

IN THE UNITED STATES COURT OF FEDERAL CLAIMS

OFFICE OF SPECIAL MASTERS

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MARILYN DAVIS,

Petitioner,

v.

SECRETARY OF HEALTH  
AND HUMAN SERVICES,

Respondent.

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No. 07-451V  
Special Master Christian J. Moran

Filed: March 16, 2010

entitlement, influenza vaccine,  
Devic’s disease, neuromyelitis  
optica (NMO), reliability of  
petitioner’s expert theory

*Ronald C. Homer & Sylvia Chin-Caplan*, Conway, Homer & Chin-Caplan, P.C., Boston, MA,  
for petitioner;  
*Darryl R. Wishard*, United States Dep’t of Justice, Washington, D.C., for respondent.

**PUBLISHED DECISION DENYING COMPENSATION\***

Marilyn Davis claims that the influenza vaccine caused her to suffer a condition caused neuromyelitis optica, which is also known as Devic’s disease. Ms. Davis seeks compensation pursuant to the National Childhood Vaccine Injury Act, 42 U.S.C. §§ 300aa-10 et seq. (2006). Ms. Davis has not established that a preponderance of the evidence supports awarding her compensation. The primary problem in Ms. Davis’s proof is that she failed to establish the

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\* Because this published decision contains a reasoned explanation for the special master's action in this case, the special master intends to post it on the United States Court of Federal Claims's website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002).

All decisions of the special masters will be made available to the public unless they contain trade secrets or commercial or financial information that is privileged and confidential, or medical or similar information whose disclosure would clearly be an unwarranted invasion of privacy. When such a decision or designated substantive order is filed, a party has 14 days to identify and to move to delete such information before the document’s disclosure. If the special master, upon review, agrees that the identified material fits within the banned categories listed above, the special master shall delete such material from public access. 42 U.S.C. § 300aa–12(d)(4); Vaccine Rule 18(b).

reliability of her expert's theory explaining how the influenza vaccine can cause, or can contribute to causing, neuromyelitis optica. The reasons for this conclusion follow.

## **I. Facts and Procedural History**

The facts that are relevant to this case can be divided into three categories. The first set of facts concerns Ms. Davis, specifically. These facts are set forth in section A below. The second set of facts is information about human biology and the particular disease that afflicts Ms. Davis, neuromyelitis optica (NMO). These facts are set forth in section B below. Section C sets forth the procedural history of this case.

### **A. Facts about Ms. Davis**

The parties do not dispute what happened to Ms. Davis. Thus, her medical history is presented summarily. Ms. Davis was born in 1948. Exhibit 3 at 1. Her medical history for the next approximately 50 years seems to be not relevant.

In March 2005, Ms. Davis was diagnosed with breast cancer. Exhibit 16 at 1. She was treated for it. Id.; exhibit 3 at 12-16, 25-27, 99; exhibit 2 at 134; exhibit 1 at 12-21. The parties dispute the extent of Ms. Davis's recovery from breast cancer. See Pet'r Br., filed Oct. 29, 2009, at 12 n.17; Resp't Br., filed Nov. 30, 2009, at 18-20. Elaborate discussion about Ms. Davis's breast cancer is not needed because another issue (the reliability of the theory propounded by Ms. Davis's expert) is decisive.

Ms. Davis received an influenza vaccination on December 4, 2006. Exhibit 16 at 2; exhibit 13 at 1; exhibit 8 at 1. On December 28, 2006, she called the surgical clinic complaining of pain in her lower back and flank and was directed to contact her primary care provider. Exhibit 3 at 1. On December 29, 2006, Ms. Davis experienced constipation and she saw her doctor for abdominal pain and constipation on January 2, 2007. Exhibit 16 at 2; exhibit 4 at 8.

Ms. Davis's problems worsened. She developed paraplegia and was eventually hospitalized. While in the hospital, Ms. Davis had an MRI that showed diffuse enhancement in her spinal cord from C6 to L1. Exhibit 5 at 509-09. When she was discharged, the diagnoses included: (1) a spinal cord lesion; (2) possible secondary malignant neoplasm of the spinal cord versus possible primary malignancy of the spinal cord; (3) paraplegia with an unknown etiology; and (4) constipation and loss of bladder control. Exhibit 2 at 3-4, 7.

Dr. Massey, a neurologist, stated that Ms. Davis could have transverse myelitis. Exhibit 11 at 130-32. Dr. Massey also considered that Ms. Davis could have NMO, or post-infectious or post-viral encephalomyelitis. Exhibit 5 at 496; Exhibit 11 at 131-132. To identify the disease from which Ms. Davis was suffering, Dr. Massey ordered various tests, including a test for the NMO antibody. Ms. Davis tested positive. Exhibit 11 at 34-36. A positive result on this test is one criterion for diagnosing NMO. Exhibit 18, tab E (DM Wingerchuk et al., Revised

Diagnostic Criteria for Neuromyelitis Optica, 66 *Neurology* 1485, 1489 (2006); see also tr. 48 (discussing this article).

Dr. Massey stated that Ms. Davis was at high risk for developing NMO. Exhibit 5 at 1041. Both of the experts in this case stated that Ms. Davis suffers from NMO. Tr. 34; tr. 49; tr. 73 (Dr. Steel); tr. 132 (Dr. Safran).

By March 2007, Ms. Davis had not recovered fully from NMO. She still used a wheelchair and did not have control of her bladder. Exhibit 16 (Ms. Davis's affidavit) at 2.

## **B. Biology**

NMO involves the immune system. The immune system controls how a person responds to a foreign substance in the body, which is known as an antigen. The adaptive immune system has two components, the T-cell system and the B-cell system. Tr. 113-15.

