In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: January 19, 2018

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PHILIP TETLOCK *and* BARBARA TETLOCK *Administrators of the Estate of* J.T., *Deceased*,	No. 10-56V
	Chief Special Master Dorsey
Petitioners,	
	Denial of Entitlement;
v.	Human Papillomavirus Vaccine (HPV/Gardasil); Amyotrophic
SECRETARY OF HEALTH AND HUMAN SERVICES,	Lateral Sclerosis (ALS); Acute Disseminated Encephalomyelitis (ADEM); FUS ALS Genetic Mutation.
Respondent.	
* * * * * * * * * * * * * *	

Lawrence R. Cohan, Anapol Weiss, Philadelphia, PA, for petitioners.
Debra A. Filteau Begley, United States Department of Justice, Washington, DC, for respondent.

DECISION[1]

I. Introduction

On January 27, 2010, Philip and Barbara Tetlock ("petitioners") filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"),[2] 42 U.S.C. § 300aa-10 et seq. (2012), as the administrators of the estate of J.T., deceased. Petitioners alleged that as a result of receiving her third Human Papillomavirus ("HPV" or "Gardasil") vaccine on March 1, 2007, J.T. died on March 15, 2009. Petition at Preamble, ¶¶ 13, 14.

[1] Because this decision contains a reasoned explanation for my action in this case, I intend to post this ruling on the website of the United States Court of Federal Claims, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 note (2012)(Federal Management and Promotion of Electronic Government Services). As provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b).

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

As their theory of causation, petitioners specifically assert that the HPV vaccination J.T. received on March 1, 2007, caused her to develop acute disseminated encephalomyelitis ("ADEM"), which in turn triggered her development of amyotrophic lateral sclerosis ("ALS"), which led to her eventual death on March 15, 2009. Respondent argued against awarding compensation, stating that petitioners failed to provide preponderant evidence that J.T.'s ALS and/or her subsequent death were caused by the HPV vaccine. Respondent also argued that J.T.'s death was caused by the FUS P525L mutation.

Petitioners have faced great personal tragedy in the loss of their daughter, for which I extend my deepest sympathy. However, after carefully analyzing and weighing all of the evidence and testimony presented in this case in accordance with the applicable legal standards, I find that petitioners have not met their legal burden and are not entitled to compensation. Petitioners have failed to provide preponderant evidence that the vaccination J.T. received on March 1, 2007, caused her ALS and subsequent death. Therefore, this case must be dismissed.

II. Procedural History

Petitioners alleged that J.T. "suffered and died from the residual effects of the third and final series of the Gardasil vaccination that she received on March 1, 2007." Petition at ¶ 14. The petition further alleged that J.T. suffered from an Amyotrophic Lateral Sclerosis ("ALS")-like lower motor neuron disease, caused by her vaccination. Id. at Preamble. Based on records subsequently filed, petitioners thereafter revised their allegations and contended that J.T.'s March 1, 2007 Gardasil vaccination caused ADEM which "eventually triggered her ALS-like condition," and that her death on March 15, 2009, was "due to respiratory failure resulting from her condition." Pet. Prehearing Submission ("Sub.") at 9, 12, 16. Respondent filed his Rule 4(c) Report on June 21, 2010, recommending against compensation. Respondent's Report ("Resp. Rept.") dated Jun. 21, 2010 (ECF No. 11) at 2.

On April 18, 2011, petitioners filed a case study involving J.T. indicating that a genetic disorder caused her symptoms. Pet. Status Report ("Rep.") dated Apr. 18, 2011 (ECF No. 20); Pet. Ex. 9. On July 20, 2011, petitioners filed a letter from Dr. Eric J. Huang, the author of the case study, describing the scope of the study. Pet. Ex. 11. Petitioners filed genetic testing records on December 27, 2011, and April 5, 2012, and respondent filed additional genetic testing records on October 22, 2012. Pet. Exs. 12, 13; Resp. Ex. C.

