In the United States Court of Federal Claims

No. 07-465V

(Filed: March 22, 2011)

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FRANCES CAMPBELL,	Vaccine case; off-table claim involving rheumatoid arthritis allegedly caused by trivalent influenza vaccine; required elements of proof for causation; first *Althen* prong; annotations of treating physicians; case reports; "biologically plausible" theory; grant of entitlement; remand for determination of compensation
Petitioner,	
v.	
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	
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OPINION AND ORDER[1]

LETTOW, Judge.

Petitioner, Frances Campbell, seeks review of a decision by a special master dated October 27, 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. Campbell alleges that her receipt of trivalent influenza vaccine in 2003 caused the onset of her rheumatoid arthritis. *See Campbell v. Secretary of Health & Human Servs.*, No. 07-465 (Fed. Cl. Spec. Mstr. Oct. 27, 2010), ECF No. 87 ("Second Entitlement Decision"). Previously, this court had considered, vacated, and remanded an earlier decision by the special master, which decision had also denied Ms. Campbell compensation. *See Campbell v. Secretary of Health & Human Servs.*, 90 Fed. Cl. 369, 388 (2009) (vacating and remanding *Campbell v. Secretary of Health & Human Servs.*,

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

2009 WL 2252550 (Fed. Cl. Spec. Mstr. July 7, 2009) ("First Entitlement Decision")). Upon remand, the special master concluded that "the record as a whole does not support a finding that Ms. Campbell has established, by a preponderance of the evidence, a theory causally connecting [the] flu vaccine to rheumatoid arthritis." Second Entitlement Decision at 9.

FACTS[2]

A. *Rheumatoid Arthritis*

Rheumatoid arthritis is "a chronic systemic disease primarily of the joints, usually polyarticular [('affecting many joints')], marked by inflammatory changes in the synovial membranes and articular structures and by muscle atrophy and rarefaction [('diminution in density and weight')] of the bones. In late stages, deformity and ankylosis [('immobility and consolidation of a joint')] develop. The cause is unknown, but autoimmune mechanisms and virus infection have been postulated." *Dorland's Illustrated Medical Dictionary* 152-59 (31st ed. 2007) (definition interrupted by photographic exemplars); *see also Dorland's* at 94, 1509, and 1617 (definitions of terms).[3] The following seven criteria for the classification of rheumatoid arthritis as developed by the American College of Rheumatology (formerly the American Rheumatology Association) appeared to be accepted by both parties: (1) "[m]orning stiffness in and around the joints, lasting at least [one] hour before maximal improvement;" (2) "[a]t least [three] joint areas simultaneously hav[ing] had soft tissue swelling or fluid;" (3) at least one of the swollen joint areas is in a wrist, or hand, or certain other areas; (4) symmetry of the arthritis on both sides of the body; (5) "[r]heumatoid nodules;"[4] (6) demonstration of abnormal amounts of "serum rheumatoid factor;"[5] and (7) erosions in or adjacent to the joints[6] visible by X-ray.

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[2]The factual background to this case has been truncated from the more detailed factual account provided in this court's prior decision. *See Campbell*, 90 Fed. Cl. at 373-77. In this recitation of 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 __." Upon remand, the special master offered the parties an opportunity to adduce additional evidence, but both declined.

[3]"Autoimmune" means "pertaining to a condition characterized by a specific humoral or cell-meditated immune response against constituents of the body's own tissue (self antigens or autoantigens)." *Dorland's* at 183; *see also id*. at 886 (humoral "pertain[s] to elements dissolved in the blood or body fluids").

[4]Dr. Robert Lightfoot, the government's expert, described "rheumatoid nodules" as "small inflammatory nodules that occur over pressure points, typically [in] the elbow." Tr. 272:4-6.

[5]"A rheumatoid factor test measures the amount of . . . proteins [in blood] produced by [the] immune system that can attack healthy tissue in [the] body." Mayo Clinic, *Rheumatoid Factor Definition*, http://www.mayoclinic.com/health/rheumatoid factor/MY00241 (last visited Mar. 18, 2011).

American College of Rheumatology, *1987 Criteria for the Classification of Acute Arthritis of Rheumatoid Arthritis*, ://www. rheumatology.org/practice/clinical/classification/ra/ra.asp (last visited Mar. 18, 2011) ("1987 Criteria"); *see* Tr. 61:25 to 62:22 (Test. of Dr. Arthur E. Brawer, petitioner's expert), 270:5 to 272:10 (Lightfoot).[7]

"For classification purposes, a patient shall be said to have rheumatoid arthritis if he [or] she has satisfied at least [four] [of] these [seven] criteria. Criteria 1 through 4 must have been present for at least [six] weeks." 1987 Criteria*; see* Tr: 115:21-24 (Brawer) (agreeing that "to have a diagnosis of rheumatoid arthritis under those [criteria] you have to [meet] at least four out of seven [criteria]"); *see also* Tr. 62:17-22 (Brawer) ("[W]hen you have pain and swelling in small and large joints symmetrically . . . [and] morning stiffness and fatigue and you have it for six to eight weeks or longer, you have rheumatoid arthritis until proven otherwise."). It is not always the case that a diagnosis of rheumatoid arthritis can be made within six to eight weeks of the initial onset of the condition, however. The experts agreed that "it may take time to prove someone has rheumatoid arthritis. Very often, [with] mild rheumatoid disease, you don't really know that's what it is until several months or maybe a year have gone by and all the other possibilities have fallen by the wayside[;] in retrospect you make the diagnosis." Tr. 230:19-24 (Lightfoot).

Other arthritic symptoms are also of relevance to this case. Acute arthritis is "marked by pain, heat, redness, and swelling, due to inflammation, infection or trauma," and reactive arthritis is "arthritis after an infection." *Dorland's* at 152. According to Dr. Lightfoot, reactive arthritis cannot "turn into rheumatoid arthritis," but "sometimes rheumatoid arthritis can start subtly" and "early on you couldn't tell reactive arthritis from rheumatoid arthritis, if the [rheumatoid arthritis] was starting in just a few joints." Tr. 319:4-7, 19-21 (Lightfoot). In those circumstances, Dr. Lightfoot testified, one would conduct a "rheumatoid factor" test. Tr. 319:10 (Lightfoot). If that test came back positive, a diagnosis of rheumatoid arthritis can be made, even in a patient experiencing "oligoasymmetrical" ("oligo" meaning "few, little, or scanty, . . . less than normal," *Dorland's* at 1337) arthritis, Tr. 319:8-10, 22, 320:1 (Lightfoot); however, a negative result would not rule out a diagnosis of rheumatoid arthritis, as "seronegative rheumatoid arthritis . . . constitutes 20 percent of rheumatoids." Tr. 319:13-16 (Lightfoot).

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[6]According to Dr. Lightfoot, joint erosions are the result of "inflammatory tissue in the joint burrow[ing] in[to] [the joint] like a tumor and caus[ing] little caves in the joint structure." Tr. 272:7-10.

[7]The American College of Rheumatology updated the diagnostic criteria for rheumatoid arthritis in 2010. *See* American College of Rheumatology, *The 2010 ACR-EULAR Classification Criteria for Rheumatoid Arthritis*, http://www.rheumatology.org/practice/clinical/classification/ra/ra_2010.asp (last visited Mar. 18, 2011). Because the 1987 criteria were used in diagnosing Ms. Campbell's rheumatoid arthritis and were addressed by Drs. Lightfoot and Brawer during the course of their expert testimony in this case, the court will conduct its review employing the 1987 criteria.

B. *Ms. Campbell's Receipt of Influenza Vaccine and her Subsequent Medical History*

On December 4, 2003, Ms. Campbell received trivalent influenza[8] and pneumonococcal vaccines[9] from her primary care physician, Dr. Thad Jackson. *Campbell*, 90 Fed. Cl. at 373. Four days later, on December 8, 2003, Ms. Campbell returned to Dr. Jackson's office, reporting that she was in her usual state of health until Sunday, December 7, 2003, at which time she was bumped by three teenagers leaving church. *Id.* Ms. Campbell reported that within a few hours of this incident she began to suffer from pain in her left arm that radiated up her left shoulder, and later experienced similar pain in her right arm accompanied by difficulty swallowing and chest heaviness. *Id.* at 373-74. Upon examining Ms. Campbell's upper extremities, Dr. Jackson observed systemic swelling and warmth in both of Ms. Campbell's upper extremities and diminished grip strength. *Id.* at 374. Dr. Jackson admitted Ms. Campbell to Grayling Mercy Hospital ("Mercy Hospital") on that same day for further evaluation and medical testing. *Id.*

At Mercy Hospital, Ms. Campbell underwent an array of tests and evaluations, including an examination by an orthopedist, Dr. Darius Davina, on December 9, 2003. *Campbell*, 90 Fed. Cl. at 374. Dr. Divina noted that both of Ms. Campbell's shoulders appeared "somewhat swollen and slightly warm to [the] touch." R. Ex. 2 at 200110. While unable to ascertain the cause of Ms. Campbell's pain, Dr. Divina noted that two conditions to "rule out" were (1) "acute inflammatory response to vaccine" and (2) "septic bursitis." R. Ex. 2 at 200109.[10] Dr. Divina noted, however, that he did not "feel at the present time" that Ms. Campbell was suffering from "septic bursitis." R. Ex. 2 at 200110. Ms. Campbell tested positive for antinuclear antibodies ("ANA")[11] and had a rheumatoid factor of 20[12] during her stay at Mercy Hospital. *Campbell*, 90

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[8]The influenza vaccine Ms. Campbell received is "a killed virus vaccine . . . [the composition of which] is changed each year in response to antigenic shifts and changes in prevalence of influenza virus strains." *Dorland's* at 2044. At various points in the testimony, the vaccine is referred to as "dead" or "inactiv[e]." *See* Tr. 26:3-9 (Brawer) (The vaccine has "been rendered dead . . . inactivated, in other words, [a]nd portions of the protein coating are taken to make the vaccine. And these proteins are what we call antigens."); Tr. 290:18-19 (Lightfoot) (The influenza vaccine is "a piece of the outside wall of a dead virus.").

[9]Ms. Campbell's receipt of the pneumonococcal vaccine is not alleged to have been a cause of her rheumatoid arthritis.

[10]Septic bursitis is "inflammation of a bursa . . . that [is] caused by infection, usually the result of bacterial inoculation due to trauma." *Dorland's* at 269. A bursa is "a sac or saclike cavity filled with a viscid fluid and situated at places in the tissues at which friction would otherwise develop." *Id.* at 266.

[11]Antinuclear antibodies are "substances produced by the immune system that attack the body's own tissues." U.S. National Library of Medicine and National Institutes of Health, MedlinePlus, *Antinuclear Antibody Panel*, http://www.nlm.nih.gov/medlineplus/ency/article/003535.htm (last visited Mar. 18, 2011).

Fed. Cl. at 374. After her pain diminished, Ms. Campbell was discharged on December 10, 2003, with a diagnosis of "[a]cute bilateral upper extremity inflammatory arthritis" of unknown cause. *Id*.; R. Ex. 2 at 200092.

