In the United States Court of Federal Claims

No. 06-868V
Filed: March 21, 2013

CLAIRE BARNETTE, a minor, by her mother, KAREN BARNETTE, and her father, TIMOTHY BARNETTE, Petitioners, v. SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES, Respondent.	Vaccine Act: The special master's conclusion that a vaccination was not a substantial factor in bringing about harm was not arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law where the special master employed the correct legal standard, carefully considered the relevant evidence, and ultimately relied on the testimony of experts judged by the special master to be qualified and credible.

Michael G. McLaren, Black McLaren Jones Ryland & Griffee, P.C., Memphis, TN, counsel for petitioners.

Ann D. Martin, with whom were Principal Deputy Assistant Attorney General Stuart F. Delery, Director Rupa Bhattacharyya, Deputy Director Vincent J. Matanoski, and Assistant Director Gabrielle M. Fielding, U.S. Department of Justice, Civil Division, Torts Branch, Washington, DC, counsel for respondent.

OPINION

WIESE, Senior Judge.

This case arises under the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-1 to -34 (2006) ("the Vaccine Act"). Petitioners, Karen and Timothy Barnette, seek review of the special master's September 26, 2012, decision denying compensation for injuries to their daughter, Claire, following her receipt of a vaccination that allegedly hastened the onset of her Dravet Syndrome.[1] In

[1] Dravet Syndrome, also known as Severe Myoclonic Epilepsy of Infancy ("SMEI"), is a severe neurologic condition characterized by the onset of seizures in (continued...)

particular, petitioners maintain that the special master's conclusion that the vaccination was not a substantial factor in bringing Claire harm was arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. Petitioners ask the court to reverse the special master's decision and remand the case for an award of compensation, reasonable attorney's fees, and other costs.

The court heard oral argument on March 7, 2013. After careful consideration of the briefs and of the exceptional presentations made by counsel, the court finds in favor of respondent. For the reasons set forth below, petitioners' motion for review is denied.

BACKGROUND

I.

Claire Barnette was born on March 18, 2005. For the first six months of her life, Claire developed normally and suffered from no serious illnesses. On September 19, 2005, at the age of six months, Claire received a series of vaccinations, including the Pediarix (DTaP/IPV/Hep B), Hib, and Prevnar vaccines.[2] That night, Claire experienced her first seizure, becoming nonresponsive to her mother's voice for approximately a two-minute period while her left arm jerked rhythmically and her head turned to the right. Paramedics responding to her parents' 911 call examined Claire and pronounced her "okay."

Claire's pediatrician examined her the following day and found her to be alert, active, oriented, and in no distress. The pediatrician noted, however, that Claire had experienced an "apparent seizure post-vaccinations" and recommended that her parents consult a neurologist and schedule Claire for an electroencephalogram ("EEG").

Approximately two weeks later, on October 4, 2005, Claire experienced a second seizure, again characterized by the rhythmic jerking of her left arm, with her

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[1](...continued)
children around six months of age. Initial seizures are usually prolonged convulsions, often triggered by fever. The intellectual development in patients with Dravet Syndrome begins to plateau or regress in the second year of life, resulting in intellectual disability.

[2] The record indicates that Claire had also received the Pediarix, Hib, and Prevnar vaccinations on two earlier occasions—May 23, 2005, and July 19, 2005—with no recorded adverse consequences.

head turned, nonresponsive, to the right. At the time, Claire had a mild illness with a cough and a runny nose. Following the seizure, Claire was taken to North Oak Regional Medical Center, where her temperature was recorded at 97.9 degrees. Claire was diagnosed with a seizure disorder and transferred to the emergency department at Le Bonheur Children's Hospital, where she was admitted the same day. Healthcare providers at Le Bonheur diagnosed a "focal seizure" and recommended that Claire's parents schedule her for a magnetic resonance imaging ("MRI"), an EEG, and a follow-up appointment with a neurologist. They additionally prescribed the drug Trileptal to treat Claire's condition.

On October 12, 2005, Claire was examined by Dr. Dave F. Clarke, a neurologist at Le Bonheur. Dr. Clarke indicated that Claire presented with a complaint of "[t]wo partial seizures, the last of which occurred approximately 1 week ago." Dr. Clarke noted that Claire's first seizure was "immediately after her 6-month vaccinations, however she had both her 2- and 4-month shots prior without any noted seizures." Dr. Clarke further observed that although Claire had no family history of seizures and the results of a prior computed tomography ("CT") scan were normal, an EEG "revealed scattered C4, F4 sharp and spike wave discharges." Dr. Clarke ordered an MRI with a follow-up visit within a one- to two-month period.

On the morning of October 16, 2005, Claire experienced a third seizure. As with her second seizure, Claire was again suffering from a mild illness, characterized by a fever, cough, and runny nose. A brain MRI conducted on October 19, 2005, was normal, with the exception of inflammatory changes attributed to sinus disease. A subsequent MRI, conducted on March 13, 2006, was also found to be a "[n]ormal study with interval resolution of sinus disease seen on previous exam."

Claire continued to experience seizures for the next few years and was followed by Dr. Clarke for what emerged as an intractable, multifocal epilepsy, which proved resistant to multiple medication therapies. On June 24, 2008, at the age of three years and three months, Claire required the placement of a vagus nerve stimulator for refractory epilepsy. Hospital records indicated that "[d]evelopmentally [Claire] is in speech therapy. She does walk but is developmentally delayed."

That same month, June 2008, Claire's parents submitted a sample of her blood to the Athena Diagnostics laboratory for an SCN1A DNA Sequencing Test.[3]

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[3] SCN1A DNA Sequencing is a test administered to detect any mutations in the SCN1A gene, the gene most clinically relevant to epilepsy. SCN1A refers to a gene identified as the "sodium channel, voltage-gated, type I, alpha subunit." SCN1A, Genetics Home Reference, http://ghr.nlm.nih.gov/gene/SCN1. The gene, which belongs to a family of genes called SCN (sodium channels), "provides (continued...)