On March 25, 2013, petitioners filed the expert report of Dr. Lawrence Steinman, a neurologist and immunologist, and a supplemental report from him on March 27, 2013. Pet. Exs. 14, 17. Respondent filed expert reports from Dr. Gerald Raymond, a pediatric neurologist, and Dr. Arun Venkatesan, a neuroimmunologist, on July 23, 2013. Resp. Exs. D, E. On December 17, 2013, petitioners filed responsive expert reports from Dr. Steinman and Dr. Paul Utz, an immunologist and rheumatologist. Pet. Exs. 20, 21. Respondent filed supplemental reports from Dr. Raymond and Dr. Venkatesan on May 30, 2014. Resp. Exs. F, G.

Petitioners filed a second supplemental report from Dr. Steinman on November 4, 2014. Pet. Ex. 31. Respondent filed second supplemental reports from Dr. Raymond and Dr. Venkatesan on March 6, 2015. Resp. Exs. H, I. Petitioners filed a third supplemental report from Dr. Steinman on February 2, 2016. See Pet. Ex. 33. Respondent filed a third supplemental report from Dr. Raymond on February 27, 2017. Resp. Ex. S. On May 16, 2017, respondent filed additional

supplemental reports from Drs. Venkatesan and Raymond. See Resp. Exs. T, U. Both parties filed extensive medical literature referenced by their respective experts.

The parties discussed settlement of this matter but were unable to resolve the case informally. See, e.g., Resp. Status Rep. dated May 29, 2013 (ECF No. 64); Resp. Status Rep. dated Apr. 21, 2014 (ECF No. 89); Resp. Status Rep. dated June 30, 2014 (ECF No. 93).

The parties filed a joint stipulation of facts on December 19, 2014, in which they stated that all experts agreed that J.T. had the P525L FUS mutation but disagreed as to the significance of this mutation with regard to her alleged vaccine injury. Joint Stipulation of Facts ("Joint Stip.") dated December 19, 2014 (ECF No. 109) at 1. The parties further stipulated that J.T.'s genetic testing was completed on November 5, 2009, as Sample ID RB14162, and that the results show "c.1574 C>T mutation in FUS gene predicts substitution of amino acid leucine at position 525 for the normal amino acid proline." Id. at 2.

An entitlement hearing was initially scheduled for February 2014 but was cancelled to allow for the filing of additional expert reports. Prehearing Order dated May 29, 2013 (ECF No. 65). The hearing was rescheduled several times thereafter to accommodate the availability of the parties' experts. An entitlement hearing was held on January 25-26, 2017, in Washington, D.C. Drs. Steinman and Utz testified on behalf of petitioners, and Drs. Raymond and Venkatesan testified on behalf of respondent. The hearing resumed on March 10, 2017, where Drs. Steinman and Utz again testified on behalf of petitioners. After the hearing, both parties continued to file additional exhibits and expert reports until the record was closed on May 25, 2017. See Order dated May 25, 2017 (ECF No. 164).

This matter is now ripe for adjudication.

III. Issues to be Decided

The parties dispute two issues: J.T.'s diagnosis and whether the condition was caused by the HPV vaccination she received on March 1, 2007. Joint Prehearing Submission ("Joint Sub.") dated April 4, 2016 (ECF No. 135) at 1-2. Petitioners maintain that the HPV vaccine administered on March 1, 2007, caused J.T. to develop ADEM. Id. Respondent disagrees that J.T. had ADEM. The parties agree that J.T. had a genetic mutation, FUS P525L, which is associated with the development of juvenile ALS ("JALS").

The parties also dispute causation. Petitioners assert that J.T.'s HPV vaccination caused her to suffer ADEM. They further assert that "J.T.'s ADEM caused her ALS." Joint Sub. at 2. Respondent disagrees that J.T. had ADEM, or that ADEM played any role in the etiology or clinical course of J.T.'s ALS. Instead, respondent asserts that J.T.'s ALS was caused by her genetic mutation.

IV. Medical Summary

a. Summary of Relevant Facts

J.T. was born on January 12, 1994. Pet. Ex. 1 at 222. She received the first two doses of the Gardasil vaccine from her primary care physician, Dr. Cuthbertson, on September 1, 2006, and

November 1, 2006, respectively. Pet. Ex. 1 at 7-9. She received the third dose of the vaccine on March 1, 2007. Id. at 9.

On May 24, 2007, J.T., age 13, fell while attempting to jump a hurdle during physical education class. Pet. Ex. 1 at 193. In July 2007, she continued to develop weakness and pain in her left leg and was walking with a limp. Id. By August 2007, she began experiencing right arm weakness. Id.