Following her discharge from Mercy Hospital, Ms. Campbell continued to experience pain, swelling, and weakness in her upper extremities which drove her to visit the emergency room on December 12, 2003, and to return to Dr. Jackson on December 19, 2003. *Campbell*, 90 Fed. Cl. at 374. The emergency room physician who examined Ms. Campbell believed that her pain was due to inflammatory arthritis. *Id.* Dr. Jackson found that Ms. Campbell was experiencing leg weakness, as well as positive rheumatoid arthritis ("RA") and ANA profiles — a medical profile which prompted Dr. Jackson to consult with Dr. Jay Jones of Physical Medicine and Rehab and Dr. Diane Donley of Neurology, both at Munson Medical Center ("Munson Medical"). *Id.* at 374-75. Dr. Jackson admitted Ms. Campbell to Munson Medical for neurological and rheumatological testing. *Id.* at 375. The rheumatological test results revealed "[p]ositive serologies,[13] polyarthiritis[,] and weakness in [Ms. Campbell,] post-influenza and [p]neumovax vaccines." *Id.* Those results prompted Dr. Donley to contact Dr. Karen Gilhooly, a rheumatologist. *Id.*

Dr. Gilhooly found tenderness along Ms. Campbell's joints in her fingers and hands and in her hip, knee, and ankles, but no synovitus (inflammation of the joint lining), and opined that Ms. Campbell could be suffering from a rheumatological reaction to her recent immunizations. *Campbell*, 90 Fed. Cl. at 375. Dr. Richard Ball, who also examined Ms. Campbell during her admission to Munson Medical, concurred with Dr. Gilhooly's opinion that Ms. Campbell had a "rheumatological problem, probably precipitated/exacerbated by her recent [p]neumovax/flu vaccines." *Id.* Thereafter, Ms. Campbell had multiple follow-up appointments both with Dr. Jackson and Dr. Gilhooly for her continuing tenderness, pain, and stiffness of the joints. *Id.* at 376-77. Eventually, Ms. Campbell was diagnosed with rheumatoid arthritis. *Id.* at 377.[14]

C. *The Special Master's First Decision*

Ms. Campbell filed a petition for vaccine-injury compensation on June 28, 2007. *Campbell*, 90 Fed. Cl. at 377. At the entitlement hearing that occurred in New York City on October 21, 2008, Dr. Arthur Brawer testified in support of Ms. Campbell's petition and offered six theories that could explain how the influenza vaccine could cause rheumatoid arthritis. *Id.* However, Dr. Brawer primarily focused upon two theories: first, that "antigens of infectious

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[12]According to Dr. Lightfoot, a rheumatoid factor of approximately 20 is normal or "negative" and a rheumatoid factor of 50 or 80 or higher can be considered abnormal or "positive." Tr. 413:21-25 (Lightfoot).

[13]Serologies indicate "the presence of antibodies against a microorganism." U.S. National Library of Medicine and National Institutes of Health, MedlinePlus, *Serology*, http://www.nlm.nih.gov/medlineplus/ency/article/003511.htm (last visited Mar. 18, 2011).

[14]Neither party disputes the accuracy of this diagnosis.

agents can cross-react with self-antigens present on immunocompetent cells, thereby triggering inflammatory systemic connective tissue diseases such as [r]heumatoid [a]rthritis," *id.*,[15] and second, "that the vaccine leads to the production of immune complexes," which are capable of triggering both innate and adaptive immune responses which can become autonomous. First Entitlement Decision at *9. Relying upon the notes and impressions of Ms. Campbell's treating physicians, the course of Ms. Campbell's illness, case reports of rheumatoid arthritis developing after vaccination, and these theories, Dr. Brawer concluded that Ms. Campbell's condition was in fact caused by the influenza vaccination. Dr. Lightfoot, the government's expert, testified that he did not believe the vaccine caused Ms. Campbell's rheumatoid arthritis. Tr. 230:5-8. Overall, Dr. Lightfoot rejected Dr. Brawer's first principal theory primarily because that theory had not been "proved or disproved," Tr. 326:24 to 327:1, and because it has not been proven or disproven that an inactive vaccine — such as the influenza vaccine — could cause an aberrant immunological response, Tr. 360:15 to 361:10, 364:20 to 366:5. Dr. Lightfoot also discounted Dr. Brawer's second theory, the immune-complex theory, testifying that "no one had ever shown in a[] [local] injection of a molecule or two from an influenza virus . . . evidence [of a] circulating immune complex[,]" but he agreed that it is "a reasonable theory to guess at." Tr. 328:6-12 (Lightfoot). Dr. Lightfoot also opined that many people will develop rheumatoid arthritis subsequent to an influenza vaccination purely by chance. Tr. 423:16 to 427:9.

The special master denied the petition on July 7, 2009, finding that Ms. Campbell had failed to establish by a preponderance of the evidence that the influenza vaccine caused her rheumatoid arthritis. *See* First Entitlement Decision at *8-*15. As a prelude to his analysis of the parties' positions on causation, the special master conducted a "[g]eneral [e]valuation of the [e]xperts," *id*. at *7-*8, concluding that Dr. Lightfoot was more "persuasive" than Dr. Brawer. *Id.* at *7. This evaluation underpinned the special master's "analysis of the three factors from *Althen* [*v. Secretary of Health & Human Servs*., 418 F.3d 1274 (Fed. Cir. 2005)]." *Id*. Regarding those factors, the special master concluded that Dr. Brawer did not sufficiently explain his theories as to how the influenza vaccine can cause rheumatoid arthritis and had failed to connect those theories to Ms. Campbell's particular case. *Id.* at *9-*10. The special master likewise concluded that statements made by Ms. Campbell's treating physicians did not support causation, and he gave little weight to the case reports submitted by Dr. Brawer in support of his hypotheses. *Id.* at *10-*15.

D. *Prior Judicial Decision*

After Ms. Campbell sought review of the special master's decision, the court determined that the special master wrongfully "'cloak[ed]' his rejection of Ms. Campbell's theory of causation in a credibility determination regarding Ms. Campbell's expert witness, Dr. Brawer[,]" and consequently had run afoul of the Federal Circuit's precedent regarding the use of credibility determinations in vaccine cases. *Campbell*, 90 Fed. Cl. at 383 (citing *Andreu v. Secretary of*

[15]As applied to Ms. Campbell's condition, the theory would postulate that "the molecular structure of a part or parts of the trivalent influenza vaccine resembled the structure of Ms. Campbell's synovial tissue or fluid because of her genomic makeup and engendered an autoimmune response." *Campbell*, 90 Fed. Cl. 384. This theory has been described in the past by the vernacular term "molecular mimicry." *Id*. at 384 n.30.

Health & Human Servs., 569 F.3d 1367 (Fed. Cir. 2009)). Dr. Brawer's candor was not in dispute, and there was no factual basis for employing the guise of a credibility determination to reject the merits of the theories proffered by Dr. Brawer. *Campbell*, 569 F.3d at 383. Because that erroneous determination had permeated the special master's analysis of Ms. Campbell's claim, his decision could not be sustained. *Id.* at 384.

The court also found troublesome the special master's reliance upon the absence of any proof of specific biological mechanisms generated by way of genetic testing of Ms. Campbell and the influenza vaccine administered to her, and the lack of epidemiological evidence rising to the level of scientific certainty. *Campbell*, 90 Fed. Cl. at 384-86. The court concluded that "to the extent that the special master reached beyond his credibility findings to draw conclusions about the validity of the principal medical theory propounded on behalf of Ms. Campbell, he proceeded on erroneous grounds [because] [t]esting and proof of specific biological mechanisms are not required in a case of this type, nor do epidemiological studies need to satisfy the requirements for scientific certainty as to causation." *Id.* at 386.

The court likewise addressed the special master's treatment of the clinical observations and diagnoses of Ms. Campbell's treating physicians, who had either proposed the possibility or stated that Ms. Campbell's rheumatoid arthritis was caused or exacerbated by her receipt of influenza vaccine. *Campbell*, 90 Fed. Cl. at 386. The court noted that the special master had wrongly discounted such statements as "ambiguous" and had "dr[a]w[n] every inference against [Ms. Campbell]." *Id*. The special master was not justified in discounting statements by treating physicians that Ms. Campbell initially appeared to have reactive, inflammatory, or acute arthritis, rather than rheumatoid arthritis, in light of the six to eight weeks of observation normally required for a diagnosis of rheumatoid arthritis. *Id.* at 386-87. The court concluded that "the special master's finding that there was no temporal association between Ms. Campbell's rheumatoid arthritis and the administration of trivalent influenza vaccine" could not stand on the record. *Id.* at 387. The court vacated the special master's decision, making "no affirmative findings of its own[,]" *id.* at 388, and remanded Ms. Campbell's case for further proceedings.

E. *The Special Master's Second Decision*

Upon remand, the special master once again denied Ms. Campbell's petition for compensation. While accepting that Dr. Brawer's testimony was indeed given in candor, the special master noted that such a determination does not necessitate a finding of reliability as to, or acceptance of, Dr. Brawer's theories of causation. *See* Second Entitlement Decision at 4. Pointing to *Moberly v. Secretary of Health & Human Servs.*, 592 F.3d 1315 (Fed. Cir. 2010), issued subsequent to the court's remand order, the special master observed that a special master is entitled to "require some indicia of reliability to support the assertion of the expert witness." Second Entitlement Decision at 5 (quoting *Moberly*, 592 F.3d at 1324). Concluding that Ms. Campbell's claim rested primarily upon Dr. Brawer's medical experience, the medical literature submitted by Dr. Brawer, and the statements of Ms. Campbell's treating physicians as support for Dr. Brawer's medical theory, the special master turned to a review of these three sources of corroboration.

The special master found that Dr. Brawer's medical experience could not provide adequate support for his theory because the "credentials of Dr. Lightfoot . . . match, and, in many respects, exceed Dr. Brawer's." Second Entitlement Decision at 5. The special master further noted that "even if it were true that Dr. Brawer had greater experience than Dr. Lightfoot, this difference in qualifications would not compel a finding that Dr. Brawer's opinion is persuasive." *Id.* at 6.

The special master also concluded that "[t]he medical articles cited by Dr. Brawer do not constitute a sufficient basis for finding Dr. Brawer's opinion that the flu vaccine can cause rheumatoid arthritis persuasive," noting that Ms. Campbell's briefs did not "explain[] how the exhibits make Dr. Brawer's opinion more likely than not" and that the government presented arguments that the literature did not support Ms. Campbell's claims. Second Entitlement Decision at 6. Respecting the case reports, the special master relied upon his prior decision and stated that "[t]he inability to distinguish causation from coincidence reduces the[ir] evidentiary value." *Id.* at 7. The special master then turned to two of the review articles submitted by Dr. Brawer. One article, Ami Schattner, *Consequence or Coincidence? The Occurrence, Pathogenesis and Significance of Autoimmune Manifestations after Viral Vaccines*, 23 SCIENCE DIRECT 3876 (2005), R. Ex. 13, listed conditions that have been associated with the flu vaccine. The other article, Yehda Schoenfeld and A. Aron-Maor, *Vaccination and Autoimmunity – "Vaccinosis," A Dangerous Liaison?* 14 J. OF AUTOIMMUNITY 1 (2000), R. Ex. 10, listed vaccines that have been associated with arthritic conditions. Based upon omissions, because the former did not list rheumatoid arthritis as such a condition and the latter did not mention the influenza vaccine, the special master found that these articles actually "suggest that the flu vaccine is unlikely to cause rheumatoid arthritis." *Id.* at 8. Concluding from these two articles that "the balance of medical literature d[id] not support [Ms. Campbell's] expert's [first] theory," the special master opined that he could and would "find that theory unreliable." *Id.*

The special master likewise concluded that the reports of Ms. Campbell's treating physicians did not support the theories proffered by Dr. Brawer, finding that "[e]ven if it were assumed that Dr. Gilhooly, the rheumatologist, and Dr. Jackson, the general physician, stated that the flu vaccine caused Ms. Campbell's rheumatoid arthritis, the views of the treating doctors are not dispositive." Second Entitlement Decision at 8. The special master further discounted any possible statements about causation by the treating physicians because none of Dr. Brawer's theories of causation were "discussed by either Dr. Gilhooly or Dr. Jackson." *Id.* at 9.