The B-cell system is also known as the humoral system. See tr. 44. The B-cell system produces antibodies. Tr. 114. An antibody responds to an antigen by locking onto the antigen and creating an antigen-antibody complex. The body then destroys the antigen-antibody complex. See tr. 70.<sup>1</sup>

NMO is an autoimmune disease, meaning that the person's immune system becomes confused and wrongly attacks the body's own tissue. The type of tissue that is attacked in NMO is a substance called myelin. Myelin surrounds nerves in the peripheral nervous system and is the equivalent of the wrapping around a wire. See tr. 151. The parts of the body usually affected in NMO are the optical nerves and the spinal cord. The brain is usually not involved. Tr. 16. Textbooks categorize NMO with other demyelinating autoimmune diseases, such as multiple sclerosis and acute disseminated encephalomyelitis (ADEM). Exhibit 18, tabs B (AH Ropper et al., Adams and Victor's Principles of Neurology, 771-796 (8th ed. 2005) and tab C (WG Bradley et al., Neurology in Clinical Practice, 1583-1613 (5th ed. 2008)), see also tr. 28; tr. 44; tr. 152. NMO is a rare disorder. Tr. 151.

Medical science knows something about NMO that is not known about other demyelinating diseases that are presumed to be autoimmune in origin. Tr. 50. For NMO, doctors have identified a specific antibody (known as NMO-IgG) and the specific antigen that is involved. The antigen is aquaporin-4 (AQP4). Exhibit 18, tab F (VA Lennon et al., A Serum Autoantibody Marker of Neuromyelitis Optica: Distinction from Multiple Sclerosis, 364 *Lancet* 2106 (2004)); tr. 50. A relatively large amount of AQP4 is found in the eyes and the spinal cord, the parts of the body afflicted in NMO. Tr. 26 (Dr. Steel); tr. 148 (Dr. Safran). According to Dr.

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<sup>1</sup> The flu vaccine is mediated through the humoral system. Tr. 34 (Dr. Steel); tr. 158 (Dr. Safran). This fact is coincidental, and does not contribute to Ms. Davis's theory of explaining how the flu vaccine can cause NMO. Tr. 124 (Dr. Steel).

Steel, AQP4 is usually hidden from the blood. Tr. 53. The location of AQP4 is discussed more extensively in section III.B.

Scientists believe that the NMO antibody causes NMO. In a study, when the amount of the NMO-IgG increased, the disease worsened. Exhibit 18, tab J, (S. Jarius et al., Antibody to Aquaporin-4 in the Long-Term Course of Neuromyelitis Optica, 131 *Brain* 3072 (Nov. 2008); tr. 56. This correlation strongly suggests that the NMO antibody is pathological, meaning that it is a cause of NMO. Tr. 56. Dr. Safran does not dispute that the NMO antibody is pathological. Tr. 136; tr. 159. Scientists believe that the way NMO causes damage is that when the NMO antibody encounters AQP4, the NMO antibody incites a reaction leading to damage in the surrounding tissue, including myelin. Tr. 22; tr. 36.

### **C. Procedural History**

Ms. Davis filed a petition on June 28, 2007. She filed her first set of medical records and her amended petition on November 13, 2007. The amended petition asserted that Ms. Davis suffered from transverse myelitis.

Respondent addressed Ms. Davis's claims in a report filed pursuant to Vaccine Rule 4. Respondent asserted that Ms. Davis was not entitled to compensation. Respondent noted that neither medical records nor a medical opinion indicated that the flu vaccine caused any injury. Resp't Rep't, filed Jan. 11, 2008, at 8.

Ms. Davis filed a motion seeking a decision to be entered in her favor based upon the records. When respondent filed her response to Ms. Davis's motion, respondent submitted the report of Dr. Arthur Safran, his curriculum vitae, and literature upon which he relied. Exhibits A-J. Dr. Safran started practicing neurology in 1970. He is board-certified in internal medicine and in neurology. Approximately ten percent of his patients have multiple sclerosis and Dr. Safran has won a medal from the National Multiple Sclerosis Society for research in multiple sclerosis. Tr. 129-31. Dr. Safran has treated two patients who had confirmed cases of NMO. "Confirmed," in this context, means that they tested positive for the NMO antibody. Tr. 170-71.

Dr. Safran stated that Ms. Davis suffers from NMO. Exhibit A at 1. Dr. Safran indicated that the cause of the NMO may be a paraneoplastic process, that is, a consequence of Ms. Davis's breast cancer. Dr. Safran stated that NMO was not associated with the influenza vaccine. Id. at 2-3.

After respondent submitted Dr. Safran's report, Ms. Davis determined that she should obtain a report from an expert. After several enlargements of time, Ms. Davis filed the report of Dr. J. Griffith Steel with the associated literature on April 30, 2009. Ms. Davis also filed Dr. Steel's curriculum vitae. Exhibit 19.

Dr. Steel graduated from medical school in 1977 and had a residency in neurology. He became board-certified in neurology in 1982. Dr. Steel joined a large neurology practice and taught neurology until 2000, when he voluntarily decided to concentrate his time on his practice. Tr. 7-10; tr. 96-97. Within the field of neurology, Dr. Steel's efforts have tended to focus on sleep disorders. Tr. 75-78. He also has seen and sees patients with demyelinating diseases such as multiple sclerosis. Tr. 11; tr. 76. He has seen one patient with NMO. Tr. 76.

Dr. Steel agreed with Dr. Safran that the appropriate diagnosis was NMO. Exhibit 18 at 1.<sup>2</sup> Unlike Dr. Safran, Dr. Steel stated that the flu vaccine was causally connected to Ms. Davis's NMO. *Id.* at 5. It is important to note that Dr. Steel's report did not set forth a theory explaining how a flu vaccine could cause NMO. At best, Dr. Steel's report concluded that the flu vaccine "triggered the immune cascade that resulted in her Neuromyelitis optica." *Id.* at 4-5.

After Ms. Davis filed Dr. Steel's report, both parties made additional submissions. Respondent submitted a supplemental expert report from Dr. Safran, exhibit K. Dr. Safran maintained that the flu vaccine was not causally connected to Ms. Davis's NMO. Exhibit K. Ms. Davis filed additional literature. Exhibits 26-38.