On August 28, 2007, J.T. saw an orthopedist, Dr. Scott Hoffinger. Pet. Ex. 7 at 40. She had pain in the anterior and lateral thigh but "no neurological signs or symptoms." Id. at 39. She had a "much harder time getting around with limping," during the month of August. Id. She was referred to physical therapy, but returned to Dr. Hoffinger on October 9, 2007, because she was not better and "possibly a little bit worse," after physical therapy. Id. At that time, Dr. Hoffinger noted that she was weaker, her limp was significantly worse, and her leg muscles had some atrophy. Id. A bone scan of J.T.'s spine, pelvis, and lower extremities and MRI of her cervical, thoracic, and lumbar spine showed no gross abnormalities. Id. at 33. J.T. returned to Dr. Hoffinger on November 13, 2007, for a routine follow-up, and on examination he noted that she had some bilateral wasting of her hands, with the left hand greater than the right. Pet. Ex. 7 at 33. He also noted decreased reflexes in her left lower extremity, and gross muscle atrophy of the left quadriceps and calf muscles. Id. His assessment was "systemic polyneuropathy with gross muscle wasting," and he referred her to a pediatric neurologist and rheumatologist. Id.

On November 21, 2007, J.T. presented to pediatric neurologist Dr. Jonathan Strober. Pet. Ex. 1 at 222-23. Dr. Strober noted that J.T. suffered from "left lower and right upper extremity weakness and atrophy with some mild weakness of the right lower extremity." Id. at 223. EMG and nerve conduction studies showed "mixed demyelinative and axonal findings," and Dr. Strober ordered a lumbar puncture "to rule out autoimmune conditions such as chronic inflammatory demyelinating polyneuropathy ("CIDP")." Id. at 224.

On December 10, 2007, J.T. presented to Dr. Richard Finkel, a neurologist at the Children's Hospital of Philadelphia ("CHOP"). Pet. Ex. 3 at 1. She was admitted to CHOP for further evaluation and treatment. By that point, she was "unable to walk consistently around school and ha[d] required a wheelchair for approximately the past [one] week." Pet. Ex. 3 at 10. J.T. was discharged December 15, 2007, with a diagnosis of CIDP/multifocal motor neuropathy. Id. at 10. She underwent five doses of intravenous immunoglobulin ("IVIG") therapy. Id. at 11.

On January 2, 2008, J.T. saw Dr. Strober again, and his records show that her condition had further deteriorated. Pet. Ex. 1 at 201. She underwent another round of IVIG but showed no improvement. Id. at 197. By the date of her follow up with Dr. Strober on January 16, 2008, she was unable to walk up the stairs and used a scooter to get around at school. Id. Due to her worsening condition despite repeated IVIG treatments, Dr. Strober prescribed a course of oral steroids. Id. at 199.

J.T. was hospitalized at Lucile Packard Children's Hospital from February 4 through 17, 2008. Pet. Ex. 2 at 822. During this admission, she was thought to have an autoimmune motor neuropathy and/or a possible motor neuron disease. Id. EMG testing indicated "pure motor neurogenic disorder with axonal features predominating." Id. Cerebrospinal fluid testing showed no signs of inflammation, oligoclonal bands and a normal IgG index. Id. at 823, 846, 864. An MRI

of her spine showed "loss of the cervical and lumbar enlargements and abnormal P2 signal, most predominantly below T8 in the spinal cord," but no enlargement of the roots. Id. at 823, 835. She was treated with five days of Solu-Medrol IV and three days of plasmapheresis. Id. A right-sided quadriceps muscle and sural nerve biopsy was "consistent with a neurogenic muscular pathology showing some group atrophy with compensatory hypertrophy." Pet. Ex. 2 at 737, 826- 27. During the admission, Dr. Lawrence Steinman, petitioner's expert, testified that he saw J.T. as a consultant.[3] Tr. 108.