The test results indicated that Claire possesses a gene mutation, referred to as a DNA sequence variant, the significance of which was not then known. Subsequent testing of Claire's parents revealed that Claire's mutation had arisen de novo (i.e., was not inherited), as neither parent shared the mutation.

A little more than two years later, in July 2010, Athena Diagnostics produced a revised report, indicating that Claire's genetic mutation, previously of unknown significance, was "re-classified as a known disease-associated mutation." The report advised that since Claire's mutation arose de novo, it "further increases the probability that this known disease-associated mutation could be causative of a severe phenotype."[4] Ultimately Athena Diagnostics reported that Claire's "test result is consistent with a diagnosis of, or a predisposition to developing, the severe phenotypes associated with SCN1A mutations, SMEI [Severe Myoclonic Epilepsy of Infancy] or SMEB [borderline SMEI]."

Notwithstanding her seizure disorder, Claire's neurologic development was normal through the first year of her life, a result typical in the progression of Dravet Syndrome. Claire's vocalization and fine motor skills were slightly behind at thirteen months of age, however, and by the age of three, she was exhibiting developmental delays and was in speech therapy. Claire's more recent medical records reflect that she continues to suffer "[i]ntractable, symptomatic partial seizures with secondary generalization of independent hemisphere origin and atypical absence seizure[s] both under good control (secondary to SCN1A gene defect)."

II.

Petitioners filed suit under the Vaccine Act on Claire's behalf on December 21, 2006. In making their case, petitioners acknowledged that Claire was born with an SCN1A gene mutation that predisposed her to developing seizures and cognitive problems. They maintained, however, that Claire's September 19, 2005, vaccination acted as an environmental trigger that caused her seizures to occur earlier and the outcome of her condition to be worse than it otherwise would have been.

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[3](...continued)
instructions for making one part (the alpha subunit) of a sodium channel called NaV 1.1. These channels are found in the brain and muscles where they control the flow of sodium into cells. In the brain, NaV 1.1 channels are involved in transmitting signals from one nerve cell (neuron) to another." Id.

[4] As explained in the hearing before the special master, a phenotype is the clinical expression of a genetic disorder, in this case Dravet Syndrome. Transcript of Hearing at 23 (Kendall), 305 (Raymond) (Jan. 19–20, 2012).

Petitioners thus argued that Claire's vaccination, by effecting an earlier onset of her Dravet Syndrome, caused her harm compensable under the Vaccine Act.[5]

The special master conducted a hearing on January 19 and 20, 2012, to evaluate petitioners' claim. In support of their theory, petitioners presented the expert testimony of Frances D. Kendall, M.D., a clinical geneticist, who testified that it was possible that an individual with Claire's same genetic mutation could have a different—and less deleterious—clinical outcome than Claire. Petitioners additionally presented the expert testimony of James W. Wheless, M.D., Claire's treating pediatric neurologist, who in turn testified that Claire's vaccination hastened the onset of her Dravet Syndrome by two to three months and that an earlier onset resulted in a more severe cognitive outcome of Claire's condition. In response, respondent presented the testimony of Gerald V. Raymond, M.D., a pediatric neurologist and clinical neurogeneticist, and Max Wiznitzer, M.D., a pediatric neurologist.

The special master rejected petitioners' claim. In a decision dated September 26, 2012, the special master determined that petitioners had "failed to establish by a preponderance of the evidence that Claire's vaccination caused or significantly aggravated her condition." Barnette ex rel. Barnette v. Sec'y of Dep't of Health & Human Servs., No. 06-868V, 2012 WL 5285414, at *1 (Fed. Cl. Sept. 26, 2012). Although the special master found that "Claire's initial seizure most likely occurred earlier than it would have absent the vaccination," he went on to conclude that the seizure had not occurred "significantly earlier . . . in light of the fact that Claire's September 19, 2005, seizure occurred at six months and this is the time frame the literature indicates infants with SCN1A mutations will begin exhibiting symptoms." Id. at *13. Further, the special master found that the timing of the onset of Claire's condition was "unimportant" because the overwhelming evidence demonstrated that Claire's SCN1A mutation was "the sole cause of her disease" and that "her vaccinations did not result in any worsening of that disease process." Id. at *13, *20. The special master thus concluded that petitioners had failed to meet their burden of proof under the Vaccine Act and accordingly denied petitioners' request for compensation. Id. at *20. On October 25, 2012, petitioners filed their motion for review of that decision in this court.

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[5] The Vaccine Act permits petitioners to seek compensation for preexisting injuries that are "significantly aggravated" by a vaccine. 42 U.S.C. § 300aa-11(c)(1)(C). The 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).

DISCUSSION

Section 300aa-12(e)(2)(B) of the Vaccine Act authorizes this court to review the decision of a special master and to "set aside any findings of fact or conclusion of law . . . found to be arbitrary, capricious, an abuse of discretion, or not otherwise in accordance with law." In conducting such a review, the court will examine a special master's findings of fact under an "arbitrary and capricious" standard and will examine the special master's legal conclusions de novo. Saunders v.Sec'y of Dep't of Health & Human Servs., 25 F.3d 1031, 1033 (Fed. Cir. 1994); Munn v. Sec'y of Dep't of Health & Human Servs., 970 F.2d 863, 870 n.10 (Fed. Cir. 1992). So long as the special master "has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate." Hines ex rel. Sevier v. Sec'y of Dep't of Health & Human Servs., 940 F.2d 1518, 1528 (Fed. Cir. 1991).

Petitioners challenge the special master's decision on three grounds. They argue first that the special master erred as a matter of law when he concluded that Claire's vaccination was not a substantial factor in significantly aggravating her condition. Second, petitioners maintain that the special master's determination that the onset of Claire's condition was not significantly earlier than it would have been absent her vaccination was arbitrary and capricious. Finally, petitioners contend that the special master erred when he concluded that petitioners had failed to make a case for the worsening of Claire's condition due to vaccination—an error, petitioners claim, that resulted both from the special master's disregard of evidence indicating that Claire's particular mutation could lead to a range of possible clinical outcomes and from the special master's incorrect emphasis on the medical literature, thereby subjecting petitioners' evidence to an unduly high standard of proof. We address these issues in turn below.