A hearing was held at which Dr. Steel and Dr. Safran testified. The parties filed briefs after the hearing<sup>3</sup> and the case is ready for adjudication.

## **II. Standards for Adjudication**

There are at least three distinct parts to evaluating whether a petitioner is entitled to compensation. One part is to articulate the elements of a petitioner's case. These elements are "what" petitioner must establish. A separate part of analysis is the quantum of evidence that a petitioner must introduce, which is the burden of proof. A final aspect is the process of weighing or evaluating the evidence that is submitted. These three portions are discussed separately.

### **A. Elements of Petitioner's Case**

Ms. Davis is entitled to compensation if she establishes, among other elements, that she "sustained, or had significantly aggravated, any illness, disability, injury or condition not set forth in the Vaccine Injury Table but which was caused by a vaccine [listed in the vaccine injury table]." 42 U.S.C. § 300aa-11(c)(1)(C)(ii)(I). Here, Ms. Davis does not argue that the vaccine "significantly aggravated" any illness. The question then becomes whether Ms. Davis

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<sup>2</sup> After Ms. Davis filed Dr. Steel's report, she consistently has claimed that she suffers from NMO. Ms. Davis has not sought to revise her amended petition, which asserted that she suffers from transverse myelitis.

<sup>3</sup> Ms. Davis's reply brief largely repeats arguments from her initial brief. Thus, this decision cites to Ms. Davis's initial brief.

established that she “sustained . . . any illness, disability, injury or condition . . . which was caused by” the flu vaccine.

When a petitioner claims compensation for an injury not listed on the Vaccine Injury table, a petitioner must establish three elements. The petitioner’s

burden is to show by preponderant evidence that the vaccination brought about [the] injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.

Althen v. Sec’y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

### **B. Burden of Proof**

For the elements that petitioners are required to prove, the petitioner’s burden of proof is a preponderance of the evidence. 42 U.S.C. § 300aa–13(a)(1). The preponderance of the evidence standard, in turn, has been interpreted to mean that a fact is more likely than not. See In re Winship, 397 U.S. 358, 371-72 (1970) (Harlan, J., concurring). Proof of medical certainty is not required. Bunting v. Sec’y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between “preponderant evidence” and “medical certainty” is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec’y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master’s decision that petitioners were not entitled to compensation); see also Lampe v. Sec’y of Health & Human Servs., 219 F.3d 1357 (2000); Hodges v. Sec’y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge’s contention that the special master confused preponderance of the evidence with medical certainty).

### **C. How to Weigh Evidence**

The preceding sections explain what a petitioner is required to establish and what level of proof satisfies the petitioner’s obligation. The remaining issue is how to evaluate the evidence submitted to meet the standard of proof on those elements. Two particular issues within this general topic are the value of statements by treating physicians and the evaluation of opinions by hired experts.

Three authorities generally instruct special masters in how to evaluate evidence. The first is Congress. In enacting the National Vaccine Injury Compensation Act, Congress provided some instructions about how special masters should analyze the evidence that are codified in section 13. Among other provisions, section 13 dictates that the special master should consider

“the record as a whole.” Section 13 also provides that the special master shall consider “any diagnosis, conclusion, medical judgment or autopsy or coroner’s report which is contained in the record regarding the nature, causation, and aggravation of the petitioner’s illness, disability, injury, condition or death.” Nevertheless, “[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court.” 42 U.S.C. § 300aa–13(b).

The second authority is the United States Court of Federal Claims. Congress authorized the Court of Federal Claims to promulgate rules of procedure for cases in the Vaccine Program. 42 U.S.C. § 300aa–12(d)(2). Collectively, the judges of the Court of Federal Claims have issued the Vaccine Rules. The Vaccine Rules, in turn, provide that the special master “must consider all relevant and reliable evidence governed by principles of fundamental fairness to both parties.” Vaccine Rule 8(b)(1).

The third authority is the United States Court of Appeals for the Federal Circuit. Decisions by the Federal Circuit are binding precedent. 42 U.S.C. § 300aa–12(e). In regard to weighing evidence, some Federal Circuit cases that reviewed decisions made by special masters were relatively silent. *E.g. Lampe*, 219 F.3d at 1359-62; *Terran*, 195 F.3d at 1316 (reviewing special master’s evidentiary determination under the abuse of discretion standard). These decisions are in accord with how the Federal Circuit has reviewed challenges to causation in contexts outside of the Vaccine Program. *See Southern California Fed. Sav. & Loan Ass’n v. United States*, 422 F.3d 1319, 1337 (Fed. Cir. 2005) (affirming trial court’s finding, despite some evidence to the contrary, that FIRREA caused the bank’s recapitalization). Within the Vaccine Program, the Federal Circuit expected that special masters would “consider[] the relevant evidence of record, draw[] plausible inferences and articulate[] a rational basis for the decision.” *Hines v. Sec’y of Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991).

Further explanation about how special masters should weigh evidence came in *Capizzano v. Sec’y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006). The Federal Circuit emphasized that statements of treating doctors have a special value in the Vaccine Program. The Federal Circuit stated that “*Althen III* explained that medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether ‘a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.’” *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1280).<sup>4</sup>

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<sup>4</sup> Although statements of treating doctors are “favored,” there may be times when a statement of a treating doctor is not dispositive. The special master is required to evaluate the record, including any judgment of a treating doctor, as a whole. Section 13(b)(1); *accord Althen*, 418 F.3d at 1279. The entire record may prevent the report of one treating doctor from controlling the outcome in at least two situations.

First, the entire record may raise questions about the reliability of a conclusion reached by a treating doctor. For example, the treating doctor may have received inaccurate or incomplete information about the patient’s medical history. In the context of reviewing claims for disability

Therefore, consistent with Capizzano, the undersigned will consider with great care any statements made by treating doctors. Besides statements of treating doctors, another topic on which the Federal Circuit has instructed special masters is the method for evaluating the reliability of an expert's opinion.