STANDARDS FOR REVIEW

Upon reviewing a special master's decision, this court must "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." 42 U.S.C. § 300aa-12(e)(2)(B). "[R]eversible 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 marks omitted) (citing *Hines ex rel. Sevier v. Secretary of Health & Human Servs.*, 940 F.2d 1518, 1528 (Fed. Cir. 1991)). The court does not "reweigh the factual evidence," "assess whether the special master correctly evaluated the evidence[,]" or "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)).

The Vaccine Act provides for two means of recovery: table claims and off-table claims. "In a table claim, a claimant who shows that he or she received a vaccination listed in the Vaccine Injury Table ("table"), 42 U.S.C. § 300aa-14, and suffered an injury listed in the table within a prescribed period is afforded a presumption of causation." *Andreu*, 569 F.3d at 1374. In an off-table case, such as Ms. Campbell's, a petitioner must prove actual causation by a preponderance of the evidence. *See Moberly*, 592 F.3d at 1321. To prove actual causation, a petitioner must "show that the vaccine was 'not only a but-for cause of the injury but also a substantial factor in bringing about the injury.'" *Id.* at 1321-22 (quoting *Shyface v. Secretary of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)). A petitioner satisfies this burden if he or she provides, by preponderant evidence,

> (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 proximate temporal relationship between vaccination and injury.

Althen, 418 F.3d at 1278.[16] A plaintiff must satisfy all three of *Althen*'s prongs by preponderant evidence. *See Capizzano v. Secretary of Health & Human Servs.*, 440 F.3d 1317, 1326 (Fed. Cir. 2006). In making this showing, "evidence used to satisfy one of the *Althen* . . . prongs can[] overlap to satisfy another prong." *Id.*[17] "A petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case, although the explanation need only be 'legally probable, not medically or scientifically certain.'" *Moberly*, 592 F.3d at 1322 (quoting *Knudsen v. Secretary of Health & Human Servs.*, 35 F.3d 543, 548-49 (Fed. Cir. 1994)).

The preponderant-evidence standard requires that a petitioner demonstrate proof "by a simple preponderance, of 'more probable than not' causation." *Althen*, 418 F.3d at 1279 (citing *Hellebrand v. Secretary of Health & Human Servs.*, 999 F.2d 1565, 1572-73 (Fed. Cir. 1993)). This standard "simply requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence." *Moberly*, 592 F.3d at 1322 n.2 (quoting *Concrete Pipe & Prods. of Cal., Inc. v. Construction Laborers Pension Trust for S. Cal.*, 508 U.S. 602, 622

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[16]In the special master's first entitlement decision, he concluded that Ms. Campbell had failed to provide sufficient proof as to all three prongs of *Althen*. First Entitlement Decision at *15. The court set aside those conclusions in its initial decision. *Campbell*, 90 Fed. Cl. at 384-88. In the second entitlement decision, the special master addressed only the first prong of *Althen*. Second Entitlement Decision at 9.

[17]In *Capizzano*, the petitioner had satisfied the first and third prongs of *Althen*. 440 F.3d at 1326 ("[T]he first prong of the *Althen III* test was satisfied by the finding that the hepatitis B vaccine can cause RA [rheumatoid arthritis]. The third prong was satisfied by the finding that Ms. Capizzano's RA appeared within days of receiving the vaccine.") (citations omitted). The court concluded that the special master had "erred in not considering the opinions of the treating physicians who concluded that the vaccine was the cause of Ms. Capizzano's injury." *Id.*

(1993)). As applied to vaccine cases, the preponderant standard means that although a claimant must provide a plausible medical theory, a claimant need not offer "identification and proof of specific biological mechanisms[—a requirement that] would be inconsistent with the purpose and nature of the vaccine compensation program." *Knudsen*, 35 F.3d at 549; *see also Capizzano*, 440 F.3d at 1325; *Althen*, 418 F.3d at 1280.[18] Thus, "[t]he fact that a link between a vaccine and

[18]In his second decision denying Ms. Campbell's petition, the special master commented that "Ms. Campbell's initial brief advanced the argument that Dr. Brawer's theories are 'biologically plausible.' Approximately one week before Ms. Campbell filed th[at] brief, the Federal Circuit rejected an argument that petitioners in the Vaccine Act program satisfy their burden of proof [as to the first prong of *Althen*] by presenting a 'biologically plausible' theory." *See* Second Entitlement Decision at 5 n.5 (quoting *Moberly*, 592 F.3d at 1322). The special master is correct that a bare theory is insufficient to satisfy the *Althen* causation test, even where accompanied by a proximate temporal association. The cited commentary by the Federal Circuit in *Moberly* was as follows:

> 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 claimant'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. In this passage, the Federal Circuit was reiterating the well-settled preponderant-evidence standard for proof of causation in off-table claims. A "biologically plausible" theory connecting the vaccination to the injury can allow a petitioner to move forward after having made a satisfactory showing as to *one* of the prongs. *See Andreu*, 569 F.3d at 1375 ("The first prong [of *Althen*] was satisfied because [the petitioner's expert] presented a 'biologically plausible' theory establishing that toxins in the whole-cell pertussis vaccine can cause seizures."). Notably, what is at issue respecting the first prong of *Althen* is a "theory," *Althen*, 418 F.3d at 1278, which, by definition, can be a hypothesis that is offered, propounded, or accepted as accounting for the known facts. *See Webster's Third New International Dictionary* 2371 (2002) (defining "theory" as "a judgment, conception, proposition, or formula (as relating to the nature, action, cause, or origin of a phenomenon or group of phenomenon) formed by a speculation or deduction or by abstraction and generalization from facts").

Instructively, as the Federal Circuit observed in *Capizzano*, the prongs of *Althen* are not to be considered independently of each other in making this causation determination. *See Capizzano*, 440 F.3d at 1326 ("We see no reason why evidence used to satisfy one of the *Althen III* prongs cannot overlap to satisfy another prong."). In *Moberly*, for example, the treating physicians had noted the temporal proximity of the vaccination to the onset of an adverse condition (seizures), but had declined to link the condition to the vaccination. 592 F.3d at 1323; *see also id*. at 1325 ("In this case, . . . there was no treating physician evidence that supported the claim of causation.").

a particular injury is a 'sequence hithero unproven in medicine' 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); *see also Capizzano*, 440 F.3d at 1324.

The Vaccine Act provides that a claimant may satisfy the preponderance standard "by medical records or by medical opinion." 42 U.S.C. § 300aa-13(a)(1). Accordingly, a special master may not require "epidemiologic studies . . . or general acceptance in the scientific or medical communities" as such prerequisites "impermissibly raise[] a claimant's burden." *Andreu*, 569 F.3d at 1378 (quoting *Capizzano*, 440 F.3d at 1325-26); *see also Moberly*, 592 F.3d at 1325; *Althen*, 418 F.3d at 1280 (requiring a claimant to provide "medical literature" "contravenes section 300aa-13(a)(1)'s allowance of medical opinion as proof."). Nor may the special master require a claimant to present proof of pathological markers or genetic predisposition to an adverse immunological response. *See Capizzano*, 440 F.3d at 1325-26. To the contrary, the Federal Circuit has made clear that "the use of circumstantial evidence [is] envisioned by the preponderance standard." *Althen*, 418 F.3d at 1280; *see also Andreu*, 569 F.3d at 1379 ("[A] paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery."). "Thus, for example, causation can be found in vaccine cases based on epidemiological evidence and the clinical picture regarding the particular [claimant] without detailed medical and scientific exposition on the biological mechanisms." *Knudsen*, 35 F.3d at 549.

Equally importantly, special masters in Vaccine Act cases are "entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. And, certainly where epidemiological evidence or medical literature is submitted, "the special master can consider it in reaching an informed judgment as to whether a particular vaccination likely caused a particular injury." *Andreu*, 569 F.3d at 1379. Such evidence, however, must be viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380.

In sum, there are no "hard and fast *per se* scientific or medical rules" for finding causation under the Vaccine Act. *Knudsen*, 35 F.3d at 548. It is evident, however, that "[t]he Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims[,]" *id.* at 549, and "close calls regarding causation are [to be] resolved in favor of injured claimants[,]" *Althen*, 418 F.3d at 1280.

ANALYSIS

A. *A Biologically Plausible Theory of Causation*

1. *Expert Testimony.*[19]

[19]Both parties' experts, Dr. Brawer and Dr. Lightfoot, are experienced and accomplished rheumatologists, who have evaluated, diagnosed, and treated thousands of patients over the

As noted, Ms. Campbell alleges that Dr. Brawer presented at least two biologically plausible theories of causation: antigen cross-reactions and immune complexes. As to antigen cross-reactions, Dr. Brawer explained:

> [A] virus has essentially got a protein capsid . . . on the outside. . . . [P]ortions of the protein coating are taken to make the vaccine. . . . [T]hese proteins are what we call antigens. . . . [I]t has been known for a long time that certain of these . . . antigens of the viral coats are similar to certain self-proteins or self-antigens in the body. . . . [I]f the immune system mounts a response to the viral antigens or the viral proteins, it could produce cross-reacting antibodies that start to attack the body's self-antigens.

Tr. 25:24-25, 26:8-9, 26:19 to 27:1 (Brawer).[20] Later in the hearing, Dr. Brawer elaborated upon the theory:

> [A]n antigen-presenting cell like a macrophage will take up the foreign antigen, the foreign protein, process it and put pieces of it on its surface. . . .
>
> It then has to present this to a cell that is capable of recognizing it and will trigger a proliferation and an appropriate immune response.
>
> How it presents the antigen is the crux of the issue because it presents the antigen in the arms of what are called Class 2 molecules.
>
> The HLA system stands for human leukocyte antigens. And everybody has molecules on the surface of all their body cells and in particular HLA Class 2 molecules are also present . . . on the immunocompetent cells.

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course of their respective careers. *See Campbell*, 90 Fed. Cl. at 382-83 (recounting the experts' education and experience). Dr. Brawer's testimony that he had encountered "probably [fifty] cases of rheumatoid arthritis initiated by various types of vaccinations, viral vaccinations[,]" Tr. 208:7-9 (Brawer), and that he had "seen maybe a half a dozen cases of influenza vaccine causing rheumatoid arthritis[,]" Tr. 207:19-21 (Brawer), confers a measure of reliability to his testimony regarding causation in Ms. Campbell's case. Neither physician's experience, however, necessitates a finding for either party. *See, e.g., Adams v. Secretary of Health & Human Servs.*, 76 Fed. Cl. 23, 40 (2007) ("[A]ssuming *arguendo* that the [g]overnment's expert had more experience . . . , that fact is irrelevant to whether [p]etitioner's expert proffered a 'medical theory causally connecting the vaccination and the injury.'" (quoting *Capizzano*, 440 F.3d at 1324)).