I.

In support of their first point—that the special master erred as a matter of law in concluding that Claire's vaccination was not a substantial factor in significantly aggravating her condition—petitioners refer the court to various principles of tort law set forth in the Restatement of Torts.[6] These tort-law principles, petitioners

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[6] Among the provisions on which petitioners rely for the proposition that Claire's vaccination was a substantial factor in significantly aggravating her condition are Sections 431, 458, and 461 of the Second Restatement of Torts and Sections 26 and 31 of the Third Restatement of Torts. See Restatement (Second) of Torts § 431(a) (1965) (providing that an actor's negligent conduct is a legal cause of (continued...)

maintain, stand for the proposition that where the evidence shows that a vaccination more probably than not hastened the onset of a disease, a petitioner is entitled to compensation as a matter of law. Based on this principle, petitioners argue that the special master, in determining that Claire's vaccination caused an earlier onset of her Dravet Syndrome, necessarily should have concluded that the vaccination caused Claire compensable harm.

Despite petitioners' charge, we see no indication that the special master employed an incorrect legal standard or disregarded relevant legal authority in reaching his decision. As the special master observed, petitioners' claim asserts a significant aggravation of an off-Table injury pursuant to Section 11(c)(1)(C) of the Vaccine Act.[7] Although the Court of Appeals for the Federal Circuit has not

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[6](...continued)
harm to another if his conduct is a "substantial factor" in bringing about the harm); Restatement (Second) of Torts § 458 (1965) (providing that "[i]f the negligent actor is liable for another's injury which so lowers the other's vitality as to render him peculiarly susceptible to disease, the actor is also liable for the disease which is contracted because of the lowered vitality."); Restatement (Second) of Torts § 461 (1965) (providing that "[t]he negligent actor is subject to liability for harm to another although a physical condition of the other which is neither known nor should be known to the actor makes the injury greater than that which the actor as a reasonable man should have foreseen as a probable result of his conduct."); Restatement (Third) of Torts § 26 cmt. b (providing that "[a]n act can also be a factual cause in accelerating an outcome that otherwise would have occurred at a later time."); Restatement (Third) of Torts § 31 (providing that "[w]hen an actor's tortious conduct causes harm to a person that, because of a preexisting physical or mental condition or other characteristics of the person, is of a greater magnitude or different type than might reasonably be expected, the actor is nevertheless subject to liability for all such harm to the person.").

[7] Pursuant to the Vaccine Act, the Secretary of Health and Human Services is directed to maintain a Vaccine Injury Table ("Table") that identifies particular vaccines, the symptoms or injuries associated with those vaccines, and the time frame within which such symptoms or injuries are expected to occur. 42 U.S.C. § 300aa–14(c); see also 42 C.F.R. § 100.3. If an individual, after the receipt of a listed vaccine, experiences an identified symptom or injury within the specified time frame (i.e., a "Table injury"), causation is presumed. de Bazan v. Sec'y of Dep't of Health & Human Servs., 539 F.3d 1347, 1351 (Fed. Cir. 2008). If an individual instead experiences a symptom or injury that is not listed on the Table, however, or experiences an indicated injury outside the specified time frame (i.e., an "off-Table injury"), causation is not presumed and a petitioner must establish
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addressed the proper standard for demonstrating significant aggravation in an off-Table injury claim, the Federal Circuit has discussed significant aggravation in the context of a Table claim. See Whitecotton v. Sec'y of Dep't of Health & Human Servs., 81 F.3d 1099 (Fed. Cir. 1996).[8] In addition, this court has suggested a framework for considering significant aggravation claims in off-Table cases by combining the test for off-Table injuries set forth in Althen v. Sec'y of Dep't of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005),[9] with the first three factors in the test for significant aggravation of Table injuries set forth in Whitecotten, thus requiring proof of the following six elements:

> (1) the person's condition prior to administration of the vaccine, (2)

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[7](...continued)
causation in fact by a preponderance of the evidence. Loving ex rel. Loving v. Sec'y of Dep't of Health & Human Servs., 86 Fed. Cl. 135, 141 (2009) (citing Althen v. Sec'y of Dep't of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005)).

[8] In Whitecotton, the Federal Circuit set forth a four-part test to govern significant aggravation claims involving Table injuries. The Whitecotton test directs that a special master must:

> (1) assess the person's condition prior to administration of the vaccine, (2) assess the person's current condition, and (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. If the special master concludes that the person has suffered a significant aggravation, the special master must then . . . (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.

[9] Althen, the seminal case addressing the standard of proof in off-Table injury claims, indicates that a petitioner, in making a prima facie case for an off-Table injury, must "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." Althen, 418 F.3d at 1278. The Federal Circuit has held that the "preponderance of the evidence" standard in the Vaccine Act means causation that is "more probable than not." Id. at 1279 (quoting Hellebrand v.Sec'y of Dep't of Health & Human Servs., 999 F.2d 1565, 1572–73 (Fed. Cir. 1993)).

> 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 ex rel. Loving v. Sec'y of Dep't of Health & Human Servs., 86 Fed. Cl. 135, 144 (Fed. Cl. 2009).

As the special master recognized in his decision, off-Table vaccine cases are to be considered "consistently with principles set forth in the Second Restatement of Torts." Barnette, 2012 WL 5285414, at *7 (quoting Stone v. Sec'y of Dep't of Health & Human Servs., 676 F.3d 1373, 1379, reh'g denied, 690 F.3d 1380 (Fed. Cir. 2012)). Indeed, as the special master further noted, many of the Restatement provisions on which petitioners rely are already incorporated into binding case law. See, e.g., Shyface v. Sec'y of Dep't of Health & Human Servs., 165 F.3d 1344, 1352–53 (Fed. Cir. 1999). The Federal Circuit has in fact held that the causation in fact standard employed in off-Table cases "is the same as 'legal cause' in the general torts context." de Bazan v. Sec'y of Dep't of Health & Human Servs., 539 F.3d 1347, 1351 (Fed. Cir. 2008) (quoting Shyface, 165 F.3d at 1352). In particular, a petitioner asserting an off-Table claim is required to show that the vaccine was "a substantial factor in bringing about the harm." de Bazan, 539 F.3d at 1351 (quoting Restatement (Second) of Torts § 431(a)).