In the Vaccine Program, an expert's opinion may be evaluated according to the factors identified by the United States Supreme Court in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993). Terran, 195 F.3d at 1316. As recognized in Terran, the Daubert factors for analyzing the reliability of testimony 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 enjoys general acceptance within a relevant scientific community.

Terran, 195 F.3d at 1316 n.2, citing Daubert, 509 U.S. at 592-95.

After Terran, decisions from judges of the Court of Federal Claims have consistently cited to Daubert. E.g. Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 742-45 (2009); Cedillo v. Sec'y of Health & Human Servs., 89 Fed. Cl. 158, 182 (2009), appeal docketed, No. 2009-5004 (Fed. Cir. Oct. 7, 2009); De Bazan v. Sec'y of Health & Human Servs., 70 Fed. Cl. 687, 699 n.12 (2006) ("A special master assuredly should apply the factors enumerated in Daubert in addressing the reliability of an expert witness's testimony regarding causation."), rev'd on other grounds, 539 F.3d 1347 (Fed. Cir. 2008); Campbell v. Sec'y of Health & Human Servs., 69 Fed. Cl. 775, 781 (2006); Piscopo v. Sec'y of Health & Human Servs., 66 Fed. Cl. 49, 54 (2005).

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benefits processed by the Office of Personnel Management and the Merit Systems Protection Board, the Federal Circuit has acknowledged that those fact-finders may evaluate opinions of treating doctors by considering "doubts about professional competence, contrary medical evidence, failure of the professional to consider relevant factors, lack of particularity in relating diagnosis to nature and extent of disability." Vanieken-Ryals v. Office of Personnel Management, 508 F.3d 1034, 1042 (Fed. Cir. 2007). Similarly, the Federal Circuit has stated that an expert's opinion about causation in the Vaccine Program is only as strong as the underlying basis for the opinion. Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (1994).

Second, the entire record also may indicate that treating doctors differ in their evaluations. If so, "favoring" one doctor may be the equivalent of "disfavoring" another treating doctor.



The Federal Circuit has recently made clear that after an expert's opinion has been admitted into evidence questions about the reliability of the expert's opinion may be considered by the fact-finder in weighing the opinion. i4i Ltd. Partnership v. Microsoft Corp., No. 2009-1504, 2010 WL 801705, at \*14 (Fed. Cir. Mar. 10, 2010).

“Although a Vaccine Act claimant is not required to present proof of causation to the level of scientific certainty, the special master is entitled to require some indicia of reliability to support the assertion of the expert witness.” Moberly v. Sec’y of Health & Human Servs., 592 F.3d 1315, 1324 (Fed. Cir. 2010), citing Terran, 195 F.3d at 1316 (internal citations omitted).<sup>5</sup> These “indicia of reliability” may take different forms because a special master may not require petitioners to submit any particular type of evidence to support the reliability of their expert’s theory. Althen, 418 F.3d at 1279-80. When petitioners introduce expert testimony and special masters should analyze scientific literature “not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act’s preponderant evidence standard.” Andreu, 569 F.3d at 1379. “In other words, a finding of causation in the medical community may require a much higher level of certainty than that required by the Vaccine Act to establish a prima facie case. The special master must take these differences into account when reviewing the scientific evidence.” Broekelschen v. Sec’y of Health & Human Servs., 89 Fed. Cl. 336, 343 (2009), appeal docketed, No. 2009-5132 (Fed. Cir. Sept. 28, 2009).

Generally, the Federal Circuit expects that a special master will present a reasonable basis for rejecting the opinion of one expert. Lampe, 219 F.3d 1361; Burns v. Sec’y of Health & Human Servs., 3 F.3d 415, 417 (Fed. Cir. 1993).

These standards will be used to determine whether Ms. Davis has established that she is entitled to compensation. For reasons explained in the following section, Ms. Davis has not met her burden of proof. Therefore, she is not entitled to compensation.

### **III. Analysis**

#### **A. Overview**

The first element from Althen is “a medical theory causally connecting the vaccination and the injury.” Althen, 418 F.3d at 1278. Special masters may evaluate the offered theory to determine whether the theory is reliable. Moberly, 592 F.3d at 1324.

During the hearing, Dr. Steel set forth a theory explaining how the flu vaccine can cause NMO. This theory necessarily involves the NMO-IgG antibody because, as explained above, medical science has determined that this antibody is a cause for NMO. Dr. Steel stated that AQP4 is located in cells that are not immediately adjacent to blood vessels. This separation means that antibodies, which circulated in the blood, do not usually come in contact with AQP4.

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<sup>5</sup> The petitioners in Moberly have filed a request for a rehearing en banc.

Tr. 53-54. Dr. Steel stated that the flu vaccine disrupts the wall of the blood vessels. (This wall is known as the endothelium. Tr. 121.) The break in the blood barrier, in turn, exposes the AQP4 to the NMO-IgG. Tr. 67-68. The meeting of the AQP4 and NMO-IgG starts the destruction of the myelin as discussed above. Dr. Steel referred to his theory as a “two-hit” theory because the first hit is the damage to the endothelium and the second hit is the damage to the myelin. Tr. 68; tr. 85.

Consequently, one critical step in Dr. Steel’s theory for explaining how the flu vaccine can cause NMO is that the flu vaccine can damage the endothelium. As set forth below in section III.B, Ms. Davis has failed to present any evidence – other than Dr. Steel’s own assertion – that demonstrates the reliability of this portion of Dr. Steel’s theory. Ms. Davis’s failure to carry her burden of proof on this issue means that she does not fulfill the first prong of Althen.

Although Ms. Davis failed to present preponderant proof for the reliability of the theory that the flu vaccine can damage the endothelium, Ms. Davis presented evidence attempting to show the reliability of the broader proposition that the flu vaccine can cause NMO. Ms. Davis’s primary evidence on this point is an article from the Mayo Clinic. Exhibit 18, tab D (DM Wingerchuk et al., The Clinical Course of Neuromyelitis Optica (Devic’s Syndrome), 53 Neurology 1107, 1014 (1999)). Ms. Davis also draws support from literature on the even more general point that the flu vaccine can cause other demyelinating diseases, such as ADEM. This evidence is discussed in section III.C.