[20] Antigen cross-reaction has been used persuasively as a theory of causation in prior Vaccine Act cases, including the *Althen* case. *See Althen v. Secretary of Health & Human Servs.*, 58 Fed. Cl. 270, 276 (2003), *aff'd*, 418 F.3d at 1282. The government asserts that "in other cases where the theory [of molecular mimicry, *i.e.*, antigen cross-reactions] has been accepted . . . it has been . . . where there is evidence of the antigen within the vaccine responding to the cell's antigens in the body." Hr'g Tr. 25:19-23 (Jan. 27, 2011). This contention is not correct; in *Althen* the petitioner's expert did not identify the specific antigens that were cross-reacting to create an abnormal immunological response. *See Althen v. Secretary of Health & Human Servs.*, 2003 WL 21439669, at *4-*5 (Fed. Cl. Spec. Mstr. June 3, 2003).

> [T]he macrophage has to take this material and put it in the arms of this Class 2 molecule so it can present it to the T lymphocyte to initiate the immune response. There are certain areas, certain amino acid sequences to the proteins of these Class 2 molecules, of the arms that the foreign protein is sitting in, that seem to be crucial as to what kind of response is going to be made. Is it only going to be to the foreign antigen or is it going to be to the foreign antigen and the body and also what kind of process will persist[?]
>
> Now as it turns out and has been known for quite a while, for probably a decade or more, the initial immune response to something foreign is both. The body mounts an immune response not only to the foreign antigen but also to its HLA antigens, to the molecules sitting on the surface of that presenting cell. . . . [In normal people, it will shut] off and get[] rid of the infection and doesn't continue to orchestrate the anti-self response.

Tr. 135:13-16, 135:19 to 136:23. Dr. Brawer stated, however, that an aberrant immunological response would only occur in persons having a particular genetic predisposition, noting that "if certain amino acid sequences of the protein of the arms of those Class 2 molecules bears some striking resemblance to the foreign protein that you're mounting the response against, then you may not shut the process off[;] [i]t may continue unabated and you hence go from eradication of infection to persistence of inflammation." Tr. 137:6-12. Dr. Brawer testified that "no one knows" "the specific antigen to implicate in the flu vaccine" for this theory. Tr. 134:22-24.

Dr. Brawer stated that "[t]he theory [of antigen cross-reactions] has not been proven nor disproven but it is extraordinarily resilient . . . [in that] it still is at the top of the list of theories about why . . . autoimmunity can happen following immunizations." Tr. 27:8-11. Dr. Brawer noted as well that recent evidence had arisen regarding a "sister [autoimmune] disease to rheumatoid arthritis [called] systemic lupus erythematosus"[21] within the past two years to support the antigen cross-reaction theory. Tr. 27:12-17.[22] He asserted that the theory was

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[21]Systemic lupus erythematosus is "a chronic, inflammatory, often febrile multisystemic disorder of connective tissue that proceeds through remissions and relapses . . . . The etiology is unknown, but it may be a failure of regulatory mechanisms of the autoimmune system, since there are high levels of numerous autoantibodies against nuclear and cytoplasmic cellular components." *Dorland's* at 1095.

[22]Dr. Brawer provided the following recitation of the recent evidence:

> Even before the development of the standard blood test for lupus, what we call ANA tests or antinuclear antibody, even before that appears and well before the clinical disease appears, before the patient gets sick, . . . there will appear in the patient's blood antibodies to certain self-antigens in the body. In other words, their own tissue. . . . [T]he immune system essentially is seeing one antigen and then through what we call epitope spreading . . . it basically starts to recognize things around it. . . .
>
> Now the striking thing about that finding is that if you take that person's serum and cross-react it . . . test it against Epstein-Barr virus, the virus that causes infectious mononucleosis which also by the way can cause autoimmune diseases

"definitely biologically plausible, especially with the recent data on lupus and the cross-reacting antibodies to the Epstein-Barr virus. There's no question that that has taken . . . us in a direction that emphasizes [antigen cross-reactions]." Tr. 48:11-16.[23]

Dr. Lightfoot testified that the theory of antigen cross-reactions has "been hanging around for [thirty] years . . . [and n]o one has yet proved or disproved [the] theory." Tr. 326:22 to 327:1. However, Dr. Lightfoot stated that the theory of antigen cross-reaction generally was "plausible" and that he had not "reviewed the in-depths, the critique . . . recently." Tr. 389:22-24. Dr. Lightfoot noted that "the hypothesis of [the] flu vaccine causing [rheumatoid arthritis]" "doesn't really" "conflict with anything that we know about what causes [rheumatoid arthritis] and how it moves. . . . But then we don't know what causes [rheumatoid arthritis] . . . [or] why it moves the way it does." Tr. 291:24 to 292:3 (Lightfoot). Dr. Lightfoot's primary criticisms of antigen cross-reactions centered around the fact that the theory itself or certain facts that would support the theory — such as, the influenza virus itself causing rheumatoid arthritis or the premise that inactivated vaccines can cause chronic disease — had not been proven or disproven to a scientific certainty. *See* Tr. 264:9-18, 267:18-25.[24]

> . . . the serum will cross-react. In other words, the patient's serum is reacting to self-antigens. . . .
>
> Now that is a fascinating piece of information because it directly supports the . . . theory of the virus getting into the body and causing some type of reaction to the virus and then the same antibody will start to react with the patient's own tissues. . . .
>
> [I]t's still a theory. No one has yet proved or disproved the theory . . . , but that is very strong evidence that something along those lines is going on.

Tr. 28:1-7, 28:14-16, 28:21 to 29:2, 29:5-13 (Brawer). Dr. Lightfoot took issue with Dr. Brawer's use of the Epstein-Barr virus data, asserting that to prove that the cross-reaction described by Dr. Brawer supported antigen cross-reactions, one would "have to do an absorption test of some sort." Tr. 392:15-25 (Lightfoot).

[23]Dr. Brawer noted that extensive research regarding the merits of antigen cross-reactions was ongoing, *see* Tr. 47:18-20, and that "[t]here are at least a dozen if not more animal models where viruses caused autoimmune diseases similar to the neurologic and rheumatologic" conditions discussed. Tr. 47:23 to 48:1 (Brawer).

[24]Dr. Lightfoot stated that "it would be possible for any antigen from any place to turn on the immune system, and maybe not turn it off, if somebody's got something wrong with their immune system, via hypothesis waiting to be proven." Tr. 361:3-7. He nonetheless took the position that it is biologically implausible for any inactive vaccine to cause any abnormal immune response because "[i]t would require the invocation of a hypothesis that has not been proven." Tr. 360:15 to 361:20. When pressed by petitioner's counsel as to how that position accords with reports of chronic arthritis following hepatitis-B vaccination, also an inactive vaccine, Dr. Lightfoot responded that he "ha[d] found reams of allegations, attestations in case

Dr. Brawer described his second theory, the immune-complex theory, as follows:

> [I]f anyone . . . receives a vaccination, you produce an antibody to the protein . . . [i]n this case, the virus.
>
> That antibody is what we call an ideotype. . . . You will also make an antibody to the antibody [an anti-ideotype] . . . .
>
> These antibodies can complex with each other and can circulate as what we call immune complexes. . . .
>
> These immune complexes . . . at times . . . are capable of triggering both innate and adaptive immune responses. And essentially, those responses can become autonomous and not subside.

Tr. 30:12-19, 30:23-24, 38:11-14. Dr. Brawer later elaborated upon this theory, stating:

> [T]he immune complexes that develop . . . can cause a little bit of vasculitis. This has also been described in the literature in case reports of vasculitis following vaccination and immunization. And the vasculitis is nothing more than an inflammation of blood vessels. And this vasculitis can produce a relative ischemia to certain tissues where the oxygen is not being delivered adequately. [T]hat ischemia can result in cell death. And you may have a situation set up whereby programmed cell death has become disordered. Apoptosis has become disordered. The nuclear debris and other debris that are antigenic and with proteins . . . are liberated from these dying cells and they elicit an immune response.

Tr. 43:8-20. Dr. Lightfoot testified that he did not "know of any evidence" associating the immune-complex theory with the influenza vaccine but that "it's a reasonable theory to guess at." Tr. 327:2-9, 328:11-12.

The above recitation of the experts' testimony demonstrates that Dr. Brawer presented in detail two theories to explain how the influenza vaccine could be capable of engendering an adverse immunological reaction resulting in rheumatoid arthritis. Dr. Brawer testified that "the development of rheumatoid arthritis following viral in[n]oculation and vaccination" would be a "rare occurrence," Tr. 99:18-20 (Brawer), but he believed that Ms. Campbell was such an exceptional case based upon her specific clinical picture. *See* Tr. 49:7 to 59:15, 64:12 to 79:9. While skeptical of both theories, Dr. Lightfoot agreed that the theory of antigen cross-reactions was "plausible" and that the immune complex theory was "reasonable." Tr. 389:22-24, 328:11-12. Dr. Lightfoot's criticism of both theories was the dearth of conclusive medical studies

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reports, that hepatitis-B virus can do many things" but the case reports and similar documents were not sufficiently probative to establish causation. Tr. 362:17-22.

Notably, Dr. Lightfoot's position on the impossibility or unlikelihood of inactive vaccines causing deviant immunological responses and chronic autoimmune conditions is directly contrary to the *Capizzano* case — in which the special master concluded by a preponderance of the evidence (but not scientific certainty), and the Federal Circuit confirmed, that hepatitis B vaccine could cause rheumatoid arthritis. 440 F.3d at 1322, 1325.

proving their merits — and the resulting absence of scientific certainty. Indeed, his testimony emphasized that the standard of causation he sought was one of medical certainty.[25]

Dr. Lightfoot's expectations of scientific certainty are very much in accordance with those of the medical community, *see Andreu*, 569 F.3d at 1380 (noting that "attribution of causation [in medicine] is typically not made until a level of *very near certainty* — perhaps 95% probability — is achieved") (internal quotations omitted); however, such prerequisites to a finding of causation have no place in Vaccine Act cases. *Id.*; *see also Moberly*, 592 F.3d at 1322; *Knudsen*, 35 F.3d at 548-49. Because Dr. Lightfoot conceded that both of Dr. Brawer's theories were plausible or reasonable and because Dr. Lightfoot's criticisms of Dr. Brawer's theories were predicated upon the fact that those theories had not been proven to a scientific certainty — a standard long-dismissed by the Federal Circuit in Vaccine Act cases — Dr. Lightfoot cannot be said to have effectively rebutted Dr. Brawer's testimony as to the plausibility of his two primary theories. *See Rotoli*, 89 Fed. Cl. at 87-88.

2. *Evidence of reliability.*

A claimant's presentation through expert testimony of a biological theory of causation connecting the vaccine to the injury which the government does not successfully rebut advances the claimant's case. *See, e.g., Althen*, 58 Fed. Cl. at 285-86 (concluding that petitioner had established theory of causation through expert testimony where government's expert did not dispute the theoretical possibility that the vaccine could have caused petitioner's injury by way of petitioner's proffered theories of causation: there, degeneracy via antigen cross-reactions and epitope spreading); *see also Adams*, 76 Fed. Cl. at 36-40 (petitioner satisfied the first prong of *Althen* where petitioner's expert proffered three medical theories causally connecting the vaccination to her injury and two of those theories were not persuasively rebutted by the government's witness). Recently, however, the Federal Circuit issued two decisions which serve to clarify the nuances of *Althen* and elucidate what factors the special masters and this court ought to consider in evaluating a claimant's theory of causation.

