In the United States Court of Federal Claims

No. 07-451V

(Filed: July 12, 2010)

MARILYN DAVIS,	)	Vaccine case; off-Table claim stemming from neuromyelitis optica allegedly caused by influenza vaccine; required elements of proof; causation; persuasiveness of expert testimony; harmless error
Petitioner,	)	
v.	)	
SECRETARY OF HEALTH AND HUMAN SERVICES,	)	
Respondent.	)	

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OPINION AND ORDER[1]

LETTOW, Judge.

Petitioner, Marilyn Davis, seeks review of a decision by a special master dated March 16, 2010, denying her compensation under the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, § 311, 100 Stat. 3743, 3755 (1986) (codified, as amended, at 42 U.S.C. §§ 300aa-1 to -34) ("Vaccine Act"). Ms. Davis alleges that her injection with an influenza vaccine in December 2006 caused her to develop neuromyelitis optica ("NMO"), a disease that damages the

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

myelin, the insulating sheath surrounding a body's nerves, and affects in particular the optical nerves and spinal cord. *See Davis v. Secretary of Health & Human Servs.*, No. 07-451, 2010 WL 1444056, at *1 (Fed. Cl. Spec. Mstr. Mar. 16, 2010) ("Entitlement Decision"). *Dorland's Illustrated Medical Dictionary*, 1237, 1726 (31st ed. 2007).

This is a so-called off-Table vaccine injury case in which the claimant must establish causation in fact.[2] The parties do not dispute that Ms. Davis has NMO. However, causation is at issue. The special master denied relief to Ms. Davis on the ground that she "failed to establish the reliability of her expert's theory explaining how the influenza vaccine can cause, or can contribute to causing, neuromyelitis optica." Entitlement Decision at *1. Petitioner challenges the decision by the special master, claiming that the theory of causation offered by her expert is "biologically plausible" and the decision by the special master rejecting her claim is arbitrary, capricious, an abuse of his discretion, and not in accordance with law. Pet'r's Mot. for Review at 2-8, 15-20 ("Pet'r's Mot.").

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[2]Trivalent influenza vaccine appears on the Vaccine Injury Table maintained by the Secretary of Health and Human Services, *see* 42 C.F.R. § 100.3 (2008), as adopted and revised pursuant to the authority of 42 U.S.C. § 300aa-14(c). Provision XIII of the Table lists "[a]ny new vaccine recommended by the Centers for Disease Control and Prevention for routine administration to children, after publication by the Secretary of a notice of coverage." 42 C.F.R. § 100.3(a) Table, Provision XIII. By a notice published on April 12, 2005, "the Secretary announce[d] that trivalent influenza vaccines are covered vaccines under the National Vaccine Injury Compensation Program." *National Vaccine Injury Compensation Program: Addition of Trivalent Influenza Vaccines to the Vaccine Injury Table*, 70 Fed. Reg. 19,092 (Apr. 12, 2005). As the Secretary explained:

> [T]wo types of influenza vaccines are routinely given to millions of individuals in the United States each year. One is an inactivated (killed) virus vaccine administered using a syringe, while the other is a live, attenuated product administered in a nasal spray. Both vaccine types are trivalent, meaning that they each contain three vaccine virus strains which are thought most likely to cause disease outbreaks during the influenza season.

Id.

However, no Table injuries are specified for this vaccine. *See* 42 C.F.R. § 100.3(a) Table, Provision XIII. For most listed vaccines, "[t]he Table lists symptoms and injuries associated with each listed vaccine and a timeframe for each symptom or injury." *de Bazan v. Secretary of Health & Human Servs.*, 539 F.3d 1347, 1351 (Fed. Cir. 2008). If a listed symptom occurs after vaccination within the specified timeframe, causation is presumed. *Id*. Injuries not listed in the Table or injuries that occur outside the specified timeframe following vaccination are deemed "off-Table" injuries, and causation is not presumed in such cases. *Id*. In this instance, however, because no injuries are specified for trivalent influenza vaccine, all claims related to that vaccine are off-Table injuries. *See Campbell v. Secretary of Health & Human Servs.*, 90 Fed. Cl. 369, 372 n.2 (2009).

FACTS

Marilyn Davis was born in 1948. Entitlement Decision at *1. Ms. Davis' medical history prior to 2005 has not been addressed by the parties, was not discussed in the Entitlement Decision, and does not appear to be relevant to her vaccine injury claim. *See id*. In March 2005, however, Ms. Davis was diagnosed with breast cancer, for which she received treatment, including chemotherapy, throughout the summer of 2005. *Id.*; R. Ex. 3 at 101.[3] By July 3, 2006, Ms. Davis' oncologist reported a "[s]table [physical] examination." R. Ex. 1 at 11.