#### **B. Can the Flu Vaccine Damage Endothelial Cells?**

As just mentioned, an essential step of Dr. Steel’s general explanation for how flu vaccine can cause NMO is that the flu vaccine can damage the endothelial cells. Ms. Davis has not established, by a preponderance of the evidence, the reliability of the assertion that the flu vaccine can damage endothelial cells.

Ms. Davis presented little persuasive evidence about the reliability of this step in Dr. Steel’s general theory. The statement that is most supportive of the idea that the endothelium must be breached in the development of NMO is an editorial, filed as exhibit 34 (M. Bradl & H. Lassman, Anti-Aquaporin-4 Antibodies in Neuromyelitis Optica: How to Prove their Pathogenetic Relevance?, 15 International MS Journal 75-78 (2008)). The editorialists concluded “Brain 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.” Exhibit 34 at 78.

This statement is not persuasive evidence that the flu vaccine can damage the endothelium for three reasons. First, it is an editorial, an expression of opinion. Second, even as an opinion, the editorial has a degree of uncertainty. The editorial seems to predict that “inflammation, induced by other mechanisms, may be instrumental.” The use of the term “may” suggests that this opinion is more about what is “possible,” rather than what is likely. The third

and most important reason is that the editorial does not mention the flu vaccine at all. Even if inflammation in the endothelium allowed the antibodies to reach the AQP4, this editorial does not suggest in any way that the flu vaccine induces the inflammation. Whether something breaches the endothelium does not matter. The only thing that matters in this Vaccine Program case is whether the flu vaccine damages the endothelium. For the reasons explained above, exhibit 34 is not persuasive evidence to support this proposition.

Dr. Steel's own testimony provides little persuasive evidence to support the reliability of the assertion that the flu vaccine damages the endothelium. It is true that Dr. Steel offered this opinion, which he described as "conjectural." Tr. 66. Dr. Steel explained that antigen-antibody complexes can lead to atherosclerotic plaque, which can damage the endothelium. Tr. 121-22. But, Dr. Steel did not know whether the flu vaccine can cause the inflammation that damages the endothelium. Tr. 122-23. When he was asked whether any literature supported the proposition that the flu vaccine caused the first hit, Dr. Steel replied that he did not know of any articles and would research further into the literature. Tr. 184. Ms. Davis has not filed additional literature to support Dr. Steel's proposition. Thus, Dr. Steel's opinion is not corroborated. In such situations, the opinion of an expert does not have to be accepted. General Electric. Co. v. Joiner, 522 U.S. 136, 146 (1997).

Dr. Safran did not accept the reliability of the assertion that the flu vaccine can damage the endothelium. When Dr. Safran was asked about this idea, he stated that "There's no data to support it." Tr. 177; accord tr. 142 (stating "it's an interesting idea, but I don't see the basis or the proof of any of that.>"). Dr. Safran's opinion, thus, undermines the reliability of the theory proffered by Dr. Steel.

In sum, Ms. Davis has failed to demonstrate that the two-hit theory proposed by Dr. Steel is reliable. It is important to recount that Dr. Steel explained how the flu vaccine contributes to the development of NMO by damaging the endothelium for the first time during his testimony. If Dr. Steel had expressed the two-hit theory in his report, then it is possible that additional work could have buttressed his opinion. (Alternatively, a disclosure before the hearing could have allowed respondent and Dr. Safran to present studies that would have countered the assertion that the flu vaccine can damage the endothelium.) Regardless of what might have happened, the existing record does not contain persuasive evidence establishing the reliability of the idea that the flu vaccine can damage the endothelium.

The assertion that the flu vaccine can damage the endothelium is one part of Ms. Davis's broader claim that the flu vaccine can cause NMO. Because Ms. Davis has failed to establish, by a preponderance of the evidence, one step in her proposed chain, Ms. Davis does not satisfy the first prong of Althen. See Moberly, 592 F.3d at 1324 (affirming denial of compensation on the ground that petitioners did not establish the reliability of one part of the expert's theory). Nevertheless, for the sake of completeness, some of Ms. Davis's additional evidence is reviewed in the following section.

### **C. Hypothesis That Flu Vaccine Causes NMO**

Separate from the question of whether the flu vaccine can damage the endothelium, Ms. Davis maintains that the flu vaccine can cause NMO and introduced some evidence that, according to Ms. Davis, supports the reliability of this proposition. See Pet'r Br. at 12-13. This evidence does not purport to establish a theory explaining how a vaccine can cause a demyelinating disease. Instead, the evidence introduced by Ms. Davis arguably shows that the flu vaccine can cause a demyelinating disease without setting forth a specific theory. Ms. Davis's evidence can be divided into two categories: studies about NMO and studies about other demyelinating diseases.

#### **1. Evidence Connecting Flu Vaccine and NMO Specifically**

Ms. Davis relies, in part, on one study about NMO. In 1999, doctors reviewed patients at the Mayo Clinic who were diagnosed with NMO between 1950 and 1997. The doctors identified 93 patients, meaning that, on average, approximately two new patients with NMO entered the Mayo Clinic each year. In this group of patients, two people received the swine flu vaccine before being diagnosed with NMO. Exhibit 18, tab D (Dean M. Wingerchuk et al., The Clinical Course of Neuromyelitis Optica (Devic's Syndrome), 53 *Neurology* 1107, 1111 (1999)); see also tr. 46-47.

Ms. Davis argues that this article supports Dr. Steel's general theory that the flu vaccine can cause NMO. Ms. Davis and Dr. Steel appear to reason that (1) the Wingerchuk article shows that the swine flu vaccine did cause two cases of NMO, and (2) because of this proposition, it is more likely that another type of vaccine can cause NMO. See exhibit 18 (Dr. Steel's report) at 5; tr. 46-47; Pet'r Br. at 13.

