removed). The Special Master noted that Petitioner "perhaps could

have" succeeded under *Loving* prong 4 if Petitioner had "rebutted evidence offered about SCN1A mutations." *Id.*, n.50.

The Special Master doubles down on his legal error. Petitioner only had to set forth a medical theory that L.M.'s February 10th vaccinations could worsen her seizure disorder. *Loving*, 86 Fed. Cl. at 144. Yet, the Special Master required Petitioner either to prove an additional medical theory—that vaccines could alter the course of an SCN1A mutation—or to disprove the applicability of SCN1A research to DYNC1H1 patients. This was not Petitioner's burden to carry.

The Special Master then determined that Petitioner separately failed to meet *Loving* prong 4 because the patient cited in the Ambry report ("Ambry patient"), a report cited by both parties' experts, effectively disproved Petitioner's medical theory. *See* J.A. 54. According to the Special Master, the Ambry patient belied Petitioner's medical theory because the Ambry patient had the same genetic mutation and same severe outcome as L.M. *See* J.A. 52–54. This conclusion is arbitrary and capricious and must be set aside. *See Paluck v. Sec'y of Health & Human Servs.*, 786 F.3d 1373, 1380 (Fed. Cir. 2015) (noting that this court has "a duty to ensure that the special master has properly applied [the] Vaccine Act . . . and articulated a rational basis for [his] decision" (internal quotation marks omitted)). Neither party established whether the Ambry patient faced any of the same environmental factors that arguably affected the outcome of L.M.'s mutation, including vaccination. If the Ambry patient was also vaccinated, then the patient's condition could also have been caused by her vaccine.[3] Additionally, even if the Ambry patient suffered

[3] The Special Master recognized that the Ambry patient may or may not have received any vaccines but found this point "only strengthens the relevance" of the Ambry

from the same condition as L.M. without vaccination, a single example cannot establish the typical progression of a disease; nor is such a singular example sufficient to disprove a medical theory that a vaccine *can* cause aggravation in *some* patients. Yet, it is clear from the record that the Special Master concluded that given the Ambry patient, L.M. was destined to have a severe outcome. *See* J.A. 25, 54. This deterministic mindset does not belong in the Vaccine Injury Program.[4]

Lastly, the Special Master found that Petitioner's medical theory—that vaccines could constitute a sufficient "environmental insult" to exacerbate the effects of L.M.'s underlying seizure disorder—was not persuasive. *See* J.A. 55; *see also* J.A. 21. Specifically, the Special Master explained that Petitioner's medical expert did not "offer literature specifically addressing the propensity of any vaccine to exacerbate a disease otherwise attributable to a

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patient. J.A. 54 n.49. For if the Ambry patient experienced the same outcome as L.M. *without* being vaccinated, the Special Master noted, "the conclusion that the vaccines had no impact on L.M.'s outcome is strengthened." *Id.* We reject this finding because it is based on an unsubstantiated fact—that the Ambry patient was not vaccinated.

[4] As the government's expert testified, geneticists "dream" of discovering a "genotype-phenotype correlation" which would allow geneticists to predict the outcome of a child with a gene mutation, but geneticists are not there yet. *See* J.A. 389: 5–12. Thus, until science provides us with better answers, it is not the place of a court to assume that a child with a genetic mutation is destined to have a severe outcome. "The role of genetic knowledge in the vaccine compensation program requires deeper understanding than [a] 'destiny' pejorative . . . ." *Oliver v. Sec'y of Health & Human Servs.*, 911 F.3d 1381, 1384 (Fed. Cir. 2009) (Newman, J., dissenting in denial of rehearing en banc).

genetic mutation and this component of his overall opinion had a conclusory character to it." J.A. 21. The Special Master's finding is legally and factually erroneous.

First, medical literature is not required under *Loving* prong 4. *See Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378–79 (Fed. Cir. 2009) (explaining that a petitioner can satisfy her burden to prove a plausible medical theory without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory). "Requiring epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id.* at 1378 (internal quotation marks omitted). Thus, the Special Master's rejection of Petitioner's medical theory due to an absence of medical literature was legal error.