On December 4, 2006, Ms. Davis received an influenza vaccine. Entitlement Decision at *1. Three weeks later, on December 28, 2006, Ms. Davis called the surgical clinic and complained of lower back and flank pain, and was directed to call her primary care doctor. *Id*. Beginning the next day, Ms. Davis began to experience bowel discomfort and constipation, for which she saw her doctor on January 2, 2007. *Id*. Petitioner was admitted to the hospital on January 3, 2007 for treatment related to her continuing constipation. R. Ex. 2 at 131-32. Ms. Davis was released from the hospital the next day, R. Ex. 7 at 247, but was readmitted on January 7, 2007 for paralysis and incontinence following a call to emergency medical services. R. Ex. 2 at 28-29. On January 9, 2007, Ms. Davis was transferred from the admitting hospital to Wesley Medical Center. R. Ex. 2 at 80. While receiving care at the Wesley Medical Center, an MRI was taken of Ms. Davis' spine, which showed "diffuse enhancement in her spinal cord from C6 to L1." Entitlement Decision at *1. Ms. Davis' treating physician, neurologist Dr. Andrew Massey, posited a diagnosis of transverse myelitis, NMO, or encephalomyelitis, either of the post-infectious or post-viral type. *Id*.[4] Ms. Davis was treated with steroids and discharged from Wesley Medical Center to a comprehensive in-patient rehabilitation program at Wesley Rehabilitation Hospital on January 17, 2007, where she continued to be monitored by Dr. Massey. R. Ex. 3 at 66-67. At this time, Ms. Davis was still suffering from paralysis. R. Ex. 11 at 77-79.

While under Dr. Massey's care, various tests were performed to determine the cause of Ms. Davis' ongoing paralysis, including a blood test for the presence of the "NMO antibody," a unique immunoglobulin ("NMO-IgG"), the presence of which is strongly indicative of the

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[3]In this recitation of the facts, the transcript of the entitlement hearing before the special master will be cited as "Tr. __" and references to documentary materials made part of the record will be to "R. Ex. __ at __." Regarding these documentary materials of record, Exhibit 18 has been subdivided into tabs. The letter after the hyphen in a citation to Exhibit 18 refers to a particular tab. The transcript of the hearing before the court held May 26, 2010 on the petition for review will be cited as "Hr'g Tr. __."

[4]"Myelitis" is "inflammation of the spinal cord." *Dorland's* at 1237. "Transverse myelitis" is "myelitis in which the functional effect of the lesions spans the width of the entire cord at a given level." *Id*. "Encephalomyelitis" is "inflammation involving both the brain and the spinal cord." *Id*. at 621.

disorder, which came back positive. Entitlement Decision at *1; Tr. 19:1-5 (Test. of Dr. J. Griffith Steel, an expert who testified on behalf of petitioner). Dr. Massey noted that Ms. Davis was at high risk for developing NMO. Entitlement Decision at *2. Ms. Davis was discharged from Wesley Rehabilitation Hospital on March 20, 2007. R. Ex. 3 at 66. As of April 30, 2007, Ms. Davis reported being "[c]hairfast, unable to ambulate[,] but . . . able to wheel [her]self independently." R. Ex. 14 at 5.[5]

Ms. Davis filed a petition for vaccine injury compensation on June 28, 2007 and an amended petition on November 13, 2007. Entitlement Decision at *3. The parties' experts agree that the proper diagnosis for Ms. Davis' condition is NMO, but disagree as to cause.[6] Petitioner's expert, Dr. J. Griffith Steel, opined that Ms. Davis' influenza vaccine caused her to develop NMO. Tr. 73:15 to 75:3 (Steel). According to Dr. Steel, injection of the influenza vaccine causes inflammation that damages the blood vessel lining, known as the endothelium, resulting in the exposure of aquaporin-4 protein (AQP-4), a protein normally hidden behind the blood-brain barrier, to the NMO antibody. Tr. 121:9-21, 68:2-24 (Steel). Aquaporin-4 is one of a family of nine three-dimensional protein "water channels" "that permit passage of water and very small solutes" in the body. *Dorland's* at 123; Tr. 19:15-18 (Steel). AQP-4 is concentrated primarily in the spinal cord, optical nerves, and hypothalamic area of the brain, Tr. 20:7-20 (Steel), and is the target antigen for the NMO antibody. Tr. 19:19-21 (Steel). According to Dr. Steel, "given the proper circumstances," the exposure of the NMO antibody to AQP-4 results in the "classic immune response [of] [the] antibody seeing and locking onto [the] antigen," "inciting[] a series of defense reactions that then result in tissue damage [to the myelin]." Tr. 20:24 to 21:10, 22:19-25, 68:21-24 (Steel) (referring to his theory as a "two hit hypothesis," with the first "hit"

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[5]Ms. Davis' condition thus improved to a significant extent, unlike the course of NMO for many prior persons who suffered from the condition. Dr. Massey's diligence in keeping abreast of the literature reporting emerging discoveries at the Mayo Clinic was commendable in contributing to this result. *See* Hr'g Tr. 25:4-10 ("An antibody that had just been discovered the previous year, her physician recognized it within a relatively brief period of time and treated her appropriately. That could be, to a certain extent, why she has survived and improved, as opposed to dying, which is the course of many of these patients with NMO in the past.").

[6]Ms. Davis' amended petition for vaccine compensation claims she suffers from transverse myelitis. Amended Pet. for Vaccine Compensation at 1. Under older criteria for diagnosing NMO, a patient needed to suffer from both transverse myelitis and optic neuritis. Tr. 32:20-25 (Steel). Contemporary medical literature, however, recognizes a "spectrum" of NMO, by which a patient, such as Ms. Davis, is recognized as having the disease even though she suffers from transverse myelitis but not optic neuritis. Tr. 33:6-13 (Steel) (stating that "contemporary literature . . . acknowledg[es] that individuals may, for example, have longitudinally extensive transverse myelitis, an NMO . . . antibody and a benign MRI of the brain [to rule out other neurological conditions], and if they have those three, which Marilyn Davis does, . . . then the likelihood of them having [NMO] is over 90 percent").

being damage to the endothelial cells with a resulting break in the blood-brain barrier and the second "hit" being damage to the myelin).[7]