In the earlier case, *Andreu*, the petitioners alleged that their son's receipt of the diphtheria-pertussis-tetanus ("DPT") vaccine caused his seizure disorder. 569 F.3d 1371. In support of their claim, they presented expert testimony offering a biologically-plausible-though-unproven theory of causation, which hypothesized that the pertussis contained within the vaccine could cross the blood-brain barrier to induce the seizure disorder. *Id*. The petitioners' expert supported this theory with articles demonstrating that the mechanism had been observed to occur in animals and by noting that the pertussis virus can cause seizures. *Id.* The child's treating physicians also testified to their belief that the child's condition was caused by the vaccination.

[25]Dr. Lightfoot indicated that he believed a "case-controlled study" would be necessary to undertake the task of finding a connection between the influenza vaccine and rheumatoid arthritis. Tr. 355:16-19. Upon the special master's inquiry, however, Dr. Lightfoot indicated that he was not aware of anyone having undertaken such a study and that he thought "it might be a difficult study to do [and] . . . the numbers [of participants required for such a study] would be huge." Tr. 410:24 to 411:1.

Id. at 1372-73. The government's expert did not dispute the plausibility of the blood-brain-barrier theory but testified only that the theory was inapplicable to the child's case, based upon the child's clinical picture. *Id.* at 1372. Given these facts, the Federal Circuit found that the claimants had met the first prong of *Althen* because their expert "presented a 'biologically plausible' theory" of causation. *Id*. at 1375. The court of appeals then continued its analysis by discussing the primacy of circumstantial evidence and statements of treating physicians which supported claimant's theory of causation, with the court ultimately concluding that petitioners had met their burden of proving causation in fact. *Id*. at 1375-83.

More recently, the Federal Circuit in *Moberly* addressed a case which presented facts similar "in several respects" to those of *Andreu*. 592 F.3d at 1324. In *Moberly,* the petitioners also alleged that their daughter's receipt of the DPT vaccine caused her seizure disorder. *Id*. at 1319. The petitioners presented evidence to satisfy *Althen* through expert testimony offering the same blood-brain-barrier theory accepted in *Andreu* and through an epidemiological study that had assigned a statistically significant risk of neurological injury for up to seven days following DPT vaccination. *Id.* at 1319-20. The special master rejected both of petitioners' theories of causation, and the Court of Federal Claims denied petitioners' motion for review. *Id.* at 1320-21. The Federal Circuit affirmed, concluding that the petitioners had failed to present sufficient "indicia of reliability" as to their theories of causation. *Id*. at 1324. The *Moberly* court distinguished *Andreu* on two grounds. First, in *Andreu*, the Federal Circuit had "held that the [petitioners'] theory should have been credited because the government's expert witness did not dispute the biological plausibility of the theory and thus failed to cast it into doubt[,]" *id*. at 1325 (citing *Andreu*, 569 F.3d at 1377); whereas in *Moberly*, "the government's expert witness did not concede the plausibility of [petitioners'] theory, and in fact testified that 'people in the field don't think it's biologically plausible.'" 592 F.3d at 1325.[26] Second, in *Andreu*, the treating physicians had testified that the DPT vaccine caused the child's seizure disorders, while in *Moberly* "there was no treating physician evidence that supported the claim of causation" and in fact, "to the extent the treating physician evidence bore on causation, it was negative, as the principal treating physician . . . expressed skepticism that [the child's] condition was caused by her DPT vaccination." *Id*.[27]

[26]In *Moberly*, the special master found petitioners' expert's testimony "contradictory and confusing." 593 F.3d at 1321. That finding "infected all other parts of [the expert's] testimony." *Moberly v. Secretary of Health & Human Servs.*, 85 Fed. Cl. 571, 591 (2009). Here, however, Dr. Brawer's testimony suffered from no such defect. *See Campbell*, 90 Fed. Cl. at 382-84.

[27]The court of appeals in *Moberly* mentioned as well that "the petitioners' expert witness [had] undercut his own position by conceding not only that the blood-brain-barrier theory had never been tested, but also that there was no evidence suggesting that it applied to [the child's] case." 592 F.3d at 1325. Correlatively in this case, lack of testability was cited by the special master as a factor against finding Dr. Brawer's theories biologically plausible. *See* First Entitlement Decision at *10. The court addressed this issue in its first opinion, *see Campbell*, 90 Fed. Cl. at 384-85, noting that Dr. Brawer explained that testing the amino acid chains of the protein within the influenza vaccination against amino acid chains found within the synovial fluid in the joint of a patient who has had arthritis initiated by the vaccination in an attempt to

Proceeding under the Federal Circuit's pronouncement in *Moberly* that a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness[,]" 592 F.3d at 1324, the special master in this case found that Ms. Campbell had failed to provide adequate support for Dr. Brawer's theories of causation. What the special master failed to acknowledge, however, is the fact that the two elements the Federal Circuit identified as pivotal distinctions between the successful petitioners in *Andreu* and the disappointed petitioners in *Moberly* favor Ms. Campbell.

As noted, Dr. Lightfoot, the government's expert, did not refute the biological plausibility of Ms. Campbell's theories, and in fact, stated instead that the theory of antigen cross-reactions generally was "plausible" and that the immune-complex theory was in fact "reasonable." Tr. 389:22-24, 328:10-12.[28] Dr. Lightfoot thus "failed to cast [Dr. Brawer's theories] into doubt." *Moberly*, 592 F.3d at 1325. Additionally, Ms. Campbell provided extensive "treating physician evidence [that] bore on causation." *Id*. This fact not only distinguishes Ms. Campbell's case from that of *Moberly*, it also provides the "indicia of reliability" needed to support Ms. Campbell's evidence regarding the first prong of *Althen*.

a. *Annotations of treating physicians*.

Ms. Campbell received the influenza vaccination on December 4, 2003. *Campbell*, 90 Fed. Cl. at 373. Upon examining Ms. Campbell on December 8, 2003, Dr. Jackson, Ms. Campbell's primary care physician, admitted her to Mercy Hospital to "[r]ule out reflex sympathetic dystrophy, Guillain Barré, new onset of multiple sclerosis, serum sickness *or*

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prove causation would be "unrewarding because the protein would usually not exist in the form it was administered in." Tr. 193:14 to 195:23 (Brawer). Indeed, Dr. Brawer explained that "[t]he body would dismember [the protein] and present only certain pieces to the immune system [, s]o it probably would not survive in its entirety to be found in the joint." Tr. 195:23 to 196:1.

In the context of the rheumatoid synovium, Dr. Brawer noted, testing would be further frustrated because there already exists within "the rheumatoid panus" "certain antibodies . . . directed toward viruses." Tr. 195:16-20; *see also* R. Ex. 17 at 2 (D.P.M. Symmons and K. Chakravarty, *Can Immunisation Trigger Rheumatoid Arthritis?*, 52 ANNALS OF THE RHEUMATIC DISEASES 843 (1993)) ("Infectious agents have long been the favo[]rite candidates as potential triggers for [rheumatoid arthritis]. However, attempts to isolate organisms directly from synovium and/or synovial fluid have, with a few exceptions, been unsuccessful. The preferred explanation is that an infection lights the blue touchpaper of the [rheumatoid arthritis] firework and then retires, often without a trace. If infections can initiate [rheumatoid arthritis] then it is certainly plausible that immuni[z]ation, whose prime purpose is to mimic the effect of infection on the immune system, will also be capable of triggering [rheumatoid arthritis].").

[28]Dr. Lightfoot's opinion as to the generic inability of any inactive vaccine to cause an abnormal immune response does not rise to the level of the government's expert's testimony in *Moberly*, which averred that "people in the field don't think [petitioner's specific blood-brain-barrier theory] is biologically plausible." *Moberly*, 592 F.3d at 1325. In this regard, Dr. Lightfoot's views rest principally on his expectation of scientific certainty.

adverse reaction to [p]neumovax and influenza vaccine." R. Ex. 2 at 200103 (emphasis added).[29] When Dr. Divina, an orthopedist, examined Ms. Campbell on December 9th at Mercy Hospital, his impression was that the physicians "*[m]ust rule out acute inflammatory response to vaccine* versus septic bursitis" while noting that he "fe[lt] at the . . . time [that] this is not septic bursitis." R. Ex. 2 at 200109. Ms. Campbell was released from Mercy Hospital on December 10, 2003 with a diagnosis of "[a]cute bilateral upper extremity inflammatory arthritis" of unknown cause. R. Ex. 2 at 200092.

When Ms. Campbell returned to Dr. Jackson on December 19, 2003, complaining of leg weakness and "intermittent episodes of severe inflammation in her knees, ankles, and joints in a polyarticular fashion[,]" Dr. Jackson's impressions included "[p]ositive RA and ANA profiles, which may represent new rheumatologic disease versus possible reactivity due to her previous influenza vaccine." R. Ex. 1 at 100022-23. The impressions of Dr. Gilhooly, the rheumatologist who examined Ms. Campbell at Munson Medical on December 19, 2003, included the following:

> 1. *Post vaccination reactive arthritis*, question myalgias,[30] weakness in a woman with positive serologies, ANA, rheumatoid factor, double-stranded DNA and a possible antecedent history of some ear symptomatology that may or may not be relevant with chronic steatohepatitis.
>   a. *I think the differential diagnosis includes in descending order of probability immunization related to autoimmune phenomenon which will probably be transient, possibility of long-lasting symptomalogy is there and while it is not well reported in literature I have seen several cases of onset of lupus more often than onset of rheumatoid arthritis after immunization.*[31]

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[29]Dr. Jackson included within his written summary of Ms. Campbell's examination on December 8, 2003, a notation relaying that he had "sp[oken] briefly with Dr. Lazaar, allergist, on the phone about the case and [Dr. Lazaar] did not feel that, to his knowledge, . . . the injections would be responsible for her current presenting symptoms." R. Ex. 2 at 200102. However, this singular notation by an allergist, not an immunologist, who had not examined Ms. Campbell and was not one of her treating physicians deserves very little weight.

[30]This phrase was the subject of some speculation at the hearing. Dr. Lightfoot maintained that "it's not clear whether the question is, is it a post-vaccination arthritis, or is it a question if she has myalgias[,]" Tr. 416:15-17, but he speculated that Dr. Gilhooly intended the word "question" to be a question mark following "post vaccination reactive arthritis," rather than a verb preceding "myalgias [and] weakness." *See* Tr. 415:23 to 416:25. While Dr. Gilhooly's death precludes direct evidence on this subject, Dr. Gilhooly's differential diagnoses and Dr. Ball's consultation, which references a conversation with Dr. Gilhooly in which Dr. Gilhooly ostensibly expressed her belief that Ms. Campbell was suffering from a rheumatological problem caused or exacerbated by her recent vaccinations, makes Dr. Lightfoot's view of this notation unlikely.

[31]This impression stated by Dr. Gilhooly is particularly noteworthy as it demonstrates her belief that Ms. Campbell was potentially suffering from a long-lasting autoimmune condition

b. *Exacerbation of underlying autoimmune proclivity* with her ear complaints one must keep in mind Sjogren's syndrome[32] although I think this is not likely without sicca and *something to consider that potentially the T cell and B cell stimulation of the concurrent immunizations revered her predilection and C less likely autoimmune hepatitis with positive serologies.*

R. Ex. 8 at 8-20 to 8-21 (emphasis added). Dr. Ball, who conducted a "neuromuscular consultation/electrodiagnostic consultation" while Ms. Campbell was at Munson Medical, stated that he "would agree with Dr. [] Gilhooly's assessment per [his] discussion with her and her written notes in the chart that this is *a rheumatologic problem, probably precipitated/exacerbated by her recent [p]neumovax/flu vaccines* obtained on [December 4, 2003] in the setting of a previously existing positive ANA, 1:300, homogeneous, and positive RA with negative double-stranded ANA." R. Ex. 8 at 8-15 (emphasis added).