Three reasons reduce the persuasive value of the Wingerchuk article. The first and least important reason is that Dr. Wingerchuk wrote this article in 1999, before the NMO-IgG was discovered. After this antibody was discovered, Dr. Wingerchuk reviewed the data, which he had analyzed in 1999, and determined that some patients did not have NMO according to the revised definition. Exhibit 18, tab E. Thus, the patients who were identified as having developed NMO after receiving the swine flu vaccine may actually not have developed NMO. See tr. 87-88; tr. 138. Respondent advances this point. Resp't Br. at 16. This logic is correct, but has limited significance. The converse is also true. The patients who developed NMO after receiving the swine flu vaccine may meet the revised criteria for NMO. There is no information to resolve this conjecture. Thus, the revision of the diagnostic criteria for NMO, by itself, is not a strong reason for discounting the value of the Wingerchuk article.

The second reason for finding that the Wingerchuk article does not support the proposition that the flu vaccine can cause NMO is that the Wingerchuk article does not indicate that the swine flu vaccine caused the NMO. Exhibit 18, tab D (Wingerchuk) at 1111. Dr. Steel's commentary was ambiguous. At one point, Dr. Steel indicated that by mentioning the swine flu

vaccine as an antecedent event, Dr. Wingerchuk was suggesting that the swine flu vaccine may be causal. Tr. 86-87. In contrast, Dr. Steel also recognized that saying that the swine flu vaccination preceded the onset of NMO is different from saying that the swine flu vaccination caused the NMO. Tr. 47; tr. 86 (stating Dr. Wingerchuk “did not specifically state he thought these were causative.”). Dr. Safran testified that the Dr. Wingerchuk did not state that the swine flu was causal. Tr. 139. Dr. Safran did not see the listing of an antecedent event, by itself, as having much significance. To Dr. Safran, a mention may inspire future study that could provide more meaningful data. Tr. 149-51.

It is difficult to understand how Dr. Wingerchuk’s mention that two cases of NMO occurred after the swine flu vaccine constitutes a statement of causality. A gross examination of the number of cases reported in the Wingerchuk article suggests that the swine flu vaccine was not causal. On average, the Mayo Clinic reported two patients per year for 47 years. Tr. 46-47. The swine flu vaccination program was conducted in one year. Assuming that the two cases of NMO following the swine flu vaccination were the only two cases of NMO reported for that particular year, then the incidence of NMO after swine flu (two cases) would appear to be the same as the incidence of NMO without swine flu (also two cases per year). If so, the statistical information would not support an inference that the swine flu and NMO were causal.

The third reason for discounting the Wingerchuk study is that Ms. Davis has not established that information about the swine flu vaccine is transferrable to the flu vaccine. The swine flu vaccine and the flu vaccine, which Ms. Davis received, are directed against different viruses. Ms. Davis has not established, by a preponderance of the evidence, that the vaccination administered during the swine flu campaign is so similar to Ms. Davis’s flu vaccination that the adverse effects of the former should be attributed to the latter.

Thus, the article advanced by Ms. Davis to show that NMO is caused by vaccines is not persuasive evidence for that proposition. In addition, other articles controvert the proposition.

One article reports about searching for ADEM associated with vaccinations. This article referenced a study from Japan where slightly more than 38 million doses of the influenza vaccine were given between 1994 and 2004. The Japanese researchers found three cases of ADEM and nine cases of Guillain-Barré syndrome. Exhibit 26 (William Huynh et al., Post-vaccination encephalomyelitis: Literature review and illustrative case, 15 Journal of Clinical Neuroscience 1315, 1317 (2008) (citing T. Nakayama and K. Onoda K, Vaccine adverse events reported in postmarketing study of the Kitasato Institute from 1994 to 2004, 25 Vaccine 570–6 (2007)); see also tr. 80-81 (Dr. Steel discussing this study). The absence of reports about NMO from Japan is notable because NMO is more prevalent among Asians and has been studied extensively in Japan. Tr. 41. Thus, a reasonable inference is that the flu vaccine did not cause cases of NMO in Japan. This inference is reasonable because Japanese researchers would have looked for cases of NMO, and, if cases were found, the Japanese researchers would have reported them. The 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.

Ms. Davis argues that epidemiological studies cannot prove a negative. Pet'r Br. at 20-21 and 28. This argument is correct. For example, it may be true that only one out of 50 million doses of flu vaccine causes a case of NMO. If so, a study involving just 38 million doses of the flu vaccine would not discover the causative relationship.

Nevertheless, a study with 38 million doses has some evidentiary value. See Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144, 1149 (Fed. Cir. 1992) (stating "epidemiological studies are probative medical evidence relevant to causation."). The Nakayama and Onoda study suggests that if flu vaccine does cause NMO, it does so in exceedingly rare instances. The incidents would be so rare that cases were not found in Japan.

There is also an absence of articles linking flu vaccine and NMO in the United States. Dr. Steel acknowledged that he could not find any articles associating NMO with flu vaccine. Exhibit 18 at 5. He estimated that he spent at least 40 hours looking for and reading articles about NMO. Tr. 103. Dr. Safran looked for literature reporting instances of NMO associated with flu vaccine. He also asked a medical librarian at a local institution to look for articles. Neither Dr. Safran nor the librarian found any articles associating NMO with flu vaccine. Tr. 138; tr. 173-74.

Much like the study from Japan, the absence of any case reports linking NMO to flu vaccine does not automatically compel the rejection of the theory that flu vaccine can cause NMO. The absence of any case reports is just another piece of evidence that calls into question the reliability of the proposition that flu vaccine can cause NMO.

According to Dr. Steel, neurologists do not discuss the idea that flu vaccine causes NMO. Tr. 184-85. This lack of discussion suggests that the theory that flu vaccine causes NMO has not been generally accepted within the community of neurologists. See Daubert, 509 U.S. at 594 (listing whether a theory is generally accepted as one factor to determine the reliability of an expert's opinion); Terran, 195 F.3d at 1316 n.2, citing Daubert.