The government's expert, Dr. Arthur Safran, testified that several facts refute an association between the trivalent influenza vaccine and NMO, noting that none of Ms. Davis' treating physicians made such an association, no study in the literature established such a correlation, and "better alternative cause[s]" existed. Tr. 137:6-12 (Safran). Dr. Safran testified about two alternative causes. "The first is the obvious one, that there's a certain background number of people who are going to get NMO and for which we will never know the cause." Tr. 142:13-16 (Safran). However, Dr. Safran believed that a second alternative cause was more likely, that Ms. Davis' NMO was triggered by her breast cancer, which had spread into her regional lymph nodes. Tr. 142:13-20 (Safran). Dr. Safran explained that the survival rate for patients like Ms. Davis, whose cancer had spread to the lymph nodes, was 93 percent at 5 years and 73 percent at 10 years, meaning that in some patients "minuscule cancer deposits in other parts of the body [remain] that cannot be detected by any clinical means." Tr. 142:21 to 143:6 (Safran). According to Dr. Safran, "remote [e]ffects of cancer on the nervous system can be caused by [these] minuscule cancer deposits," Tr. 143:3-4 (Safran), indicating that "as of around 2003, something on the order of 25 or some such cases [existed of women who had breast cancer later developing necrotic myelopathy]." Tr. 145:2-10 (Safran).[8]

In the Entitlement Decision, the special master rejected Dr. Steel's "two hit" hypothesis, finding that damage to the endothelium was a critical step in the hypothesis, and that "Ms. Davis [had] not established, by a preponderance of the evidence, the reliability of the assertion that the influenza vaccine can damage endothelial cells." Entitlement Decision at *8. The special master found that although Dr. Steel referred to several medical articles relating to endothelial-cell damage during his testimony, none were directly supportive of the proposition that the influenza vaccine in particular can damage the endothelium. *Id*. Specifically, first, Dr. Steel offered an editorial published in 2008 in *The International MS Journal*, which concluded that "[b]rain inflammation, induced by other mechanisms, may be instrumental to allow AQP-4 antibodies to reach their target antigen in the nervous system and to induce tissue injury." *Id*. (quoting R. Ex. 34 (M. Bradl & H. Lassmann, *Anti-Aquaporin-4 Antibodies in Neuromyelitis Optica: How to Prove Their Pathogenic Relevance?*, 15 Int'l MS J. 75-78 (2008) ("Bradl & Lassmann, *Anti-Aquaporin-4 Antibodies*"))). However, the special master found this editorial to be inadequate,

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[7]Dr. Steel did not include a detailed discussion of the "two hit" hypothesis in his report, *see* R. Ex. 18 (Medical Expert Report of Dr. J. Griffith Steel ("Steel Report")), but rather offered a relatively complete exegesis of this theory for the first time during his testimony at the entitlement hearing. Entitlement Decision at *8-9.

[8]A "myelopathy" is "any of various functional disturbances or pathological changes in the spinal cord, often referring to nonspecific lesions in contrast to the inflammatory lesions of myelitis." *Dorland's* at 1239.

being limited to expressing an opinion as to what "may" be possible and not mentioning the trivalent influenza vaccine as a possible "mechanism" by which AQP-4 antibodies are exposed. *Id*.

Second, significant time during the entitlement hearing was devoted to discussion of an article written by Dr. Dean M. Wingerchuk of the Mayo Clinic in 1999, which identified 93 patients of the Mayo Clinic diagnosed with NMO from 1950 through 1997, or an average of two per year. Entitlement Decision at *9-10 (citing R. Ex. 18-D (Dean M. Wingerchuk *et al.*, *The Clinical Course of Neuromyelitis Optica (Devic's Syndrome)*, 53 Neurology 1107 (1999)) ("Wingerchuk on *Clinical Course of NMO*")); Tr. 45:13 to 46:9 (Steel). For each patient diagnosed with NMO, Dr. Wingerchuk listed antecedent illnesses or events, and, in two cases, Dr. Wingerchuk noted a swine flu vaccination as an "antecedent illness or event." Tr. 46:13-24 (Steel); Entitlement Decision at *9-10 (citing Wingerchuk on *Clinical Course of NMO* at 1111).[9] Neither Dr. Steel nor Dr. Safran were able to find any articles in the literature which explicitly associated trivalent influenza vaccine and NMO. R. Ex. 18 at 5 (Steel Report); Entitlement Decision at *11.[10]

STANDARDS FOR REVIEW

Under the Vaccine Act, when reviewing a decision of a special master on a motion for review, the court has jurisdiction to "undertake a review of the record of the proceedings" and may take any of the following actions:

> (A) uphold the findings of fact and conclusions of law of the special master and sustain the special master's decision,
> (B) set aside any findings of fact or conclusion of law of the special master found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and issue its own findings of fact and conclusions of law, or
> (C) remand the petition to the special master for further action in accordance with the court's direction.

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[9]The experts disagreed as to whether by listing the swine flu vaccinations as antecedent events Dr. Wingerchuk was implying causation. Dr. Steel believed that there was some indication of causation, but Dr. Safran opined that just as in a case report, Dr. Wingerchuk was merely "seeking out possible correlations," hoping that in the event others came across similar cases, they would document them. Tr. 139:5-13 (Safran).

[10]The influenza vaccine Ms. Davis received was a "trivalent" vaccine, meaning it "contain[ed] three vaccine virus strains which are thought most likely to cause disease outbreaks during the influenza season." *See supra* at 2 n.2. By contrast, the swine flu vaccination was a "monovalent" vaccine, meaning that it contained only the one virus strain responsible for swine flu.