When Ms. Campbell returned to Dr. Jackson on December 24, 2003, Dr. Jackson's impression was that Ms. Campbell had "[i]nflammatory arthritis, etiology indeterminate." R. Ex. 1 at 100021. On January 13, 2004, Dr. Gilhooly noted that Ms. Campbell visited "for [a] follow-up regarding *question post-vaccination immune phenomenon versus triggering of primary autoimmune phenomenon such as lupus, Sjogren's, or rheumatoid*." R. Ex. 7 at 7-22 (emphasis added). Dr. Gilhooly also had the following impression at that time:

> Question autoimmune disease, undifferentiated, with positive serologies across the board. Keep in mind Sjogren's, rheumatoid, lupus versus immune phenomenon simply triggered by the immunization that will gradually resolve. I think we are still in that window where she may yet resolve and we need to follow her prospectively and treat her symptomatically without trying to mask symptoms significantly.

Id. Dr. Gilhooly examined Ms. Campbell once again on February 25, 2004, and had the following impression of Ms. Campbell's condition: "*[q]uestion inflammatory arthritis*; question forme frusta of lupus triggered by immunization." Ex. 7 at 7-21 (emphasis in original). When Ms. Campbell returned to Dr. Jackson on March 11, 2004, Dr. Jackson noted that Ms. Campbell "had difficulty with an inflammatory arthritis after she received a flu vaccine." R. Ex. 1 at 100020. His impression following this visit was that Ms. Campbell was suffering from "[g]eneralized arthralgias and myalgias with [a] working diagnosis of postinflammatory arthritis

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related to her immunizations, and that the autoimmune condition was potentially rheumatoid arthritis. It is also significant as it demonstrates that Dr. Gilhooly had seen at least some cases of the onset of rheumatoid arthritis caused by immunizations, albeit less frequently than lupus.

[32]Sjogren's syndrome is a "symptom complex of unknown etiology" which is marked by several manifestations, including "the presence of a connective tissue disease, usually rheumatoid arthritis." *Dorland's* at 1871. "An abnormal immune response has been implicated" for Sjogren's. *Id.*

status post flu injection." R. Ex. 1 at 100020.[33]

As of September 27, 2004, Dr. Jackson's allergy list for Ms. Campbell included a notation that she had an "*adverse reaction to the influenza vaccine*" in 2003, R. Ex. 1 at 100015 (emphasis added), and Dr. Gilhooly's allergy list for Ms. Campbell included the "[f]lu vaccine[,]" R. Ex. 7 at 7-1. At a subsequent visit with Dr. Jackson on November 12, 2004, Dr. Jackson noted that Ms. Campbell was "*[p]ositive for severe adverse reaction to influenza vaccine last year requiring hospitalization*." R. Ex. 1 at 100013 (emphasis added).[34] By the time Ms. Campbell was under the care of Dr. Bachman, a rheumatologist, in 2006, her medical records included the notation that Ms. Campbell had been told by Dr. Bachman "never to have any *vaccinations* in the future." Ex. 4 at 400005 (emphasis in original).[35]

Notably and importantly, *each* of the physicians who examined and treated Ms. Campbell stated at some point their belief that the influenza vaccination probably either exacerbated or caused the ongoing arthritic symptoms — which turned out to be rheumatoid arthritis — from which Ms. Campbell was suffering following that vaccination. While statements that plainly paint a chronological picture will not themselves suffice to establish causation, *see Moberly*, 592 F.3d at 1323, the statements of Ms. Campbell's treating physicians rise far above simple observations of temporal association. The impressions and differential diagnoses of

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[33]In his first entitlement decision, the special master noted that a "limitation" on the probative value of some of the statements of Ms. Campbell's treating physicians "is that they sometimes did not say that the vaccination 'caused' a problem. Instead the doctors presented a chronology." First Entitlement Decision at *14. It should be noted, however, that a physician's listing of an injury as "post-immunization" can itself signify the physician's belief that a causal relationship might exist. *See* R. Ex. 17 at 2 (Symmons & Chakravarty, *supra*, at 18 n.27, at 844 ("If there is an identifiable putative trigger [of the rheumatoid arthritis] then an alternative label of 'post-viral arthritis' or 'post-immuni[z]ation arthritis' may be used.")).

[34]Dr. Jackson also noted that Ms. Campbell's diagnosis at that time was "unclear" but she had "apparently [a] working diagnosis of lupus, Sjogren's syndrome and possibly psoriatic arthritis as well." R. Ex. 1 at 100013.

[35]"A treating doctor's recommendation to withhold a particular vaccination can provide probative evidence of a causal link between the vaccination and an injury a claimant has sustained." *Andreu*, 569 F.3d at 1376-77 (citing *Capizzano*, 440 F.3d at 1320, 1326 ("[T]he chief special master erred in not considering the opinions of the treating physicians who concluded that the vaccine was the cause of the [the claimant's] injury" and who had recommended that she receive no future hepatitis B inoculations.)); *see also Kelley v. Secretary of Health & Human Servs.*, 68 Fed. Cl. 84, 98, 100 (2005) (relying on treating doctor's recommendation to withhold future tetanus vaccinations as evidence of causation); *Almeida v. Secretary of Health & Human Servs.*, 1999 WL 1277566, at *3 (Fed. Cl. Spec. Mstr. Dec. 20, 1999) (finding causation under the Vaccine Act where a claimant had an afebrile seizure on the evening she received a DPT vaccination and her "doctors ordered the elimination of the pertussis component from future shots").

Dr. Gilhooly, Ms. Campbell's rheumatologist, are particularly telling in this respect.[36] That none of the physicians immediately stated that Ms. Campbell had rheumatoid arthritis that was due to the influenza vaccine is not significant. All of them strongly suspected an arthritic condition that might evolve to rheumatoid arthritis or a related rheumatoid condition, such as Sjogren's syndrome. Shortly after the vaccination, a definitive statement could not have been expected regarding rheumatoid arthritis. Rheumatoid arthritis takes at least six to eight weeks to diagnose, and Dr. Lightfoot, the government's expert, testified that "[v]ery often, mild rheumatoid disease, you don't really know that's what it is until several months or maybe a year have gone by and all the other possibilities have fallen by the wayside, in retrospect you make the diagnosis." Tr. 230:19-24.

The special master employed inappropriate reasoning in dismissing the formidable probative strength of the treating physicians' notations. The special master first commented that "[e]ven if it were assumed that Dr. Gilhooly . . . and Dr. Jackson . . . stated that the flu vaccine caused Ms. Campbell's rheumatoid arthritis, the views of the treating doctors are not dispositive because 'there is nothing in *Andreu* that mandates that the testimony of a treating physician is sacrosanct — that it must be accepted in its entirety and cannot be rebutted.'" Second Entitlement Decision at 8 (quoting *Snyder v. Secretary of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009)). He also opined that the statements of the treating physicians were of "limited support for the first prong of *Althen*" because "[n]either molecular mimicry [antigen cross-reactions] nor any other theory mentioned by Dr. Brawer [was] discussed by either Dr. Gilhooly or Dr. Jackson." Second Entitlement Decision at 9 (citing *Broekelschen v. Secretary of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010)). He discounted further the statements of Ms. Campbell's treating physicians in addressing *Capizzano*'s guidance that "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.'" Second Entitlement Decision at 9 (quoting *Capizzano*, 440 F.3d at 1326). In his view, that guidance was inapplicable to Ms. Campbell's case because, unlike the *Capizzano* claimant, she had failed to satisfy the first prong of *Althen*. *Id.* at 9.

Any expectation that treating physicians will record the precise biological theories behind their belief that a patient's condition was caused by a particular trigger is discordant with the reality of medical treatment. Doctors are and must be concerned with treating patients, not with articulating the precise biological theories upon which they base their diagnoses. In support of his position on this matter, the special master cited *Broekelschen*, 618 F.3d at 1347, in which the Federal Circuit upheld the special master's determination that the claimant actually suffered from anterior spinal artery syndrome, not transverse myelitis as the claimant had urged. In that connection, the Federal Circuit commented that "the special master noted that the doctors in their post-hospitalization notes did 'not provide any reasoning for their statements [diagnosing the petitioner with transverse myelitis].'" *Id.* That comment in *Broekelschen* was made in the context of a case in which "the treating doctors were 'not consistent in their diagnoses,'" *id.*, and the rationale of the treating physicians was critically important in that regard. There is no dispute about Ms. Campbell's diagnosis in this case, and her treatment was not dependent upon

[36]Dr. Gilhooly could not have been called as a witness in the case because she had been tragically killed in an automobile accident. *See Campbell*, 90 Fed. Cl. at 388 n.35.

any particular biological hypothesis as a cause for her condition.

"Medical records, in general, warrant consideration as trustworthy evidence. The records contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. With proper treatment hanging in the balance, accuracy has an extra premium. These records are also generally contemporaneous to the medical events." *Cucuras v. Secretary of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). The evidence Ms. Campbell has presented consists of the explicit types that the Vaccine Act contemplates could provide proof of causation: *viz*., "medical records" and "medical opinion." 42 U.S.C. § 300aa-13(a)(1). That evidence supports Ms. Campbell's theories of causation and also causally connects the influenza vaccine and rheumatoid arthritis specifically in the context of Ms. Campbell's case. The special master's refusal to credit this evidence on the grounds that it was not sacrosanct was in error. A finder of fact can only dismiss so much evidence on the grounds that such evidence is not "binding" until it appears, as it does in this case, that he simply failed to consider genuinely the evidentiary record before him.

b. *Medical literature.*

Ms. Campbell also submitted medical literature, namely case reports and two review articles, in support of the plausibility of a causal link between the influenza vaccine and rheumatoid arthritis. Again, such literature was not required, but upon submission, the special master was entitled to consider it "from the vantage point of the Vaccine Act's preponderant evidence standard." *See Andreu*, 569 F.3d at 1380.[37] The special master considered the case reports and review articles but gave them short shrift.

The special master dismissed the case reports submitted by Dr. Brawer primarily based upon his conclusion that such reports hold little evidentiary weight because they present a chronological picture only, not a biological chain of causation. *See* Second Entitlement Decision at 7. Case reports do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value compared particularly to formal epidemiological studies. Nonetheless, the fact that case reports can by their nature only present an indicia of causation does not deprive them of all evidentiary weight. *See, e.g., Rotoli*, 89 Fed. Cl. at 86-87 (finding that petitioner had satisfied the first prong of *Althen* even though "only a handful" of case reports supported claimant's theory of causation). In fact, in this instance, the case reports Ms. Campbell submitted provide some limited support. Of the approximately eight case reports

[37]The special master discounted Ms. Campbell's medical literature because her "primary brief . . . does not contain any argument explaining how the [literature] make[s] Dr. Brawer's opinion more likely than not." Second Entitlement Decision at 6. The lack of detailed discussion of the medical literature in Ms. Campbell's brief is unremarkable upon a review of the hearing transcript because that transcript reveals that the medical literature submitted by Dr. Brawer was discussed in detail by Dr. Brawer himself on direct and cross-examination and upon the special master's own inquiry. *See* Tr. 79:16 to 84:12 (direct), 96:21 to 99:12 (direct), 158:16 to 171:11 (cross-examination), 179:3 to 190:19 (special master's inquiry), 198:18 to 203:22 (special master's inquiry).

that concerned the onset of an arthritic or rheumatic condition following a vaccination, one recites the onset of rheumatoid arthritis following administration of the influenza vaccine,[38] three case reports discuss the onset of related arthritic or rheumatic conditions following the influenza vaccine,[39] three additional case reports address the onset of related arthritic or rheumatic conditions following other vaccines,[40] and a further case report recites the onset of rheumatoid arthritis following a different vaccination.[41] Included within her submissions as well is an article generally inquiring whether immunizations can trigger rheumatoid arthritis; the article answers that question, unsurprisingly, by concluding that the possibility has not been proven or disproven and that it is cause for further study.[42] This smattering of case reports provides mild support for Ms. Campbell's case; they certainly do not undermine it.