On March 14, 2008, J.T. presented to Dr. Wang complaining of progressive weakness over the past few days, which rendered her unable to stand, even with a walker. Pet. Ex. 1 at 182. J.T. was then admitted to the hospital for a more aggressive regimen of Solu-Medrol and plasmapheresis. Id. at 183. On the third day of her hospitalization, J.T. suffered from a seizure. Pet. Ex. 2 at 683. The attending neurologist noted her diagnosis as "motor neuropathy of unknown cause," and the differential diagnosis could include a possible form of amyotrophic lateral sclerosis ("ALS").[4] Pet. Ex. 3 at 684. J.T. had another seizure on March 20, 2008. Pet. Ex. 2 at 698. The attending rheumatologist ordered continued IVIG, plasmapheresis, "metabolic/genetic/mitochondria evaluation STAT," and consultation with expert Dr. Bob Miller to rule out ALS. Pet. Ex. 2 at 701. Dr. Miller reluctantly concluded that J.T. had "a pure lower motor neuron syndrome, or progressive muscular atrophy." Tr. 314-15. He noted that "evidence for an autoimmune dysfunction or demyelinating condition … [was] not convincing." Id. at 314.

On April 5, 2008, J.T. saw Dr. Wang and Dr. Frankvich for a follow-up appointment. J.T. continued to have progressive weakness, and she was undergoing experimental treatment for primary muscular atrophy with lithium and planned to start Riluzole, a drug used to slow the process of ALS, in one to two weeks' time. Pet. Ex. 1 at 169-72.

J.T. saw Dr. Frankovich at Lucile Packard Children's Hospital for a follow-up in the Pediatric Rheumatology Clinic on April 17, 2008. Dr. Frankovich noted that J.T.'s strength and endurance had continued to deteriorate to the point that she was experiencing difficulty feeding herself, rolling over at night, and maintaining an upright position. Pet. Ex. 1 at 162. Dr. Frankovich noted that the lab tests did not confirm or refute an underlying autoimmune process. Id. at 165. Dr. Frankovich gave J.T. a steroid taper to further decrease her dosage of Prednisone. Id.

On April 29, 2008, J.T. presented to Dr. Wang for follow-up treatment. At that visit, Dr. Wang noted that J.T. had previously received the Gardasil vaccination. Dr. Wang wrote, "[I]t is uncertain whether this vaccine may have played a role in her motor neuron degeneration." Pet. Ex. 1 at 160.

J.T. saw an ALS specialist, Dr. Catherine Lomen-Hoerth, on April 30, 2008. Pet. Ex. 1 at 126. Dr. Lomen-Hoerth opined that J.T. had evidence of a "pure lower motor neuron syndrome with the exception of crossed adductor reflexes." Id. at 128 (parentheticals omitted). She noted that J.T.'s "extensive work-up for a mitochondrial disorder" was negative. Id. Due to her diaphragm

[3] While Dr. Steinman testified that he consulted in J.T.'s case during her hospitalization, he did not make or create any medical records, or sign any of J.T.'s records. Tr. 12.

[4] See Section IV(e) for a detailed explanation of ALS.

involvement, Dr. Lomen-Hoerth suggested that J.T. use a bilevel positive airway pressure ("BiPAP") machine to help her breathe, which she began using on June 6, 2008. Id.

J.T. returned to Dr. Lomen-Hoerth on August 11, 2008. Her condition had failed to improve despite a "variety of alternative medications and traditional treatments for ALS." Pet. Ex. 1 at 67. Her prognosis was "difficult to determine since in some ways she resemble[d] [spinal muscular atrophy] patients which may have a better prognosis." Pet. Ex. 1 at 68. Dr. Lomen-Hoerth ordered hospice care for J.T. the same day. Id. at 69.

On March 9, 2009, J.T. was admitted to the University of California San Francisco Medical center with respiratory failure, and she subsequently died on March 15, 2009, of an "atypical amyotrophic lateral sclerosis (ALS)–like motor neuron disease." Pet. Ex. 6 at 2. Subsequent genetic testing on J.T. reported on November 5, 2009, by Dr. Robert Brown, Professor and Chair of the Department of Neurology at the University of Massachusetts Medical School, revealed that J.T. had a P525L mutation in FUS exon 15 ("FUS P525L"). Resp. Ex. C at 1-2; Tr. 254.

b. Autopsy

On March 16, 2009, an autopsy was conducted by Drs. Lomen-Hoerth, Maurice S. Zwass, Bradley A. Stohr, and neuropathologist Eric J. Huang, at the University of California San Francisco. They concluded that J.T. died "from an atypical amyotrophic lateral sclerosis (ALS)-like lower motor neuron disease leading to respiratory failure." Pet. Ex. 6 at 1.