42 U.S.C. § 300aa-12(e)(2); *see also* RCFC Appendix B, Rule 27.[11] The Vaccine Act requires this court to analyze conclusions of law made by a special master to determine whether they "accord[] with law." 42 U.S.C. § 300aa-12(e)(2). Factual findings by a special master may be set aside if they are found to be arbitrary or capricious or if a special master has abused his or her discretion in making such findings. *See id*. The Federal Circuit has commented that, "reversible error is extremely difficult to demonstrate if the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision." *Lampe v. Secretary of Health & Human Servs.*, 219 F.3d 1357, 1360 (Fed. Cir. 2000) (internal quotation omitted) (citing *Hines ex rel. Sevier v. Secretary of Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991)). While "it is not . . . the role of [the reviewing] court to reweigh the factual evidence, or to assess whether the special master correctly evaluated the evidence . . . [,] [or to] examine the probative value of the evidence or the credibility of the witnesses," *Lampe*, 219 F.3d at 1360 (quoting *Munn v. Secretary of Health & Human Servs.*, 970 F.2d 863, 871 (Fed. Cir. 1992)), a special master may not "frame[] her [or his] rejection of [a petitioner's] theory of causation under the rubric of a 'credibility' determination," *Andreu v. Secretary of Health & Human Servs.*, 569 F.3d 1367, 1379 (Fed. Cir. 2009), nor may a special master "cloak the application of an erroneous legal standard in the guise of a credibility determination, and thereby shield it from appellate review." *Id*.

In adopting the Vaccine Act, Congress sought to "establish a [f]ederal 'no-fault' compensation program under which awards can be made to vaccine-injured persons quickly, easily, and with certainty and generosity." H.R. Rep. No. 99-908, at 3 (2d Sess. 1986), *reprinted in* 1986 U.S.C.C.A.N. 6334, 6334. To pursue the goal of a generous remedial program, Congress established a Vaccine Injury Table.[12] When a petitioner "[b]ring[s] [a] case within the timetable and specifications of a Table [i]njury[,] . . . the statute does the heavy lifting – causation is conclusively presumed." *Hodges v. Secretary of Health & Human Servs.*, 9 F.3d 958, 961 (Fed. Cir. 1993). For a petitioner to be able to avail himself or herself of the Vaccine Injury Table, the

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[11]Prior to 1989, the judges on this court had the option of either "adopt[ing] the findings of the special master as [their] own judgment, or mak[ing] a de novo determination of any matter and issu[ing] [their] judgment accordingly." Randall B. Keiser, *Deja Vu All Over Again? The National Childhood Vaccine Injury Compensation Act of 1986*, 47 Food & Drug L.J. 15, 23 (1992). The statute was amended in 1989 to eliminate the ability of the judges on this court to review any portion of the special master's decision de novo. *See* Omnibus Budget Reconciliation Act of 1989, Pub. L. No. 101-239, § 6601(h), 103 Stat. 2106, 2289 (codified at 42 U.S.C. § 300aa-12(e)).

[12]The initial Vaccine Injury Table was published at 42 U.S.C. § 300aa-14(a). The Table can be, and has been, revised by the Secretary of Health and Human Services acting pursuant to notice-and-comment rulemaking under the authority of 42 U.S.C. § 300aa-14(c). The current version of the Vaccine Injury Table, as amended, is set out at 42 C.F.R. § 100.3. *See supra*, at 2 n.2.

claimant must "establish that [he or] she received a listed vaccine and experience[s] such symptoms or injuries within the specified timeframes." *de Bazan*, 539 F.3d at 1351.

However, if a petitioner is unable to bring a claim that falls within the scope of the Table, the individual is required to prove causation in fact by a preponderance of the evidence. 42 U.S.C. §§ 300aa-11(c)(1)(C)(ii), -13(a)(1)(A); *Althen v. Secretary of Heath & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005).[13]

In *Althen*, the Federal Circuit held that to prove causation in fact, a petitioner must show, by preponderant evidence, the following:

> (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. Elaborating on these criteria for causation, the Federal Circuit stated that "[a] persuasive medical theory is demonstrated by proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury, the logical sequence being supported by reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Id*. (internal quotation omitted) (citation omitted); *see also Capizzano v. Secretary of Health & Human Servs.*, 440 F.3d 1317, 1324-27 (Fed. Cir. 2006) (applying the *Althen* test). Once the petitioner has made a prima facie case for entitlement, "the burden shifts to the government to prove by a preponderance of the evidence that the petitioner's injury is due to factors unrelated to the . . . vaccine." *de Bazan*, 539 F.3d at 1352 (internal quotation omitted) (citation omitted). The Federal Circuit "has interpreted the 'preponderance of the evidence' standard . . . as one of proof by a simple preponderance, of 'more probable than not' causation." *Althen*, 418 F.3d at 1279 (citation omitted). "'[C]lose calls regarding causation are resolved in favor of injured claimants.'" *Andreu*, 569 F.3d at 1378 (quoting *Capizzano*, 440 F.3d at 1325-26).