The special master's treatment of the two review articles, however, is different because he was wrong as a matter of logic in the inference he drew from those articles. The articles were general surveys: Ami Schattner, *Consequence or Coincidence" The Occurrence, Pathogenesis, and Significance of Autoimmunce Manifestations after Viral Vaccines*, 23 SCIENCE DIRECT 3876 (2005), R. Ex. 13, and Yehda Schoenfeld and A. Aron-Maor, *Vaccination and Autoimmunity — "Vaccinosis," A Dangerous Liaison?* 14 J. OF AUTOIMMUNITY 1 (2000), R. Ex. 10. The Schattner review article lists adverse conditions that have been associated with the influenza vaccine, and the Shoenfield article lists vaccines that have been associated with arthritic conditions. They did not mention or list rheumatoid arthritis and the influenza vaccine, respectively. Based upon those omissions, the special master indicated that the articles "suggest that the flu vaccine is unlikely to cause rheumatoid arthritis." Second Entitlement Decision at 8. This finding led the special master to conclude that "the balance of medical literature d[id] not support [Dr. Brawer's] theory," thus entitling him to "find that theory unreliable." *Id*. Reasoning from two negatives or omissions to a positive postulate is always questionable. Here,

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[38]*See* R. Ex. 23 (M.A. Brown & J.V. Bertouch, *Rheumatic Complications of Influenza Vaccination*, 24 AUST. N.Z. J. MED. 572 (1994)).

[39]*See* R. Ex. 25 (D. Biasi et al., *A Case of Reactive Arthritis after Influenza Vaccination*, 13 CLINICAL RHEUMATOLOGY 645 (1994)); R. Ex. 26 (P. Iyngkaran et al., *Rheumatoid Vasculitis following Influenza Vaccine*, 42 BRITISH SOC'Y FOR RHEUMATOLOGY 907 (2003)); R. Ex. 27 (J. Asakawa et al., *Reactive Arthritis after Influenza Vaccination: Report of a Case*, 15 MODERN RHEUMATOLOGY 283 (2005)).

[40]R. Ex. 29 (H.M. Silby et al., *Acute Monarticular Arthritis after Vaccination*, 62 ANNALS OF INTERNAL MEDICINE 347 (1965)); R. Ex. 30 (M. Nussinovitch et al., *Arthritis after Mumps and Measles Vaccination*, 72 ARCHIVES OF DISEASE IN CHILDHOOD 348 (1995)); R. Ex. 31 (A.J. Tingle et al., *Rubella-associated Arthritis; Comparative Study of Joint Manifestations associated with Natural Rubella Infection and RA 27/3 Rubella Immunization*, 45 ANNALS OF THE RHEUMATIC DISEASES 110 (1986)).

[41]R. Ex. 24 (A.S.M. Jawad & D.G.I. Scott, *Immunisation Triggering Rheumatoid Arthritis?*, 48 ANNALS OF THE RHEUMATIC DISEASES 174 (1989)).

[42]R. Ex. 17 (Symmons & Chakravarty, *supra*, at 18 n.27).

that mode of analysis is especially problematic. The absence of rheumatoid arthritis from the Schattner article and the absence of influenza vaccine from the Shoenfeld article could lead to a number of possibilities, *see* Tr. 179:3 to 180:9 (Brawer); Tr. 188:7-8, 21-24 (Brawer), but they cannot reasonably be said to stand for the proposition that the influenza vaccine does not cause rheumatoid arthritis. Neither can one say, based solely upon those two articles, that the "balance of medical literature" is against such a causal connection.

In actuality, an examination of the review articles shows that they tended to support a finding of causation. The Schattner article listed a number of rheumatic conditions associated with the influenza vaccine including: "[v]asculitis ([g]iant cell arteritis, polymyalgia rheumatica, PAN, Henoch-Schoenlein purpura, microscopic polyangitis, etc.), [r]eactive arthritis (ER [extremely rare]), and [c]ryoglobulinemia (ER [extremely rare])." R. Ex. 13 at 13-4. Upon inquiry by the special master as to the probative value of the Schattner article, Dr. Brawer testified that he had direct experience because he had conducted the only "prospective study" researching polymyalgia rheumatica, "[t]o watch the natural course of the illness and see how it evolves over time" over the course of approximately five years. Tr. 188:25 to 189:20, 190:3-5. Dr. Brawer's research revealed that "[seventy-five] percent of the patients who presented with the polymyalgia rheumatica syndrome evolved into rheumatoid arthritis." Tr. 189:21-23 (Brawer). Dr. Brawer thus stated that the Schattner article's listing of polymyalgia rheumatica as one of the conditions associated with the influenza vaccine supported Ms. Campbell's case because "[within his patient population] three quarters of those patients would have evolved into rheumatoid arthritis." Tr. 189:24 to 190:3. Dr. Brawer additionally testified that the listing of reactive arthritis within the Schattner article supported Ms. Campbell's case because "reactive arthritis can easily be the diagnosis in the beginning but not necessarily sustainable" as the condition evolves over time, leading him to the suspicion that "some of those patients [within the Schattner article] are also rheumatoid arthritis patients." Tr. 190:6-13.[43]

In sum, the special master unduly discounted the putative support in case reports for Ms. Campbell's case, drew an irrational inference from the two review articles, and compounded that error by concluding, quite remarkably, that the two review articles meant that "the balance

[43]The Schattner article lists a variety of autoimmune disorders associated with the hepatitis B vaccination, including "[r]heumatoid arthritis (new onset or relapse)," R. Ex. 13 at 13-3, and the Shoenfeld article likewise lists the hepatitis B vaccine as one associated with arthritis, R. Ex. 10 at 10-9. In exploring the association between the hepatitis B vaccine and rheumatoid arthritis, the Shoenfeld article stated that although there were "but few cases" of rheumatoid arthritis developing after the hepatitis B vaccination, the test results of a series of eleven patients who had developed rheumatoid arthritis following the vaccination "suggest that genetic factors linked to HHC class II molecules may represent a risk factor for post-vaccine arthritis (even though there are undoubtedly other determining factors, given the frequency of these HLA class II molecules in the healthy population)." R. Ex. 10 at 10-11 to 10-12; *see also id.* at 10-3 (listing "molecular mimicry" (antigen cross-reaction) and the immune-complex theories as "[p]ossible mechanisms of induction of autoimmune phenomena by vaccines"). The Schattner article likewise lists antigen cross-reaction and immune complexes as potential theories of possible causal mechanisms for vaccine-related injury. *See* R. Ex. 13 at 13-6.

of medical literature" stands against Dr. Brawer's theories, when they in actuality tended to support them. Second Entitlement Decision at 8.

c. *Synopsis*.

The Federal Circuit specified in *Moberly* that "treating physician evidence . . . [can] support[] the claim of causation." 592 F.3d at 1325. The court observed in that case: "Had any of [the claimant's] treating physicians provided such an opinion [a "solid statement that . . . [the] vaccination [probably] caused . . . [her] condition"], it could have been probative with respect to causation." *Id.* at 1323 (citing *Capizzano*, 440 F.3d at 1326). That happened in this case. Numerous statements by Ms. Campbell's treating physicians extending over the entire year following her vaccination, state that it was probable or certain that she was suffering from a then-unidentified autoimmune or arthritic condition due to her influenza vaccine. There is no dispute that that condition ultimately was diagnosed as rheumatoid arthritis. Ms. Campbell's case is thus similar to that presented by the claimants in *Andreu* and *Althen* — she presented a biologically plausible theory buttressed by strong statements of causation from treating physicians — and she additionally provided support via case reports and review articles.

B. *A Logical Sequence of Cause and Effect*

Ms. Campbell must also demonstrate "a logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. Regarding this second prong of *Althen*, the Federal Circuit has stated "if close temporal proximity, combined with the finding that [the] vaccine can cause [the injury], demonstrates that it is logical to conclude that the vaccine was the cause of the [the injury] (the effect), then medical opinions to this effect are quite probative." *Capizzano*, 440 F.3d at 1326; *see also Adams*, 76 Fed. Cl. at 40-41 (looking to treating physicians' statements for logical sequence).

In his prior decision, the special master asserted that Ms. Campbell could not demonstrate a logical sequence of cause and effect because "the statements of Ms. Campbell's treating physicians are not clear statements that the flu vaccine caused Ms. Campbell to develop rheumatoid arthritis." First Entitlement Decision at *14. Yet, as noted, the statements of the treating physicians were entirely appropriate within the context of rheumatoid arthritis — a disease of unknown etiology for which there is no definitive test, which requires prolonged observation and symptomatology to diagnose, and which can often present as acute or reactive arthritis in its early stages. Initially, a few of those statements were not categorical but rather suggested the possibility that the vaccine was causing Ms. Campbell's symptoms. *See* R. Ex. 2 at 200103 (Dec. 8, 2003) (must "[r]ule out" "adverse reaction to [p]neumovax or influenza vaccine"); R. Ex. 2 at 200109 (Dec. 9, 2003) ("[m]ust rule out acute inflammatory response to vaccine"). As Ms. Campbell's condition progressed, however, the statements began to reflect the treating doctors' belief that it was more likely than not or certain that the vaccine caused her illness. *See* R. Ex. 8 at 8-20 to 8-21 (Dec. 19, 2003) (immunization-related autoimmune disease at top of Dr. Gilhooly's differential diagnosis list, followed by exacerbation of underlying autoimmune proclivity by immunizations); R. Ex. 8 at 8-15 (Dec. 19, 2003) ("rheumatologic

problem, probably precipitated/exacerbated by her recent [p]neumovax/flu vaccines").[44] In sum, the evidence demonstrates that (1) Ms. Campbell did not have rheumatoid arthritis prior to her vaccination; (2) she had an adverse reaction to the vaccine within two days' time; (3) the treating doctors' diagnostic impression was that the vaccine was the cause of her condition;[45] and (4) there were no other causes that the treating doctors believed were more likely than the vaccine. These facts, coupled with the other evidence Ms. Campbell has presented, give rise to preponderant evidence that a logical sequence of cause and effect existed between her receipt of the influenza vaccination and the onset of her rheumatoid arthritis.

C. *Proximate Temporal Relationship*

Finally, *Althen* requires that Ms. Campbell show "a proximate temporal relationship between [the] vaccination and [the] injury." 418 F.3d at 1278. This third prong of *Althen* "requires preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." *de Bazan v. Secretary of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008); *see also Pafford v. Secretary of Health & Human Servs.*, 451 F.3d 1352, 1358 (Fed. Cir. 2006) ("Evidence demonstrating petitioner's injury occurred within a medically acceptable time frame bolsters a link between the injury alleged and the vaccination at issue under the 'but-for' prong of the causation analysis.").