Although the special master went on to describe this legal framework as not being "critical,"[10] we read his decision as correctly applying the factors identified in

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[10] With respect to this legal framework, the special master concluded as follows:

> Given the concessions made in this claim by petitioners regarding the SCN1A mutation, as well as the narrow issued presented, the legal environment is not critical. That is that given that petitioners agree that an SCN1A mutation causes SMEI, Claire's injury, and the undersigned's finding that petitioners failed to demonstrate that an arguably earlier onset of Claire's seizures affected the outcome of her condition caused by her gene mutation, it remains a given that the gene mutation was the sole cause of Claire's condition.

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Loving for assessing significant aggravation of off-Table injuries. In particular, the special master concluded that "[t]here was simply no reliable evidence presented that Claire's September 19, 2005 vaccination caused her inevitable disease process to result in a worse outcome." Barnette at *5. The special master found, in other words, that petitioners had not met their burden under Loving of demonstrating that Claire's current condition constitutes a "significant aggravation" of her condition prior to vaccination. We thus conclude that the special master adequately accounted for all applicable law addressing the "substantial factor" element in his analysis and conclusions.

Nor can we accept petitioners' contention that the Restatement provisions on which they rely stand for the proposition that a petitioner is entitled to compensation as a matter of law where the evidence shows that a vaccination more probably than not hastened the onset of a disease. What is missing from their argument is any showing that the earlier onset of Claire's Dravet Syndrome aggravated her condition or altered its natural course. An earlier onset, by itself, does not demonstrate harm; rather, as indicated above, the standard for compensation is whether a preexisting condition was significantly aggravated by the vaccination, defined 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).[11] On this point, the special master found that petitioners' had not made their case.

In particular, the special master concluded that petitioners' contention that there is a broad spectrum of outcomes that can result from Claire's gene mutation was not supported by the evidence. Id. at *14. The special master accordingly rejected petitioners' assertion that the age of onset affects the outcome for patients with Dravet Syndrome, finding instead that "variability in outcome is affected by the

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[10](...continued)
Barnette at *7.

[11] Petitioners took the position at oral argument that an earlier onset of seizures itself constitutes harm compensable under the Vaccine Act, even if the timing of the seizures has no impact on the ultimate severity of Claire's condition. Section 11(c)(1)(D), however, sets forth additional requirements for establishing compensable harm under the Vaccine Act, including that a petitioner must demonstrate that he or she "suffered the residual effects or complications of such illness, disability, injury, or condition for more than 6 months after the administration of the vaccine." Thus, an earlier onset of seizures without more (i.e., with no worsening of Claire's ultimate condition) would not satisfy the requirement that Claire have suffered the residual effects of the injury for more than six months after the administration of the vaccine.

location and type of mutation." Id. The special master thus concluded that "the evidence convincingly demonstrates that someone with Claire's specific mutation is more likely than not going to manifest at the severe end of the spectrum of Dravet." Id. at *15.

The special master's conclusion finds ample support in the record. As the special master observed, Claire's medical records from Athena Diagnostics indicated that Claire's specific genetic mutation is a "disease-associated mutation," and that her DNA sequence variant "has been reported in the literature to be associated with SMEI or SMEB, the severe phenotypes associated with SCN1A mutations." Id. at *9. The special master additionally noted that experts from each side—Dr. Kendall for petitioners and Dr. Raymond for respondent—indicated that they knew of several individuals with Claire's exact genetic mutation who had the same medical condition, Dravet Syndrome. Id. at *14. Based on these observations, the special master concluded that "Claire's mutation is one that has been reported, studied, followed, and is known to have a severe outcome, Dravet Syndrome." Id.

The special master went on to identify various factors that, in his estimation, additionally demonstrate that Claire's specific mutation is likely to be disease causing. In particular, the special master observed that Claire's mutation is located in a highly conserved region of a splice site, indicating that the mutation is going to have a significant, deleterious effect on the formation of the protein and a poor outcome for the patient. Id. (quoting Transcript of Hearing at 64–65 (Kendall), 317, 321 (Raymond) (Jan. 19–20, 2012)).[12] In addition, the special master noted that Claire's mutation had arisen de novo (i.e., was not present in her parents), a pattern of inheritance that, in the words of the Athena Diagnostics lab, "is observed in most SMEI or SMEB patients, and further increases the probability that this known disease associated mutation could be causative of a severe phenotype." Barnette at *14. Further, the special master observed that "Claire's clinical history, as agreed by the parties' experts, is consistent with the typical picture of Dravet, which the experts

[12] As the special master explained in his decision, "DNA provides the blueprint for cellular structure and function" and determines how a protein is made. Id. at *7. A change or mutation in the DNA can affect the functionality of the protein and consequently cause disease. Id. (citing Tr. at 276–300 (Raymond)); see also Tr. at 24 (Kendall) (describing a gene mutation as an "alteration in the genetic blueprint that's considered deleterious or damaging to that gene in its subsequent functioning"). The special master added that "[t]he gene at issue in Claire's case, the SCN1A gene, encodes for a sodium channel in the brain, which is 'a portion of a channel that allows the transport of sodium molecules across cell membranes in the neurons.'" Id. at *8. A mutation in Claire's SCN1A gene results in an alteration in the protein that is part of this sodium channel and "ultimately results in cortical network problems and epileptic encephalopathy." Tr. at 62 (Kendall).

agree is caused by a mutation in the SCN1A gene." Id. at *15.