Proof by a preponderance of the evidence does not require "scientific certainty." *Bunting v. Secretary of Health & Human Servs*., 931 F.2d 867, 873 (Fed. Cir. 1991). "[D]etermination 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." *Knudsen ex rel. Knudsen v. Secretary of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994) (citations omitted). "[A]scertaining precisely how and why . . . vaccines sometimes destroy the health and

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[13] As noted, the inclusion of trivalent influenza vaccine on the Table is not accompanied by any listing of Table injuries or any time period for first symptom or manifestation of onset or of significant aggravation after vaccine administration. *See supra*, at 2 n.2. Thus, no claims related to administration of trivalent influenza vaccine can be said to fall within the Table, and all such claims necessarily must be for off-Table injuries.

lives of certain [individuals] while safely immunizing most others . . . is for scientists, engineers, and doctors working in hospitals, laboratories, medical institutes, pharmaceutical companies, and government agencies." *Id*. at 549. The absence of "a link between a vaccine and a particular injury," or "that the state of medical knowledge regarding a causal link . . . can be characterized as 'controversial,'" "will not bar recovery, because 'the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." *Rotoli v. Secretary of Health & Human Servs.*, 89 Fed. Cl. 71, 79 (2009) (quoting *Althen*, 418 F.3d at 1280). Thus, a finding of causation in fact in vaccine cases can be "based on epidemiological evidence and the clinical picture . . . without detailed medical and scientific exposition on the biological mechanisms." *Knudsen*, 35 F.3d at 549.

"[P]ursuant to 42 U.S.C. § 300aa-13(a)(1), a finding of preponderant evidence of causation[]in[]fact must be substantiated by medical records or by medical opinion." *Rotoli*, 89 Fed. Cl. at 80 (citing *Althen*, 418 F.3d at 1279). A finding of preponderant evidence of causation in fact may be based on medical opinion alone, *id.* (citing *Althen*, 418 F.3d at 1280); however, "the special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly v. Secretary of Health & Human Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010) (citing *Terran v. Secretary of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). Where medical literature or epidemiological evidence "'is [also] submitted, the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury.'" *Rotoli*, 89 Fed. Cl. at 80 n.9 (quoting *Andreu*, 569 F.3d at 1379-80, and *citing Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 593-97 (1993) for the proposition that "one factor in assessing the reliability of expert testimony is whether the theory espoused enjoys general acceptance within a relevant scientific community").

ANALYSIS

A. *Neuromyelitis Optica*

Neuromyelitis Optica or "NMO" is a rare autoimmune demyelinating disease involving the spinal cord and optical nerves. Tr. 16:8-16 (Steel).[14] Although extremely uncommon, the disease recently has received considerable attention in the medical literature due to two scientific breakthroughs at the Mayo Clinic in 2006 and 2007, respectively. In 2006, the NMO antibody was discovered at the Mayo Clinic, followed by the discovery of the target antigen, the cellular target against which the antibody is directed, in 2007, also at the Mayo Clinic. Tr. 18:24 to 19:12 (Steel). As discussed previously, "[t]he NMO-IgG antibody is targeted against a specific protein complex which is called aq[u]aporin. . . . [T]here are nine aquaporins. . . . [T]he NMO-IgG antibody is directed specifically against aquaporin-4." Tr. 19:12-20 (Steel). Aquaporin-4 is concentrated in the spinal cord, the optical nerves, and the hypothalamic area of the brain, and is

[14] "Demyelination" is the "destruction, removal, or loss of the myelin sheath of a nerve or nerves." *Dorland's* at 493.

also found in parts of the kidneys and stomach. Tr. 20:10-15 (Steel). Demyelination is the result of an immune response triggered by the formation of an antigen-antibody complex between the NMO antibody and aquaporin-4, its target antigen. Tr. 20:24 to 21:14 (Steel).

Petitioner's affliction with NMO in 2006 and 2007 thus coincided in time with the scientific discoveries about NMO at the Mayo Clinic that provided a markedly greater understanding of the biological mechanisms causing the condition. Nonetheless, petitioner's claim for compensation under the Vaccine Act is positioned at or near the outer boundaries of medical knowledge.

B. *Petitioner's Medical Theory*

To prove "actual causation" or "causation in fact" by a preponderance of the evidence, *Althen*, 418 F.3d at 1278,[15] petitioner must present "a medical theory causally connecting the vaccination and the injury," *id*. at 1278, that need only be "'logical' and legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49. Temporal proximity between the vaccination and the injury is a factor to be considered in the analysis of causation, *see Capizzano*, 440 F.3d at 1326, as is testimony from treating physicians and from experts. *See Moberly*, 592 F.3d at 1325 (citing *Andreu*, 569 F.3d at 1376). "Weighing the persuasiveness of particular evidence often requires a finder of fact to assess the reliability of testimony, including expert testimony, and . . . special masters have that responsibility in Vaccine Act cases." *Id.* (citing *Terran*, 195 F.3d at 1316). Petitioner argues that she met her burden of proof under *Althen* by presenting a "plausible" medical theory to explain how the influenza vaccine can cause NMO. *See* Pet'r's Mot. at 2-8.