Dr. Brawer testified that when viral vaccinations initiate abnormal immunological responses the average expected time period within which a patient will begin to display symptoms is "[two] days to [fourteen] days, give or take a few things." Tr. 52:5-9. Based upon Ms. Campbell's medical records, Dr. Brawer concluded that the onset of her symptoms occurred roughly two days after the vaccination, when she began to experience pain in her left upper arm. Tr. 57:25 to 58:8. That initial onset was followed by "constitutional symptoms [such as a fever, morning stiffness and fatigue]" and "phenomenon distant from the immunization site in multiple other joints [including, joint pain, swelling, stiffness and limited movement of her limbs]" which persisted "uninterrupted ever since." Tr. 58:6 to 59:3 (Brawer). Dr. Brawer testified that

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[44]During the time period in which Ms. Campbell's diagnosis was uncertain, her treating physicians continued to hypothesize as to the etiology of her condition. *See* R. Ex. 7 at 7-22 (Jan. 13, 2004) ("question post-vaccination immune phenomenon"); Ex. 7 at 7-21 (Feb. 5, 2004) ("[q]uestion inflammatory arthritis; question forme frusta of lupus triggered by immunization"). As her condition progressed, their conclusions regarding the influenza vaccine became more definite. *See* R. Ex. 1 at 100020 (Mar. 11, 2004) (Ms. Campbell "had difficulty with an inflammatory arthritis after she received a flu vaccine"); R. Ex. 1 at 100015 (Sept. 27, 2004) (Ms. Campbell had "adverse reaction to the influenza vaccine"); R. Ex. 1 at 100013 (Nov. 12, 2004) (Ms. Campbell was "[p]ositive for severe adverse reaction to influenza vaccine last year requiring hospitalization.").

[45]As the special master noted in *Capizzano* when considering *Althen* prong II upon remand: "The fact that the vaccine was considered a possible cause shows that from the treaters' vantage point, the clinical sequence was logical." *Capizzano v. Secretary of Health & Human Servs.*, 2006 WL 3419789, at *14 (Fed. Cl. Spec. Mstr. Nov. 8, 2006).

Ms. Campbell's case thus presented the appropriate temporal relationship between her vaccination and the onset of her symptoms, leading him to conclude that "the vaccine directly initiated the onset of her rheumatoid arthritis." Tr. 57:2-10; *see also* Tr. 59:7-15 (Brawer). Initially, Dr. Lightfoot stated that he "d[id]n't think" there was "any way . . . to determine when the onset of [Ms. Campbell's rheumatoid arthritis] in this case was." Tr. 242:1-4. However, he later testified that he thought Ms. Campbell's rheumatoid arthritis began "probably some time in the late '03, early '04 to mid' 04 time period [but] it's hard to tell." Tr. 268:2-7.

Ms. Campbell received her influenza vaccine on December 4, 2003. *Campbell*, 90 Fed. Cl. at 373. Within two days, she experienced radiating pain in her left arm, similar pain in her right arm, difficulty swallowing, and chest heaviness. *Id.* at 373-74. On December 8, 2003, Dr. Jackson noted that Ms. Campbell had systemic swelling and warmth in both of her extremities, along with diminished grip strength. *Id.* at 374. On December 9, 2003, Ms. Campbell was observed to have swollen left and right shoulders that were slightly warm to the touch, a positive ANA test, and a rheumatoid factor of 20. *Id.* at 374. On December 10, 2003, she was discharged from the hospital under the working diagnosis of "[a]cute bilateral upper extremity inflammatory arthritis." *Id.* On December 12, 2003, Ms. Campbell returned to the emergency room, reporting pain in her extremities, including her left foot. *Id.* The emergency room doctor who examined Ms. Campbell had the impression that she was suffering from inflammatory arthritis. *Id*. A diagnosis of arthritis literally means that Ms. Campbell was suffering from "inflammation of a joint." *Dorland's* at 152.

On December 19, 2003, Dr. Jackson noted that Ms. Campbell had been experiencing, prior to that visit, "intermittent episodes of severe inflammation in her . . . joints in a polyarticular fashion." R. Ex. 1 at 100023. Additionally, within Dr. Gilhooly's notes summarizing her examination of Ms. Campbell on December 19, 2003, Dr. Gilhooly recounted Ms. Campbell's prior symptoms stating that:

> [Ms. Campbell] was in her usual state of relatively good health until [December 4, 2003] when she presented for a well person followup . . . . At the time of that evaluation she was administered [p]neumoax and influenza vaccine. *Within [forty-eight] hours [Ms. Campbell] began to have difficulty with upper extremity pain, stiffness and generalized edema, not just of the joints but of the extremities themselves. The joints involved were wrists, elbows, MCPs, PIPs, which were painful, stiff, and swollen.*

R. Ex. 3 at 300024. It is difficult to imagine more unequivocal pronouncements that Ms. Campbell was suffering from swelling in her joints and thus that she was manifesting the early symptoms of rheumatoid arthritis squarely within the appropriate time frame for that injury to have been vaccine-induced.

Nevertheless, in his initial decision, the special master found that Ms. Campbell had not established a temporal association between the vaccination and the onset of her rheumatoid arthritis, stating that "Ms. Campbell presented little persuasive evidence that she was suffering from inflammation in her joints within two weeks . . . after vaccination[,]" and joint inflammation is "the hallmark of rheumatoid arthritis." First Entitlement Decision at *12-*13.

The special master dismissed the diagnosis of arthritis because Dr. Jackson "did not provide a basis for his conclusion that Ms. Campbell suffered from inflammatory arthritis." *Id.* at *12. Acknowledging that Dr. Jackson may have considered, in arriving at that diagnosis, that Ms. Campbell's "upper extremities were swollen and filled with fluid" and "Ms. Campbell's test for ANA was positive[,]" *id.*, the special master discounted these possible bases for a proximate temporal relationship because Dr. Lightfoot testified that swollen, fluid-filled extremities "would be a very unusual presentation of rheumatoid arthritis . . . though not unheard of[,]" Tr. 241:2-14 (Lightfoot), and because "a positive ANA is not [necessarily] diagnostic for rheumatoid arthritis." First Entitlement Decision at *12.[46] The special master also slighted Dr. Jackson's observation of arthritis because he used the term "inflammatory arthritis" whereas Dr. Gilhooly later used the term "reactive arthritis" initially to describe Ms. Campbell's condition. *Id.* at *12-13. Because these conditions can be symptomatically alike, this use of terminology appears to be a distinction without a meaningful difference. As the court noted in its prior opinion, "[b]oth 'inflammatory' or 'acute' arthritis and 'reactive' arthritis share many attributes . . . and on a preliminary diagnosis may not appear to be appreciably different." 90 Fed. Cl. at 387; *see also* Tr. 319:19-21 (Lightfoot) ("[E]arly on you couldn't tell reactive arthritis from rheumatoid arthritis, if the [rheumatoid arthritis] was starting in just a few joints.").[47]

Still further, however, the special master inferred that because Dr. Gilhooly recorded no synovitis, during her examination of Ms. Campbell on December 19, 2003, she "did not diagnose rheumatoid arthritis" at that time. First Entitlement Decision at *13. The special master's inference on this point is both unreasonable and irrelevant. The parties agreed, and medical authorities concur, that Ms. Campbell could not have been diagnosed with rheumatoid arthritis prior to six to eight weeks of experiencing the constellation of symptoms listed by the American College of Rheumatology. *See supra*, at 2-3. Dr. Gilhooly's failure to diagnose rheumatoid arthritis at that time was appropriate, and inapposite as to whether Ms. Campbell experienced the onset of symptoms within the prescribed time period to causally link her condition to the vaccine.[48] In fact, Dr. Gilhooly's differential diagnoses provided on December 19, 2003, which

[46]The special master also discounted Dr. Jackson's impressions because he "did not prescribe any medications usually given to treat inflammatory arthritis." First Entitlement Decision at *12. In his discharge summary, Dr. Jackson wrote, "At this point in time have chosen not to treat her with steroids. She is intolerant of nonsteroidal medications and will therefore withhold these as well." R. Ex. 2 at 200094. Shortly thereafter, however, on January 6, 2004, Ms. Campbell was being treated with steroids. Dr. Gilhooly recited within her notes regarding Ms. Campbell's January 13, 2004 visit that Ms. Campbell had been "off steroids about a week." R. Ex. 7 at 7-22.

[47]Additionally, the special master did not mention the additional diagnosis of inflammatory arthritis by the emergency room physician on December 12, 2003, and Dr. Jackson's and Dr. Gilhooly's recitation of Ms. Campbell's joint inflammation on December 19, 2003.

[48]Also, if Ms. Campbell did not present with synovitis on a particular visit to the physician's office it does not mean she was not then suffering from the onset of rheumatoid arthritis. Dr. Lightfoot provided testimony that bears on this point, stating that "if I examined

listed rheumatoid arthritis caused by Ms. Campbell's vaccination as a potential diagnosis, was strikingly prescient and favors Ms. Campbell's claim. *See* R. Ex. 8 at 8-20.

In sum, the special master lacked a rational basis for his conclusion that Ms. Campbell failed to provide sufficient evidence under the third prong of *Althen*. Ms. Campbell has demonstrated a temporal relationship between the onset of rheumatoid arthritis symptomatology and her receipt of the influenza vaccine.

SYNOPSIS

The special masters indeed have "the unenviable job of sorting through these painful cases." *Hodges v. Secretary of Health & Human Servs.*, 9 F.3d 958, 961 (Fed. Cir. 1993). Throughout that endeavor, one must remain mindful of the significant variance between the medical standard of causation and legal standards of causation for the Vaccine Program. *See Andreu*, 569 F.3d at 1380. It is the rare case in which an off-table Vaccine Act claimant will be able to present his or her case through a foundation of definitive statements of causation and epidemiological certainty. If that were to happen, the Vaccine Table should be revised to add a table injury. More often, a claimant must build a causal framework piece by evidentiary piece, each fragment building upon and supporting the other until the preponderant silhouette of causation is achieved.

In these circumstances, however, the court takes guidance from the Federal Circuit. While a causal connection between the influenza virus and rheumatoid arthritis is undoubtedly "a sequence hitherto unproven in medicine," *Althen*, 418 F.3d at 1280, the court concludes that the totality of the evidence Ms. Campbell has presented — the biological plausibility of the influenza vaccine causing rheumatoid arthritis, medical literature consisting of case reports and review articles, the strong temporal proximity between the vaccination and the onset of her symptoms, and the statements of her treating physicians — are sufficient to meet the Vaccine Act's preponderant standard for causation.

CONCLUSION

For the reasons stated, petitioner's motion for review is GRANTED. The decision of the special master dated October 27, 2010, denying compensation is SET ASIDE and replaced by the court's own findings of fact and conclusions of law. Based upon those findings and conclusions, the court determines that entitlement has been proven, and the case is REMANDED for a determination by the special master of the compensation due Ms. Campbell. In accord with 42 U.S.C. § 300aa-12(e)(2), the court allows the maximum permissible time, 90 days, for the completion of proceedings on remand.

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her now, I would either see synovitis or I wouldn't see synovitis, but it wouldn't mean — if I saw her today in this courtroom with no swelling, it wouldn't mean she didn't have rheumatoid arthritis. It would mean it's in remission, or it's not a bad enough case to show swelling today." Tr. 334:22 to 335:3.

It is so ORDERED.

s/ Charles F. Lettow
Charles F. Lettow
Judge