There were three principle neuropathological findings: (1) extensive "macrophage[5] infiltrates, lymphocytic[6] infiltrates, and severe astrogliosis[7] in the affected regions of the spinal cord," attributed to "an extensive demyelinating[8] process involving the anterior and lateral columns[9]

[5] Macrophages are mononuclear phagocytes, which kill and ingest particulate matter and microorganisms. They also play a role in the "digestion and presentation of T and B lymphocytes." Dorland's Illustrated Medical Dictionary ("Dorland's"), 32nd Ed. (2012) at 1093, 1423.

[6] Lymphocytes are mononuclear leukocytes, which make up the body's immune cells, and are divided into two classes: T and B lymphocytes. Dorland's at 1084.

[7] Astrogliosis, or gliosis, is an "excess of astroglia [astrocytes are collectively referred to as astroglia] in damaged areas of the central nervous system." Dorland's at 784. Astrocytes are neuroglial cells, which make up the supporting structure of nervous tissue. Id. at 1265.

[8] Myelin is "the substance of the cell membrane of Schwann cells that coils to form the myelin sheath," which is made up of proteins and acts as an "electrical insulator." Dorland's at 1218. The process of demyelination occurs when the myelin sheath is destroyed. Id.

[9] The anterior column of the spinal cord is "the anterior portion of the gray substance of the spinal cord; it contains neurons that innervate the skeletal muscles of the neck, trunk, and limbs. In transverse section it is seen as a horn." Dorland's at 390. The lateral column is the intermediate column of the spinal cord; it is "the lateral portion of the gray matter of the spinal cord, extending from the second thoracic to the first lumbar segment of the spinal cord; in transverse section it is seen as a horn." Id.

at all levels of the spinal cord;" (2) "severe loss of motor neurons,"[10] at all levels of the spinal cord; and (3) cytoplasmic inclusions[11] in scattered neurons in the cortex, medulla oblongata and spinal cord. Pet. Ex. 6 at 7.

In addition to the three principle findings, the neuropathologist also wrote a lengthy description of the findings related to the spinal cord, stating in pertinent part:

> The principal findings in the spinal cord are extensive demyelination involving the anterior column, lateral column and anterior horn. There are macrophage infiltrates, lymphocytic infiltrates and severe astrogliosis in the affected regions of the spinal cord. Many of the inflammatory infiltrates are identified around blood vessels. These findings are present at all levels of the spinal cord. Although the demyelination does not appear to involve the posterior column, scattered macrophages and lymphocytes are also identified in the posterior column. The anterior horn of the spinal cord at all levels shows a severe loss of motor neurons. Furthermore, all anterior nerve roots emanating from the ventral aspect of the spinal cord show extensive loss of axons and marked demyelination. All of the lesions in the spinal cord appear to be the same age.

Pet. Ex. 6 at 7.

In addition, the pathologists suggest that the progressive neurological disease was "mediated by immune responses leading to extensive demyelination in the spinal cord." Pet. Ex. 6 at 8. They describe two examples of immune-mediated demyelinating diseases that had some of the neuropathological features seen in the autopsy, including ADEM and multiple sclerosis ("MS"). Id. However, they note that MS rarely presents in patients younger than age 15, and that ADEM affects adolescents. As for ADEM they stated, "Due to the rapid progressive nature of ADEM, the pathological features are typically of the same age, and are frequently characterized by perivascular cuffing of macrophages, diffuse demyelination, and macrophage and lymphocytic infiltrates. Astrogliosis can be detected in ADEM, but [it is] usually not as robust as that seen in chronic MS lesions." Id. at 9. The pathologists did not, however, conclude that J.T. had either MS or ADEM. J.T.'s final diagnosis was "atypical progressive lower motor neuron disease," or "atypical ALS." Id.

A list of references was included in the autopsy. Some of these references discussed neuropathological findings seen in motor neuron diseases (ALS) and demyelinating diseases (principally MS). Greenfield's Neuropathology Text describes the findings seen in J.T.'s autopsy as consistent with motor neuron diseases (ALS). ALS is characterized by loss of motor neurons and surviving neurons may contain inclusion bodies. Pet. Ex. 69 at 959. As for myelin abnormalities

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[10] Neurons are "any of the conducting cells of the nervous system. A typical neuron consists of a cell body, containing the nucleus and the surrounding cytoplasm (perikaryon); several short radiating processes (dendrites); and one long process (the axon), which terminates in twig-like branches [ ] and may have branches [ ] projecting along its course." Dorland's at 1267.