The special master's denial of Ms. Davis' petition for compensation rested largely on the absence of confirming medical literature for the postulate that trivalent influenza vaccine can damage the endothelium. *See* Entitlement Decision at *8. Dr. Steel was unable to locate any literature to provide direct support for that "critical step" in his theory. *Id*. The government's expert, Dr. Safran, was similarly unaware of any literature on that subject. Tr. 142:3-5 (Safran) ("I think [Dr. Steel's theory is] interesting thinking and it's an interesting idea, but I don't see the basis or the proof of any of that."). The existing literature contains hints along those lines but no direct evidence. For example, the editorial in *The International MS Journal* suggested that brain inflammation "may be instrumental" in exposing AQP-4 to NMO antibodies, *see* R. Ex. 34. (Bradl & Lassmann, *Anti-Aquaporin-4 Antibodies*), but this publication identified topics of future research interest without offering conclusions and without specifically mentioning the influenza vaccine. Entitlement Decision at *8. Dr. Steel was candid in stating that although "the role of

[15] "The burden of showing something by a 'preponderance of the evidence,' the most common standard in the civil law, simply requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the [judge] of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2 (citation omitted).

inflammation in damaging blood vessel walls and thereby unleashing a whole sequence or a whole cascade of things that ought not to happen is pretty well-established in medicine," he "did not know" whether it has also been established that the trivalent influenza vaccine can cause the inflammation which damages the endothelium. Tr. 122:20 to 123:2 (Steel). Some indirect support for that proposition was provided by the article written by Dr. Wingerchuk of the Mayo Clinic in 1999. *See* Wingerchuck on *Clinical Course of NMO*. As noted earlier, Dr. Wingerchuk had identified two patients as having developed NMO following a swine flu vaccination. Entitlement Decision at *11. However, the special master found that "the Wingerchuk article [did] not [persuasively] support the proposition that the flu vaccine can cause NMO [because] the Wingerchuk article does not indicate that the swine flu vaccine *caused* the NMO," and further, "Ms. Davis ha[d] not established that information about the swine flu vaccine is transferrable to the flu vaccine." *Id*. at *10-11.

Yet a third study, one not put forward by the parties, was considered by the special master in his analysis. The special master went outside the record to consider a Japanese study, T. Nakayama and K. Onoda, *Vaccine Adverse Events Reported in Postmarketing Study of the Kitasato Institute from 1994 to 2004*, 25 Vaccine 570-76 (2007) ("Nakayama & Onoda, *Vaccine Adverse Events*"), which purportedly found three cases of acute disseminating encephalomyelitis ("ADEM") and nine cases of Guillian-Barre Syndrome in Japan following administration of 38 million doses of influenza vaccine between 1994 and 2004. Entitlement Decision at *11. The study had been cited in another article submitted for the record by petitioner. *See id*. (citing R. Ex. 26 (William Huynh, *et al.*, *Post-Vaccination Encephalomyelitis: Literature Review and Illustrative Case*, 15 J. Clinical Neuroscience 1315, 1317 (2008) ("Huynh, *Post-Vaccination Encephalomyelitis*")), which cited Nakayama & Onoda, *Vaccine Adverse Events*). Based on the Nakayama & Onoda article, the special master inferred that "the flu vaccine did not cause cases of NMO in Japan . . . because Japanese researchers would have looked for cases of NMO, and, if cases were found, the Japanese researchers would have reported them." Entitlement Decision at *11. From this inference, the special master concluded that "[t]he fact that no cases of NMO were reported after the more than 38 million doses of flu vaccine in Japan is some evidence that flu vaccine does not cause NMO." *Id*. However, the special master had given the parties no notice or indication that he would examine and rely on the Nakayama & Onoda study and had taken no steps to insure that the study was in the record or that the parties had an opportunity to examine and address it. Hr'g Tr. 50:22 to 52:17.

In this regard, petitioner specifically contests the special master's factual reliance on a study not present in the record and which the parties had not addressed. Pet'r's Mot. at 14 & n.20; Hr'g Tr. 51:4 to 52:1. By contrast, the government emphasizes a special master's "broad discretion to determine the credibility of witnesses and weigh evidence," Resp.'s Opp'n at 7, and argues that here he "appl[ied] the correct evidentiary standard." *Id*. at 12.

It is axiomatic that special masters in vaccine cases have great leeway in building a record for decision. The rules in effect governing the conduct of hearings by special masters provide for "flexible and informal standards of admissibility of evidence." 42 U.S.C. § 300aa-

12(d)(2)(B); *see* RCFC Appendix B, Rule 8(b)(1) ("In receiving evidence, the special master will not be bound by common law or statutory rules of evidence but must consider all relevant and reliable evidence governed by principles of fundamental fairness to both parties."); *Hines*, 940 F.2d at 525 (noting that the Federal Rules of Evidence need not be applied in proceedings before a special master). In addition, by statute, a special master has great flexibility in requiring parties to submit information and testimony "as may be reasonable and necessary." 42 U.S.C. § 300aa-12(d)(3)(B)(i).[16] Nonetheless, a special master must act on the record after adequate notice. The requirement to decide on the record is specifically stated in 42 U.S.C. § 300aa-13(a)(1), which provides in pertinent part that "[c]ompensation shall be awarded under the Program to a petitioner if the special master or court finds *on the record as a whole* [that the petitioner is entitled to relief]." *See also* 42 U.S.C. § 300aa-13(c) (defining "record"); RCFC Appendix B, Rule 8(b)(1) (requiring the special master to consider "all relevant and reliable evidence").[17] The correlative requirement that a special master provide adequate notice to the parties of evidentiary issues and matters stems from 42 U.S.C. § 300aa-12(d)(3)(B)(iv), (v) (a special master "shall afford all interested persons an opportunity to submit relevant written information" and "may conduct such hearings as may be reasonable and necessary"), as well as RCFC Appendix B, Rule 8(b)(1) (a "[s]pecial master . . . must consider all relevant and reliable evidence governed by principles of fundamental fairness to both parties"). Manifestly also, core concepts of due process apply to proceedings before a special master. *See Campbell v. Secretary of Health & Human Servs.*, 69 Fed. Cl. 775, 776-77, 781-82 (2006) (finding the introduction into the record