Finally, according to Dr. Safran, the theory that flu vaccine can cause NMO is a testable theory. Dr. Safran suggested that the theory could be tested by comparing the amount of NGO-IgG in a person before and after the person received the flu vaccine. Dr. Safran recognized that such a study would have a cost, as all studies do. Tr. 161. The fact that this study has not been undertaken is another point suggesting that the theory that flu vaccine can cause NMO is not reliable. See Daubert, 509 U.S. at 593.

In sum, the evidence about flu vaccine and NMO strongly favors a finding that the theory that the flu vaccine can cause NMO is not reliable. The primary study offered in favor of the proposition, the 1999 article by Wingerchuk, has limited value. Other evidence — the Huynh article, which reported the Nakayama and Onoda study from Japan; the lack of case reports showing that the flu vaccine is associated with NMO; the lack of discussion among neurologists; and the lack of testing of this theory — indicates that this theory is not reliable.

## **2. Evidence Connecting Flu Vaccine and Demyelinating Diseases Generally**

Ms. Davis also introduced evidence to support the proposition that flu vaccine can cause other demyelinating diseases, such as ADEM. Ms. Davis's reasoning appears to be that these other diseases are sufficiently similar to NMO that a reasonable inference is that what causes ADEM should be accepted as causing NMO. See Pet'r Br. at 8-9, 13.<sup>6</sup> Dr. Steel made a similar analogy. See tr. 74; tr. 83.

Respondent, in turn, questioned this reasoning. Respondent argued that vaccines do not cause ADEM. Resp't Br. at 16. Dr. Safran also opined that the flu vaccine does not cause multiple sclerosis or optic neuritis, which are other demyelinating diseases. Tr. 134; tr. 140.

In terms of causation, ADEM and multiple sclerosis appear to differ from NMO in some respects. This difference is reflected in the theories offered by petitioners' experts. In almost all cases in which petitioners with a demyelinating disorder such as ADEM or multiple sclerosis have sought compensation, petitioners have advanced a different theory known as molecular mimicry. E.g., Schmidt v. Sec'y of Health & Human Servs., No. 07-20V, 2009 WL 5196169, at \*5, 7, 11 (Fed. Cl. Spec. Mstr. Dec. 17, 2009) (discussing whether flu vaccine can cause transverse myelitis via molecular mimicry); Shaw v. Sec'y of Health & Human Servs., No. 01-707V, 2009 WL 3007729, at \*23 (Fed. Cl. Spec. Mstr. Aug. 31, 2009) (petitioner's expert asserted that the hepatitis B vaccine can cause demyelination by molecular mimicry) mot. for review dismissed, 88 Fed. Cl. 463 (2009). The basis for molecular mimicry is that a component of the vaccine resembles (or mimics) a component of the body, such as myelin. The theory is that the body's immune system becomes confused and wrongly attacks the myelin.

Molecular mimicry is not the theory advanced by Dr. Steel in the present case. Dr. Steel stated that the effect of the flu vaccine is "indirect." Tr. 71; tr. 85. Dr. Steel also distinguished NMO from multiple sclerosis because in multiple sclerosis the direct antigen is the myelin. Tr. 23. As explained above, the NMO, the direct antigen is AQP4. In short, the theory offered to

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<sup>6</sup> Ms. Davis also argues that because the respondent has agreed to settle some cases involving flu vaccine and demyelinating disorders, respondent should agree to compensate her. Pet'r Br. at 8-9 and 38. This argument is not correct. Settlements have no persuasive value. Hart v. Sec'y of Health & Human Servs., No. 01-357V, 2004 WL 3049766, at \*3 n. 6 (Fed. Cl. Spec. Mstr. Dec. 17, 2004); see also Advanced Cardiovascular Sys., Inc. v. Medtronic, Inc., 265 F.3d 1294, 1308 (Fed. Cir. 2001) (affirming district court's refusal to permit discovery into settlement negotiations in favor of a policy to protect settlement negotiations from being admitted as evidence, thus serving to encourage settlements.); KMS Fusion, Inc. v. United States, 29 Fed. Cl. 593, 598-599 (1997) (upholding defendant's argument that its settlement of many of the outstanding issues prior to trial should not be used as evidence that its position was not substantially justified. The court stated that such a result would have a chilling effect on settlement negotiations.)

explain how the flu vaccine causes demyelinating conditions, such as ADEM and multiple sclerosis, differs from the theory Dr. Steel offered to explain how the flu vaccine can cause NMO. Thus, there is no persuasive reason to extend any “finding” – assuming that there were one – that the flu vaccine can cause ADEM or multiple sclerosis to a case involving the flu vaccine and NMO.

Furthermore, attempting to determine in Ms. Davis’s case whether flu vaccine causes ADEM or multiple sclerosis would not be prudent. This decision can be reserved for cases in which the issue is raised directly, such as cases in which petitioners claim that the flu vaccine has caused them ADEM or cases in which petitioners claim that the flu vaccine caused them multiple sclerosis. In these future cases, the parties will address the issue more extensively than the parties did in Ms. Davis’s case.

#### **D. Ms. Davis’s Legal Arguments**

Ms. Davis presents various arguments in support of finding that she established the first prong of Althen. Ms. Davis touches on Dr. Steel’s two-hit theory only in passing. Pet’r Br. at 14 & 14 n. 19. Other arguments primarily concern the weight to be given to the evidence. For the reasons explained above, Ms. Davis’s arguments about the weight are not persuasive. Ms. Davis presents additional arguments that are primarily legal in nature. These arguments are addressed in this section.

Ms. Davis argues that in determining the reliability of an expert’s theory, special masters should consider the expert’s methodology, not the expert’s conclusion. Pet’r Br. at 19-20. For this proposition, Ms. Davis cites the Supreme Court’s decision in Daubert. Ms. Davis is correct that the method employed by the expert is a criterion that special masters should consider in evaluating the reliability of an expert’s theory. As noted by Ms. Davis, Daubert says as much.