Second, contrary to the Special Master's determination, the record shows that Petitioner's medical theory was not merely based on "personal supposition." J.A. 55. Rather, Petitioner's medical theory was substantiated by the government's medical expert, Dr. Descartes. Dr. Descartes explained in her expert report that "[s]eizures induce neuro-inflammation, which in turn fosters further seizures; pre-existing neuro-inflammation decreases the seizure threshold, worsening the consequences of seizure-triggering event." J.A. 309. Additionally, Dr. Descartes testified that regardless of the absence of medical literature, viral infections "could very well interact" with a DYNC1H1 mutation. J.A. 414. She testified that "when a person has an infection, even a cold or a virus or a bacteria . . . it's under stress, definitely, and it could probably affect the system." *Id.* She further testified that "[i]t's not uncommon that children that have genetic problems do not handle infections better than children that do not have

genetic problems, because . . . the genetic condition they have puts them at extra risk of deterioration." *Id.* The Special Master even acknowledged that the government's expert "allow[ed] that a wild virus infection could constitute an environmental factor that might interact with the sequelae primarily stemming from a genetic variant, due to a reduced tolerance to infection." J.A. 26. Given this record, in which both parties' experts agree that vaccinations can adversely interact with a DYNC1H1 gene mutation, the Special Master's rejection of Petitioner's medical theory was arbitrary and capricious and must be set aside. *See Paluck*, 786 F.3d at 1380. To hold otherwise would effectively require Petitioner to provide conclusive evidence linking L.M.'s February 10th vaccinations to her seizure disorder, which is not Petitioner's burden to carry. *See Andreu*, 569 F.3d at 1378 (holding that the special master erred in requiring conclusive evidence in the medical literature linking the DPT vaccine to afebrile seizures).

C. *Loving* prong 5

Loving prong 5 requires a petitioner to show "a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation." *Loving*, 86 Fed. Cl. at 144. In other words, Petitioner had to show that the vaccinations "did" cause a worsening of the L.M.'s seizure disorder. *See id.*

Here, the Special Master acknowledged that L.M.'s condition changed for the worse immediately after her February 10th vaccinations. *See* J.A. 56. The Special Master, however, noted that "if L.M.'s seizure activity (like her underlying genetic DYNC mutation) predated vaccination, *it becomes more difficult* to conclude that the February 10th vaccinations worsened it." *Id.* (emphasis added). The Special Master then concluded that Petitioner failed to meet *Loving* prong 5 because, in part, "it is quite likely that L.M.'s seizures in fact began prior to vaccination." *Id.* This reasoning is erroneous and must be set aside. *See Paluck*,

786 F.3d at 1380. A significant aggravation claim, by definition, requires a petitioner to have a pre-existing injury. Here, L.M.'s pre-existing injury was her seizure disorder. *See* J.A. 18, 55. Thus, that L.M. experienced some seizure episodes before receiving her vaccination should have no negative affect on Petitioner's case. In light of this flawed reasoning, the Special Master's finding under *Loving* prong 5 must be set aside.[5]

D. "Factor Unrelated"

Lastly, Petitioner challenges the Special Master's finding under the "factor unrelated" inquiry. As noted earlier, if a petitioner carries her initial burden to prove causation-in-fact, the burden shifts to the government to show by a preponderance of the evidence that a "factor unrelated" to the vaccine was the "sole substantial factor in bringing about the injury." *Hammit ex rel. Hammit v. Sec'y of Health & Human Servs.*, 98 Fed. Cl. 719, 726 (2011), *aff'd sub nom. Stone ex rel. Stone v. Sec'y of Health & Human Servs.*, 676 F.3d 1373 (Fed. Cir. 2012). If the government fails to carry its burden, the petitioner is entitled to compensation. *See* 42 U.S.C. § 300aa–13(a)(1)(A)–(B).