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[16]In full, 42 U.S.C. § 300aa-12(d)(3)(B) provides:

> (B) In conducting a proceeding on a petition a special master –
>
> (i) may require such evidence as may be reasonable and necessary,
>
> (ii) may require the submission of such information as may be reasonable and necessary,
>
> (iii) may require the testimony of any person and the production of any documents as may be reasonable and necessary,
>
> (iv) shall afford all interested persons an opportunity to submit relevant written information –
>
> (I) relating to the existence of the evidence described in section 300aa-13(a)(1)(B) of this title, or
>
> (II) relating to any allegation in a petition with respect to the matters described in section 300aa-11(c)(1)(C)(ii) of this title, and
>
> (v) may conduct such hearings as may be reasonable and necessary.
>
> There may be no discovery in a proceeding on a petition other than the discovery required by the special master.

[17]At the hearing before the court on the petition for review of the special master's decision denying entitlement, counsel for the government argued that the special master "is allowed to consider evidence and submit evidence that's not part of the record." Hr'g Tr. 52:12-14. That statement of the law is patently wrong. The special master is allowed to cause materials to be made part of the record, but not to act outside the record.

of medical articles obtained from the Internet by the special master, without providing a hearing, to be inconsistent with the "[s]pecial [m]aster's responsibility for conducting a proceeding consistent with the principles of fundamental fairness"); *cf. Hines*, 940 F.2d at 1526 (finding the special master's failure to provide petitioner with advance notice that he intended to take judicial notice of a medical textbook which was not introduced at the hearing did not violate any principles of fundamental fairness because petitioner "*did* have a chance to discredit and rebut the information contained in that textbook on review before the Claims Court" and chose not to do so); *Morris v. Secretary of Health & Human Servs.*, 57 Fed. Cl. 383, 390-91 (2003) (acknowledging petitioners' argument that "'it is improper for a [s]pecial [m]aster to perform her own medical research and not allow the parties . . . [an] opportunity to even comment upon what she has discovered'" but finding that "[w]here, as here, the [s]pecial [m]aster adequately substantiated her conclusion with the information in the record, performance of outside research . . . is not an abuse of discretion").

Here, it was improper for the special master to draw support from the Nakayama & Onoda study to dismiss as inadequate the medical literature offered as support for Dr. Steel's medical theory of causation because the study was not in the record and the parties were not on notice that it would be considered.[18] However, it also was harmless error. There is substantial other evidence in the record that supports the special master's decision to deny Ms. Davis compensation. *See Hines*, 940 F.2d at 1526 ("In any event, even if it was error [for the special master to fail to inform petitioner in advance of his intended reliance of the medical textbook], it was harmless because, . . . the special master's decision was based on a number of factors and [petitioner] has not shown that reliance on the [information] derived from the textbook was likely critical to the result.").

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[18]Because the Nakayama & Onoda article was not made part of the record, the complete results of that study are unknown. The Huynh article cited the Nakayama and Onoda study for the proposition that they had "found 3 cases of ADEM and nine of Guillain-Barre among 38.02 million doses of influenza vaccine administered between 1994 and 2004." R. Ex. 26 at 1317 (Huynh, *Post-Vaccination Encephalomyelitis*). However, the Huynh article did not specify whether cases of other demyelinating diseases, such as NMO, were also found by Nakayama & Onoda, or whether the researchers were even looking for diseases other than ADEM and Guillain-Barre Syndrome. *See id.* In addition, the Nakayama & Onoda study ended in 2004, prior to the discovery of the NMO antibody at the Mayo Clinic in 2006. Subsequent revision of the diagnostic criteria for NMO recognizes a "spectrum" of NMO, where a patient need not suffer from both transverse myelitis and optic neuritis to be classified as having NMO. *See supra*, at 4 n.6. In short, if Nakayama & Onoda were looking for NMO, known as "spino optical MS" in Japan, Korea, and China, where incidentally the disease is "much more common," Tr. 41:12-16 (Steel), they necessarily would have employed superseded diagnostic criteria that did not take into account transverse myelitis plus a positive NMO antibody test. As a consequence of these circumstances, the Nakayama & Onoda study does not allow the negative inference the special master drew.

In addition to considering the medical literature, the special master invoked *Daubert* in his analysis of the reliability and persuasiveness of Dr. Steel's expert testimony. Entitlement Decision at *12. In *Daubert*, the Supreme Court laid out four factors which may assist a trial judge in determining whether to admit expert testimony pursuant to Fed. R. Evid. 702. *Daubert*, 509 U.S. at 592-95. These are: (1) whether a theory or technique can be and has been tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and, (4) whether the theory or technique is generally accepted within a relevant scientific community. *Id*. These factors have come to be used as a matter of course by federal trial judges in exercising their "gate-keeping" capacity over expert witnesses and testimony. However, uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted, at least in bench proceedings conducted by special masters in vaccine cases. *See Terran*, 195 F.3d at 1316 (rejecting plaintiff's contention that the only appropriate use of the *Daubert* factors is "to prevent the introduction of 'junk science' into trials, rather than as a broader tool for analyzing the admissibility of scientific testimony"); *see also Moberly*, 592 F.3d at 1324 (citing *Terran* as "holding that the factors set forth in *Daubert* . . . may be applied in assessing the reliability of an expert witness's testimony").