Nor, in the special master's view, did the medical literature support petitioners' assertion that the age of onset affects the outcome for patients with Dravet Syndrome. Id. at *15–19. In particular, the special master noted that the McIntosh study,[13] an article upon which both parties rely, specifically examined whether or not "vaccination affected the . . . outcome" of patients with Dravet Syndrome by analyzing "whether patients who had onset of Dravet syndrome shortly after vaccination had any specific clinical, molecular, or outcome differences that could suggest the disorder in these patients represents a separate entity." Pet. Ex. 92 at 1, 2.[14] On this point, the McIntosh authors found as follows:

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[13] In the McIntosh study, Ann M. McIntosh, et al., *Effects of Vaccination on Onset and Outcome of Dravet Syndrome: A Retrospective Study*, 9 Lancet Neurol. 592–98 (2010), researchers addressed the question of whether an association exists between vaccination and the onset of seizures in patients with Dravet Syndrome. In conducting the study, the McIntosh authors retrospectively analyzed the medical and vaccination records of 40 patients with Dravet Syndrome, dividing the subjects into a vaccination-proximate group (defined as patients who had had a seizure the day of or the day after vaccination) and a vaccination-distant group (defined as patients who had had a seizure before vaccination or two or more days after vaccination). The authors found that the mean age at seizure onset in the vaccination-proximate group was 18.4 weeks, but that the mean age at seizure onset in the vaccination-distant group was 26.2 weeks, a difference that was found to be statistically significant. The vaccination-proximate group, in other words, experienced disease onset a mean of 7.8 weeks sooner than the vaccination-distant group, causing the study's authors to conclude that "[v]accination might trigger earlier onset of Dravet syndrome in children who, because of an SCN1A mutation, are destined to develop the disease." Pet. Ex. 92 at 1.

[14] The McIntosh authors described their approach to this inquiry as follows:

> We analysed the clinical characteristics and distribution of molecular lesions in the two groups to establish whether the vaccination-proximate group had a different outcome or other distinguishing clinical or molecular features compared with the vaccination-distant group. Intellectual outcome was classified, according to a detailed assessment of developmental milestones and present functioning of each patient, as normal intellect (documented normal educational achievement), mild intellectual disability (definite mild intellectual impairment), moderate intellectual disability (limited speech and cognition but able to do some aspects of daily living), or

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> [A]lthough vaccination might sometimes seem to trigger the onset of Dravet syndrome, there is no evidence that patients in the vaccination-proximate group had a different disorder from those in the vaccination-distant group. In particular, the similarity in clinical and outcome measures between patients in the vaccination-proximate group and those in the vaccination-distant group is not consistent with vaccination itself affecting the severity of the disorder . . . .
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> * * * * *
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> Outcome was not influenced by vaccination after clinical onset . . . and thus vaccination does not seem to cause brain damage.

Pet. Ex. 92 at 5–6.

Focusing on this conclusion, the special master observed that "[i]t is important to note" that McIntosh found "no evidence that vaccinations before or after disease onset affect [the patients'] outcome." Barnette at *11 (quoting Pet. Ex. 92 at 1). The special master accordingly found that the "McIntosh study directly addresses the petitioners' theory in this case and the McIntosh study findings squarely reject it." Barnette at *16.

The special master went on to consider several other studies cited by respondent in support of the proposition that the age of onset does not affect the outcome for Dravet Syndrome patients with an SCN1A mutation. In a 2011 retrospective study referred to as the Ragona article,[15] for instance, the authors

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[14](...continued)
> severe intellectual disability (limited or no speech and dependent for activities of daily living—i.e., going to the toilet and dressing). Classification was done by assessors masked to mutation type or relation to vaccination. For binary analyses, we grouped together children with normal intellect and mild intellectual disability and compared them with those with moderate or severe intellectual disability. Intellectual regression was defined as prolonged (4 weeks or more) or permanent loss of skills and was coded as present or absent.

Pet. Ex. 92 at 2.

[15] Francesca Ragona, et al., *Cognitive Development in Dravet Syndrome: A* (continued...)

(including Charlotte Dravet, the neurologist who discovered the disorder) examined "the role of epilepsy and genetic background in determining the cognitive outcome of patients with Dravet syndrome" and sought to "clarify the respective contribution of epilepsy and of the underlying genetic abnormality in determining cognitive outcome." Resp. Ex. QQ at 1, 2. Significant to the special master, the Ragona authors concluded that "[t]he variability of outcome, and the appearance of neurologic deficits hardly ascribable to epileptic activity . . . suggest that the channelopathy [i.e., gene mutation] itself is probably crucial in determining the phenotype." Id. at 6. Further, as the special master observed, the authors of the Ragona study, like the authors of the McIntosh study, found that "[s]tatistical analysis failed to detect any significant correlation between the severity of cognitive impairment and . . . age of seizure onset." Barnette at *18 (quoting Resp. Ex. QQ at 5). The special master also pointed to the Ceulemans article,[16] a study examining four children with Dravet Syndrome, for the proposition that there "is a strong argument favouring the genetic disorder itself as probably being the most important factor for developmental problems in these patients." Barnette at *18 (quoting Resp. Ex. U at 4).

Petitioners challenge various aspects of the evidence cited by the special master, including the special master's interpretation of several of the key articles discussed at length during the proceedings. In particular, petitioners maintain that contrary to the special master's findings, neither the McIntosh study nor the Ragona article excludes the possibility that an earlier onset of seizures in a patient with Dravet Syndrome causes a worse cognitive outcome. As explained by Dr. Wheless, the McIntosh and Ragona studies were not powered with a statistically significant number of infants to conclude that there is no correlation between the age of onset and outcome in people with Dravet Syndrome—a point, petitioners maintain, wholly ignored by the special master. See Tr. at 548–56 (Wheless).[17] Further, petitioners

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[15](...continued)
Retrospective, Multicenter Study of 26 Patients, 52(2) Epilepsia 386–92 (2011).