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[5] In certain cases, a petitioner can establish a logical sequence of cause and effect between a vaccination and the injury (*Loving* prong 5) with a medical opinion to that effect where the petitioner has proved that the vaccination can cause the injury (*Loving* prong 4) and that the vaccination and injury have a close temporal proximity (*Loving* prong 6). *See Moriarty ex rel. Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1333 (Fed. Cir. 2016). While we believe that this is such a case, we hesitate to determine that in the first instance. Thus, on remand, the Special Master should consider whether Petitioner's showing under *Loving* prongs 4 and 6 satisfies *Loving* prong 5.

Here, the Special Master found that L.M.'s DYNC1H1 gene mutation was the sole, substantial factor in causing L.M.'s seizure disorder. The record does not support this finding.

L.M.'s mutation is located in the stem region of the DYNC1H1 gene. The record shows that mutations in this region of the gene generally result in non-severe, non-cognitive disorders, such as spinal muscular atrophy with lower extremity predominance (a disorder that causes weak and poorly coordinated legs). J.A. 8, 24, 53, 373–75, 412–13, 187–88, 193, 216–17, 221–50. The record also shows that it was generally the exception for a stem region mutation to lead to a severe, cognitive disorder, such as L.M.'s seizure disorder. J.A. 8, 19–20, 24, 51–53, 373–75, 412–13, 216–17. The government's expert even testified that a stem mutation in the DYNC1H1 gene resulting in a "severe" outcome is the "exception." J.A. 397: 13–16. Rather, the evidence in the record indicates that severe cognitive disorders were generally associated with mutations in the *motor* region of the DYNC1H1 gene, a separate region from the stem region. J.A. 8, 19, 24–25, 53–54, 373–77, 396–97, 410–13, 192–93, 216–18. The Special Master acknowledged that the severity of a disorder varies between stem region and motor region mutations. J.A. 54 (noting that the "location of the mutation affects phenotype").

Thus, against this backdrop, there is no substantial evidence to support the conclusion that L.M.'s stem mutation was *more likely than not* the *sole, substantial* factor causing her severe seizure disorder. The science in the record uniformly supports the opposite—a stem mutation in the DYNC1H1 gene is generally more likely than not going to lead to a non-severe, non-cognitive disorder. Thus, the Special Master's "factor unrelated" finding must be set aside as arbitrary and capricious. *Paluck*, 786 F.3d at 1380.

To uphold the Special Master's finding would effectively allow the government to prevail under the "factor unrelated" inquiry with mere proof of a gene mutation. As a result, children with gene mutations will be shut out from the Vaccine Injury Program. Congress did not intend such a result. Congress envisioned that children with pre-existing conditions, such as gene mutations, could potentially recover. In particular, Congress allowed for significant aggravation theories based on pre-existing conditions:

> in order not to exclude serious cases of illness because of possible minor events in the person's past medical history. This provision does not include compensation for conditions which might legitimately be described as pre-existing (e.g., a child with monthly seizures who, after vaccination, has seizures every three and a half weeks), but is meant to encompass serious deterioration (e.g.[,] *a child with monthly seizures who, after vaccination, has seizures on a daily basis*).

H.R. Rep. 908, 99th Cong., 2d Sess. Pt. 1 (1986), *reprinted in* USCCAN 6344, 6356–57 (emphasis added).

In sum, this off-table claim presents the difficult but important task of determining whether a child's receipt of vaccinations significantly aggravated her seizure disorder in the face of an underlying genetic mutation. Our case law is clear that given the complexity of a significant aggravation claim, a petitioner should not be required to disprove that a pre-existing genetic mutation caused her significant aggravation. Because the Special Master placed this extra burden on Petitioner and because the Special Master made factual findings unsupported by the record, we vacate the Special Master's denial of Petitioner's off-table claim and remand this claim for further proceedings.

CONCLUSION

We have considered the parties' remaining arguments but find them unpersuasive. For the above reasons, we affirm the Special Master's denial of Petitioner's on-table claim and vacate and remand the Special Master's denial of Petitioner's off-table claim for further proceedings.

AFFIRMED IN PART, VACATED AND REMANDED IN PART

COSTS

Costs to the Petitioner.