In this context, however, the Federal Circuit has appended caveats, noting that the *Daubert* factors are designed functionally to guide the gate-keeping aspect of admitting or excluding expert testimony, *see de Bazan*, 539 F.3d at 1353 n.4 ("*Daubert* is inapposite here because the special master did not exclude any expert evidence under *Daubert*. Rather, the special master admitted and weighed both parties' evidence but simply decided that the government's evidence was more persuasive."), and cautioning that the factors should not be used to raise the evidentiary bar to recovery in vaccine cases. *See Andreu*, 569 F.3d at 1378 ("Requiring "epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants.") (internal quotation omitted) (citation omitted). In *Kumho Tire Co. v. Carmichael*, 526 U.S. 137 (1999), the Supreme Court dropped hints along the lines of these caveats, when it commented that

> [w]e also conclude that a trial court *may* consider one or more of the more specific factors that *Daubert* mentioned when doing so will help determine that testimony's reliability. But, as the court stated in *Daubert*, the test of reliability is 'flexible' and *Daubert's* list of specific factors neither necessarily nor exclusively applies to all experts or in every case. Rather, the law grants a district court the same broad latitude when it decides *how* to determine reliability as it enjoys in respect to its ultimate reliability determination.

Id. at 141-42. In that regard, the Supreme Court in *Kumho Tire* was echoing the observation in

Daubert that "[t]he inquiry envisioned . . . is, we emphasize, a flexible one. Its overarching subject is the scientific validity and thus the evidentiary relevance and reliability – of the principles that underlie a proposed submission . . . *not* . . . *the conclusions they generate*." *Daubert*, 509 U.S. at 594-95 (emphasis added).

In this case, the special master employed two of the *Daubert* factors in analyzing Dr. Steel's testimony. In addressing the persuasiveness of Dr. Steel's two-hit hypothesis, the special master took into account Dr. Steel's testimony that he has not heard other neurologists discuss his theory. Entitlement Decision at *12. The special master concluded that "[t]his lack of discussion suggests that the theory that flu vaccine causes NMO has not been generally accepted within the community of neurologists." *Id*. (citing *Daubert*, 509 U.S. at 594). The special master also considered Dr. Safran's testimony that Dr. Steel's two-hit hypothesis could theoretically be tested by measuring the amount of the NGO-IgG antibody in a person before and after receipt of an influenza vaccination, concluding that "[t]he fact that [such a] study has not been undertaken is another point suggesting that the theory that flu vaccine can cause NMO is not reliable." *Id*.

In this instance, problems arise in applying the two *Daubert* factors to assess medical acceptance of Dr. Steel's hypothesis. Only recently have significant discoveries been made in understanding the pathology of NMO, and science has not advanced sufficiently far to address Dr. Steel's hypothesis, let alone to allow it to progress far enough to be generally accepted. Moreover, the testability of Dr. Steel's hypothesis is more of a conceptual construct than a practical possibility. It is very doubtful that a study such as that suggested by Dr. Safran would ever in fact be undertaken. Given the rarity of NMO and the extraordinarily large number of people receiving a trivalent influenza vaccine who would need to be tested to obtain useful results, conducting such a study would be akin to looking for the proverbial needle in a haystack. No funding or resources would likely be available for such an endeavor. In all events, however, the special master limited his consideration of the testability factor of *Daubert* by commenting that testability was merely "another point suggesting that the theory that flu vaccine can cause NMO is not reliable." Entitlement Decision at *12. In *Kumho Tire*, the Supreme Court emphasized that "the law grants a [trial] court the same broad latitude when it decides *how* to determine reliability as it enjoys in respect to its ultimate reliability determination," and cited *General Electric Co. v. Joiner*, 522 U.S. 136, 143 (1997), for the proposition that "courts of appeals are to apply [an] 'abuse of discretion' standard when reviewing [a trial] court's reliability determination." 526 U.S. at 142. Here, this court might quibble with aspects of how the special master used the *Daubert* factors to address reliability and the persuasiveness of Dr. Steel's expert testimony, but the key question still focuses on the special master's ultimate determination about the persuasiveness of Dr. Steel's causation hypothesis.

Discounting the special master's use of the *Daubert* factors to evaluate the expert testimony of record, what is left then are very few indicia that either tend to support, or negate, the persuasiveness of petitioner's medical theory for how the trivalent influenza vaccine can cause NMO. In the absence of testimony from Ms. Davis' treating physicians linking the vaccine

and injury, the special master relied on the dearth of medical literature supportive or dismissive of Dr. Steel's hypothesis to bolster his conclusion that Ms. Davis had not met her burden under *Althen*. In doing so, the special master weighed the evidence of record and made determinations as to persuasiveness in accord with law. Dr. Steel's postulates may ultimately be proven to be correct, as a scientific matter, but medical science has not yet advanced sufficiently far to conclude that his conceptual approach to causation can now be said to be established by a preponderance of the evidence.[19] Accordingly, applying an abuse-of-discretion standard to the special master's findings regarding causation, the court concludes that the special master's finding of a lack of causation was lawful based on the record before him.

CONCLUSION

For the foregoing reasons, petitioner's motion for review is DENIED, and the decision of the special master rendered March 16, 2010 is AFFIRMED.

It is so ORDERED.

s/ Charles F. Lettow
Charles F. Lettow
Judge

[19]In this respect, Dr. Steel's hypothesis is "not proven" in a way that resembles the somewhat archaic "Scotch verdict" in the context of the criminal law of Scotland, meaning "equivalent in result to not guilty, but carrying with it a strong suspicion of guilt not fully proved." *Black's Law Dictionary* (8th ed. 2004).