[16] Berten Ceulemans, *Overall Management of Patients With Dravet Syndrome*, 53 (Suppl. 2) Dev. Med. Child Neurol. 19–23 (2011).

[17] Dr. Wheless explained that something is considered statistically significant in medicine if it has a P value of .05 or lower (indicating that if the study is repeated, 95 times out of 100 the results will be the same). According to Dr. Wheless, the P values identified in Table 1 of the McIntosh study demonstrate that the relationship between vaccination and age of seizure onset was statistically significant (a P value of .004), but that the relationships between vaccination and both intellectual regression and intellectual disability were not statistically significant (P values of .5 (continued...)

note that the McIntosh authors themselves acknowledged the need for further study as follows:

> Our study design and absence of a control group of patients with Dravet syndrome who did not have DTP vaccinations precluded us from examining a gene-environment interaction. However, our observation of an environmental effect (vaccination) temporally shifting the age at onset of an age-specific genetic neurological disease with no apparent effect on outcome suggests that Dravet syndrome would be an ideal model, both clinically and in experimental animals, with which to formally assess and examine the basis of such an interaction.

Pet. Ex. 92 at 6. Similarly, petitioners note that the Ragona authors conceded that "[i]t is conceivable that the genetic determinants (type of mutations, and modulating and epigenetic factors) may underlie different epilepsy and mental phenotypes, and that epilepsy is just one of the variables that concur in determining the overall outcome." Resp. Ex. QQ at 6.

In reviewing the disputed literature, we, like petitioners, have some difficulty reconciling the data (as for instance the P values) with some of the statements set forth therein. We note, however, that the special master reached his conclusions about the McIntosh and Ragona articles with the aid of testimony from experts reasonably judged by the special master to be both qualified and credible. We cannot therefore conclude that the special master, in choosing the interpretation of one qualified expert over another, committed reversible error.

Nor do we think, as petitioners suggest, that respondent's experts based their ultimate conclusion that the age of onset does not affect the severity of the condition exclusively—or even primarily—on the disputed articles. Both Dr. Raymond and Dr. Wiznitzer offered multiple reasons for their conclusion that age of onset does not affect outcome, including the unrebutted testimony that the location of Claire's mutation at a "highly conserved region of a splice site" indicates that the mutation will have a significant, deleterious effect on the patient's outcome. Tr. at 317, 321 (Raymond). We thus believe that even if the disputed literature were removed from the case and from the special master's decision, his conclusion would nevertheless

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[17](...continued)
and .7). See Pet. Ex. 92 at 4; Tr. at 552–53, 555 (Wheless). Similarly, Dr. Wheless noted that the Ragona study, in making the claim that "[s]tatistical analysis failed to detect any significant correlation between severity of cognitive impairment and . . . age at seizure onset," Resp. Ex. QQ at 5, did not provide a P value to indicate the statistical significance of their finding.

stand, still fully supported by the remaining evidence.

In light, then, of the special master's thorough and well-reasoned analysis of the medical records, the expert testimony, and the medical literature, we find that the special master "considered the relevant evidence of record, dr[ew] plausible inferences and articulated a rational basis for the decision." Hines, 940 F.2d at 1528. We accordingly conclude that the special master's determination that there was "no reliable evidence that Claire's vaccinations caused a more severe outcome of her Dravet Syndrome or significantly aggravated her condition in any way" should not be disturbed. Barnette at *19.

II.

In their second challenge to the special master's decision, petitioners argue that the special master's finding that the onset of Claire's disease was not significantly earlier than it would have been in the absence of her vaccination is arbitrary and capricious. In support of this view, petitioners rely on the expert testimony of Dr. Wheless, a pediatric neurologist, who testified, based on the findings in the McIntosh study, that Claire experienced the onset of her Dravet Syndrome as much as two to three months earlier than she would have if she had not been vaccinated. Tr. at 151 (Wheless).[18]

Notably, in rejecting Dr. Wheless's assertion, the special master nevertheless agreed with petitioners' other expert, Dr. Kendall, that the onset of Claire's Dravet Syndrome likely occurred earlier than it would have had Claire not received the vaccination. Barnette at *13. The special master further agreed with Dr. Kendall, however, that the question of how much earlier the onset occurred could not be predicted. Id. But given that Claire experienced her first seizure at six months—the average age, in the opinion of all testifying experts, that typically marks the onset of

[18] As Dr. Wheless explained during the hearing, the McIntosh article demonstrates with statistical significance that vaccination "might trigger earlier onset of Dravet syndrome in children who, because of an SCN1A mutation, are destined to develop the disease," and indicates that the mean age at disease onset for children in the vaccination-proximate group (like Claire) is 7.8 weeks earlier than for children in the vaccination-distant group. Pet. Ex. 92 at 1. The difference between the mean age of onset in the two groups was 7.8 weeks with a 95% confidence interval, ranging from 2.6 weeks on the low end through 13.1 weeks on the upper end. Id. From this data, Dr. Wheless theorized that Claire experienced her first seizure up to two to three months (i.e., 7.8 to 13.1 weeks) earlier than she would have in the absence of the vaccination. Tr. at 151 (Wheless).

Dravet Syndrome[19]—the special master concluded that the onset of Claire's condition was not significantly earlier than it otherwise would have been. Id. Further, the special master agreed with Dr. Raymond that Dr. Wheless could not extrapolate from the group population statistics set forth in the McIntosh study to create a concrete fact about Claire's individual case. Id. (citing Tr. at 339 (Raymond) ("you can't take the individual and say that individual seized eight weeks earlier because she's in the vaccine-proximate group")). Finally, the special master observed that Dr. Wheless, in employing the McIntosh data to prove that the vaccination hastened the onset of Claire's condition by two to three months (7.8 to 13.1 weeks), ignored the lower end of the confidence interval (2.6 weeks), while utilizing the upper end of the confidence interval (13.1 weeks). Barnette at *13.