However, the expert’s methodology is not entirely divorced from the expert’s conclusion. The Supreme Court explained “trained experts commonly extrapolate from existing data, but nothing . . . requires a district court to admit opinion evidence that is connected to existing data only by the ipse dixit of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion.” General Electric, 522 U.S. at 146. This passage indicates that trial courts should consider not only the methodology, but also the conclusion reached by the expert. Cedillo, 89 Fed. Cl. at 182; Snyder, 88 Fed. Cl. at 742-3; Moberly v. Sec’y of Health & Human Servs., 85 Fed. Cl. 571, 596 (2009), aff’d, 592 F.3d 1315 (Fed. Cir. 2010).

Even if Ms. Davis’s distinction between methodology and conclusion were valid, Ms. Davis does not explain how examining Dr. Steel’s methodology (as opposed to his conclusion) advances her case. Ms. Davis did not explain the method used by Dr. Steel in concluding that the flu vaccine can cause NMO. See Pet’r Br. at 19-20. Without a discussion of Dr. Steel’s methodology, the undersigned cannot determine whether this methodology is reliable.



A second argument concerns what evidence can satisfy the first prong of Althen. Ms. Davis maintains that “A medical theory is nothing more than biologic plausibility.” Pet’r Br. at 22. The Federal Circuit rejected this argument in Moberly, which was decided after Ms. Davis submitted her brief:

While the petitioners acknowledge that the statute requires proof of causation by a preponderance of the evidence, . . . they appear to be arguing for a more relaxed standard. They repeatedly characterize the test as whether [the child’s] condition was “likely caused” by the DPT vaccine. By that formulation, however, they appear to mean not proof of causation by the traditional “more likely than not” standard, but something closer to proof of a “plausible” or “possible” causal link between the vaccine and the injury, which is not the statutory standard.

Moberly, 592 F.3d at 1322 (citation and footnote omitted).

In this context, Ms. Davis explained how the first prong of Althen can be met. Ms. Davis identified six factors. “It is done by presenting the circumstantial evidence contained in the medical records regarding [1] timing, [2] alternate causes, and [3] the opinions of treating doctors. It is done by showing [4] case reports, [5] animal studies, and [6] supporting statements in the scientific literature.” Pet’ Br. at 22 (bracketed numbers added).

The first factor identified by Ms. Davis, timing, is relevant to determining whether a petitioner is entitled to compensation. The medically appropriate temporal relationship is the third prong of Althen. Appropriate timing, by itself, does not demonstrate that the vaccine caused the disease. Grant, 956 F.2d at 1148.

The second of Ms. Davis’s factors, the exclusion of alternate causes, does not contribute to the reliability of the expert’s theory that a vaccine can cause an injury. An expert must first “rule in,” a potential cause – that is determine why a particular substance can cause the injury for which compensation is being sought – before explaining why other potential causative factors were excluded. Ruggiero v. Warner-Lambert Co., 424 F.2d 249, 254 (2d Cir. 2005) (affirming trial court’s exclusion of an expert’s opinion on the ground that the opinion was not reliable according to the Daubert standard).

The third factor is the opinions of treating doctors. These statements are especially probative for the second prong of Althen. See Capizzano, 440 F.3d at 1326. Statements of treating doctors that a vaccine caused a person’s injury are also relevant to the reliability of an assertion that a vaccine can cause an injury. The statement that a vaccine “did cause” an injury necessarily implies that a vaccine “can cause” an injury. See id. Statements of treating doctors that a vaccine caused a person’s injury, by themselves, do not compel an award of compensation.

See Snyder, 88 Fed. Cl. at 746 n.67; see also 42 U.S.C. § 300aa-13(b)(1) (statements of treating doctors are not binding upon special masters).

In this case, none of Ms. Davis's treating doctors reported that the flu vaccine caused her NMO. Ms. Davis attempts to minimize this lack of support from her treating doctors by stating "it appear likely her physicians were never informed" that she received the flu vaccine. Pet'r Br. at 29. This assertion is not accurate. See exhibit 2 at 18, 20, 79; see also Resp't Br. at 2 (addressing Ms. Davis's assertion). Regardless of the reason for the lack of an affirmative statement from a treating doctor, Ms. Davis cannot advance the statement of a treating doctor as support for theory that the flu vaccine can cause NMO.

The remaining factors offered by Ms. Davis – case reports, animal studies and supporting statements in the scientific literature – are factors relevant to evaluating the reliability of an expert's theory. Ms. Davis has not advanced any case reports or animal studies. As discussed above, the scientific study upon which Ms. Davis primarily relies, the Wingerchuk article, has limited evidentiary value.

In conclusion, Ms. Davis has offered Dr. Steel's "two-hit" theory in which the flu vaccine damages the endothelial cells and the interaction between the NMO-IgG antibody and the AQP4 antigen damages the myelin in the spinal cord and the eyes. A preponderance of the evidence does not establish the reliability of this theory. Therefore, Ms. Davis has failed to meet her burden of proof with regard to the first prong of Althen. Because Ms. Davis must satisfy each of the prongs from Althen to be entitled to compensation, discussion of the remaining two prongs from Althen is not necessary. Similarly, whether Ms. Davis's breast cancer, a factor not related to the flu vaccine, caused her NMO is also not resolved.

#### **IV. Conclusion**

Ms. Davis suffers from NMO. Medical science understands that the interaction between the NMO-IgG antibody and the AQP4 antigen contributes to causing NMO. Ms. Davis has attempted to introduce the flu vaccine as an additional causal factor. Ms. Davis, however, has not established, by a preponderance of the evidence, that the two-hit theory offered by Dr. Steel is reliable. Thus, Ms. Davis has not fulfilled the first prong of Althen and is not entitled to compensation. The Clerk's Office is instructed to enter judgment in accord with this decision unless a motion for review is filed.

IT IS SO ORDERED.

S/ Christian J. Moran

Christian J. Moran

Special Master