We can find no error with the special master's conclusion. As an initial matter, we do not believe, as petitioners assert, that the special master incorrectly and inconsistently rejected the application of group statistics to Claire for one purpose (to determine how much earlier Claire experienced the onset of her disease as a result of the vaccination), but nevertheless applied group statistics to Claire for another purpose (to confirm that the timing of Claire's onset was consistent with the average age of onset in children with Dravet Syndrome). As respondent points out, analyzing whether the specific facts of Claire's case match up with population statistics is entirely appropriate and far different from using population statistics to create specific facts about Claire's case.[20] Petitioners' own expert, Dr. Kendall, herself declined to employ the McIntosh statistics in this way. See Tr. at 75–76 (Kendall).

More importantly, however, the question of whether Dr. Wheless's two- to

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[19] As Dr. Raymond explained, six months marks the point in an infant's development when a switch occurs from the fetal or embryonic sodium channel Nav. 1.3 to the more mature sodium channel Nav. 1.1. Tr. at 345–47 (Raymond). In cases like Claire's, where a mutation of the SCN1A gene impacts production of the Nav. 1.1 protein, the mutation begins to manifest by seizures, generally starting with temperature-sensitive seizures, at that point in the infant's development when the Nav. 1.3 protein is replaced by the damaged Nav. 1.1 protein. An SCN1A mutation, in other words, does not reveal itself until the transition occurs from the Nav. 1.3 sodium channel to the Nav. 1.1 sodium channel.

[20] Even were we to accept that the group statistics of the McIntosh study can be used to project facts about Claire's individual case, however, we share the special master's concern that Dr. Wheless appears to have ignored the lower end of the confidence interval indicating that onset was accelerated by a mere 2.6 weeks. Notably, that two-week time frame is consistent with the actual seizure Claire experienced—accompanied by the possible trigger of a mild illness—on October 4, 2005.

three-month estimate had a reliable scientific basis has no impact on the outcome of this case because the special master in fact accepted the proposition that Claire's initial seizure most likely occurred earlier than it would have absent the vaccination. Barnette at *13. Ultimately, though, the special master determined that the issue of whether or not Claire's vaccination hastened the onset of her disease was unimportant because "the evidence overwhelmingly demonstrated that Claire's condition was not made worse or aggravated by her vaccinations or September 19, 2005, seizure." Id. Given this analysis, we cannot find the special master's determination that Claire's first seizure did not occur significantly earlier than it would have absent her vaccinations to be either arbitrary or capricious.

III.

In their third and final challenge to the special master's decision, petitioners argue that the special master erred in concluding that they had failed to make a case for the worsening of Claire's condition due to vaccination. In making this assertion, petitioners maintain first that the special master ignored evidence that there exists a range of possible clinical outcomes associated with Dravet Syndrome in general and with respect to Claire's genetic mutation in particular. In addition, petitioners contend that the special master imposed an improperly high evidentiary standard on them by focusing on the medical literature as, for instance, when the special master observed that Dr. Wheless had failed to make a case for the worsening of Claire's condition by reference to the medical literature, id. at *19, or when the special master rejected one of petitioners' arguments on the ground that it was "plainly incorrect and was clearly rejected by McIntosh," id. at *17. In petitioners' view, such statements demonstrate that the special master rejected their theory on the basis of medical literature, thereby ignoring the Federal Circuit's fundamental admonishment that "requiring medical literature . . . contravenes [the Vaccine Act's] allowance of medical opinion as proof." Althen, 418 F.3d at 1280; see also Knudsen ex rel. Knudsen v. Sec'y of Dep't of Health & Human Servs., 35 F.3d 543, 548–49 (Fed. Cir. 1994) (recognizing that a "determination of causation in fact under the Vaccine Act involves ascertaining whether a sequence of cause and effect is 'logical' and legally probable, not medically or scientifically certain").

We read the special master's decision, however, not as disregarding evidence or as applying a heightened standard of proof to petitioners' theory, but as evaluating that theory with a reasoned and thorough analysis of the proof put forward in support of it. Notably, petitioners offered no clinical evidence that the earlier onset of Claire's Dravet Syndrome in any way altered the course of her condition or resulted

in a worse disease outcome for Claire.[21] In the absence of such clinical evidence, petitioners made the case that there is a broad spectrum of outcomes that can result from Claire's gene mutation and that studies have shown that earlier seizures have worse outcomes. Given these two assertions, petitioners contend that they have satisfied their burden of showing that it was "logical" or "legally probable" that vaccination worsened Claire's condition.

The special master carefully considered but ultimately rejected both aspects of petitioners' argument. With respect to the range of possible outcomes associated with SCN1A gene mutations,[22] the special master acknowledged that "[i]t is uncontested that SCN1A mutations have variability in outcome," including Dravet Syndrome, certain other epilepsy syndromes, and familial hemiplegic migraine. Barnette at *14 (quoting Tr. at 304 (Raymond)). Despite recognizing that "variability is demonstrated in SCN1A mutations in general," however, the special master concluded that "the evidence convincingly demonstrates that someone with Claire's specific mutation is more likely than not going to manifest at the severe end of the

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[21] In fact, during the hearing before the special master, petitioners' expert, Dr. Kendall, testified as follows:

> THE COURT: If you pull the vaccine out of this case, do you see anything in Claire's history that strikes you as unexpected with regard to the progression of onset and through the progression of Dravet?
>
> WITNESS: Nothing specific that comes to mind.

Tr. at 90–91 (Kendall). Similarly, petitioners' other expert, Dr. Wheless, testified as follows:

> RESPONDENT: But what we're trying to figure out here is whether or not the vaccine significantly aggravated her condition. And so we have to look at outcome and we need to look at the outcome in the end because the question is whether her clinical course now is significantly worse than it would have been but for the vaccine. The answer that I'm hearing from you is that you can't give me an answer on that.
>
> WITNESS: No, I can't and that's what I said . . . .

Tr. at 195 (Wheless).

[22] Dr. Kendall testified that the SCN1A gene has more than 500 reported mutations. Tr. at 35 (Kendall).

spectrum of Dravet." Barnette at *15. In so concluding, the special master distinguished the Suls study, an article upon which Dr. Kendall relied, on the ground that the genetic mutations identified in the article "were completely distinct from Claire's known disease causing variant." Id. (citing Tr. at 397–98 (Kendall)).[23]

The special master similarly took issue with Dr. Wheless's line of testimony asserting that an earlier onset of seizures would result in a worse cognitive outcome because it occurred earlier in the brain's development. Barnette at *17. According to Dr. Wheless, Dravet Syndrome is similar to infantile spasms in that both conditions are a form of epileptic encephalopathy of infancy. Tr. at 108 (Wheless). Further, Dr. Wheless explained, in the context of epileptic encephalopathy of infancy, an earlier onset of seizures is always associated with a worse prognosis. Tr. at 113–14, 119–20, 135, 139, 150, 196, 202, 552 (Wheless). The special master ultimately concluded, however, that Dr. Wheless "relie[d] on literature that is . . . not on point" and that Dr. Wheless's interpretation of the medical literature was "entirely unpersuasive." Barnette at *17, *19.

The special master was instead persuaded by the testimony of Dr. Wiznitzer who rejected Dr. Wheless's parallel between infantile spasms and Dravet Syndrome as "comparing apples and oranges." Tr. at 507 (Wiznitzer). As Dr. Wiznitzer explained, infantile spasms are a form of epileptic encephalopathy in which early seizure onset impacts prognosis, but Dravet Syndrome is a different form of epileptic encephalopathy in which the prognosis is impacted not by the age of seizure onset but by the channelopathy resulting from the gene mutation. Tr. at 501–08 (Wiznitzer). Quoting Dr. Wiznitzer, the special master went on to observe that "infantile spasms

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[23] Dr. Kendall argued that the Suls study, A. Suls, et al., *Four Generations of Epilepsy Caused by an Inherited Microdeletion of the SCN1A Gene*, 75 Neurology 72–76 (2010), provides evidence that individuals with the same SCN1A gene mutation can have variable clinical expressions and suggests that Dravet Syndrome caused by an SCN1A haploinsufficiency can be extensively modified by other environmental factors (like vaccines). Tr. at 44 (Kendall). Dr. Kendall explained that the Suls study looked at a four-generation family containing four individuals who suffered both from generalized epilepsy and from a chromosomal deletion in the SCN1A gene. Tr. at 43–44 (Kendall). The study revealed that the family members presented with both moderate and severe phenotypes, ranging from an individual who appeared developmentally normal to one with classical clinical features of Dravet Syndrome. Tr. at 44 (Kendall). The Suls authors interpreted their results as demonstrating that "SCN1A haploinsufficiency can cause a significant intrafamilial clinical variability including moderately affected to syndromal patients." Pet. Ex. 91 at 1. The authors went on to speculate that the "involvement of multiple genetic and environmental factors could be the basis of this difference in phenotype severity." Id.

are a totally different creature" from Dravet Syndrome, Barnette at *17 (quoting Tr. at 501 (Wiznitzer)). Further quoting Dr. Wiznitzer, the special master explained this point as follows:

> Once you stop the [infantile] spasms with treatment . . . the encephalopathy is gone. It's time limited. . . . [I]n contrast, Dravet Syndrome is an epileptic encephalopathy, but it never stops . . . because the sodium channel abnormality is always present. [Dravet kids just get] worse and worse developmentally, from the second year or after. And that's long after the seizure . . . Dravet [S]yndrome has started. In infantile spasms, the problems with cognition are immediate.

Barnette at *17 (internal quotations and citations omitted). The special master thus endorsed Dr. Wiznitzer's conclusion that "you cannot apply the findings of [a study that focused on infantile spasms] to Dravet Syndrome. You can only apply [those findings] to infantile spasms . . . ." Id.

Relying, then, on the testimony of respondent's experts, the special master proffered credible rationales for rejecting each of the articles Dr. Wheless cited. See id. at *17–18. Thus, although the special master found that all the experts who testified were "well qualified," he ultimately determined that the testimony offered by respondent's experts was a "far more persuasive interpretation of the scientific literature, the medical records, and the specific clinical evidence regarding Claire's genetic mutation." Id. at *20. Such an assessment, we believe, is well within the special master's purview. As the Federal Circuit observed in Moberly ex rel. Moberly v. Sec'y of Dep't of Health & Human Servs., 592 F.3d 1315, 1325 (Fed. Cir. 2010):

> [T]o say that proof in the form of epidemiological studies or well-established medical experience is not mandatory does not mean that the special masters in Vaccine Act cases are precluded from inquiring into the reliability of testimony from expert witnesses. Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and we have made clear that the special masters have that responsibility in Vaccine Act cases.

The special master considered the medical literature not, as petitioners assert, as a means of holding petitioners to an impermissibly high evidentiary standard of medical certainty, but as a way of testing a theory that relied on parallels drawn to various medical articles in the absence of clinical evidence that Claire's condition in fact had been aggravated. It was in this context that the special master concluded that Dr. Wheless "stretch[ed] the reasonable bounds of the submitted literature" and that

petitioners' theory was found wanting. Barnette at *5. We can find no fault with the special master's assessment.

In the final analysis, the special master concluded that "the overwhelming evidence presented demonstrates that Claire's specific SCN1A mutation was the sole cause of her disease and that her vaccinations did not result in any worsening of that disease process." Id. at *20. The special master provided a thorough analysis of the medical records, the medical literature, and the opinions of both parties' experts and reached a conclusion that was clearly articulated, well supported, and entirely reasonable. We can find no error with the special master's decision.

CONCLUSION

For the reasons set forth above, we find that the special master's decision was not arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. Accordingly, petitioners' motion for review is denied and the special master's decision is affirmed. The Clerk is directed to enter judgment consistent with this opinion.

IT IS SO ORDERED.

s/John P. Wiese
John P. Wiese
Judge