[11] Cell inclusions are "usually lifeless, often temporary, constituent[s] of the cytoplasm of a cell, such as an accumulation of proteins, fats, carbohydrates, pigments, secretory granules, crystals, or other insoluble components." Dorland's at 928.

seen in ALS, Greenfield's explains, "white matter of the spinal cord shows myelin loss in the corticospinal tracts associated with astrocytic gliosis and accumulation of microglial macrophages." Id.

Similar findings are also described in demyelinating conditions, specifically MS. In the Textbook of Neuropathology, Raine explains that MS is characterized by "selective loss of myelin with relative sparing of axons." Pet. Ex. 68 at 627. Acute MS is characterized by myelin pallor, lesions that are "intensely inflammatory with small mononuclear cells," perivascular cuffing, macrophages, and T cell involvement in lesions. Id. at 669.

c. Dr. Eric J. Huang's Article[12]

Approximately one year after J.T.'s death, Dr. Huang and colleagues presented J.T.'s case, along with one other case, in an article entitled "Extensive FUS-Immunoreactive Pathology in Juvenile Amyotrophic Lateral Sclerosis with Basophilic Inclusions." Pet. Ex. 9 at 1. The autopsies from both cases revealed a severe loss of motor neurons in the spinal cord. Many of the remaining neurons contained "intra-cytoplasmic basophilic inclusions." Id. at 3. Immunohistochemistry staining revealed that these "basophilic inclusions were strongly positive for FUS." Id. Basophilic inclusions were also found in parts of the cerebral cortex and medullar oblongata. Id. The "abnormal FUS protein accumulations" (basophilic inclusions) were noted to be "the most striking finding," underscoring "the critical role of abnormal FUS protein accumulations in [JALS]." Id.

As for the white matter[13] pathology, the authors suggested it may be "a manifestation of the disease process in rapidly progressive ALS." Id. at 8. They stated that future studies are needed to determine the significance of the "white matter pathology" in FUS/ALS patients. Id. Unlike J.T.'s autopsy report, in the article there is no suggestion of an immune-mediated response or reference to ADEM or MS.

d. Dr. Huang's Letter, July 2, 2011

More than two years after J.T.'s death, and in response to an apparent inquiry from petitioner's counsel, Dr. Huang wrote the following letter, dated July 2, 2011, to Mr. Cohan:

> This letter is in response to your request to opine on whether the case study entitled "Extensive FUS-Immunoreactive Pathology in Juvenile Amyotrophic Lateral Sclerosis with Basophilic Inclusions" analyzed whether Gardasil was a contributing factor in causing [J.T.]'s juvenile ALS.
>
> To answer your inquiry, while our study did initially consider Gardasil as a potential contributing factor in causing [J.T.]'s juvenile ALS, we were unable to reach any definitive conclusion on that issue. The hypothesis that Gardasil may have

[12] Huang, Eric J., *Extensive FUS-Immunoreactive Pathology in Juvenile Amyotrophic Lateral Sclerosis with Basophilic Inclusions*, 20 BRAIN PATHOLOGY 1 (2010) [Pet. Ex. 9].

[13] White matter is "the white nervous tissue, constituting the conducting portion of the brain and spinal cord; it is composed mostly of myelinated nerve fibers arranged in anterior, posterior, and later funiculi in the spinal cord and in a number of named fasciculi in the brain." Dorland's at 1793.

> contributed in some way to [J.T.]'s disease was based on a number of case reports on the adverse effects of Gardasil in the central nervous system and, in [J.T.]'s case, the temporal relationship of the onset of juvenile ALS after the administration of the Gardasil vaccination. Due to the difficulty to establish a direct cause-effect relationship, however, we decided to focus our study on the neuropathological features of [J.T.]'s disease. In my opinion, Gardasil may still have a plausible role in the initiation and/or progression of [J.T.'s] condition, but it was not within the purview of our study to examine whether such a mechanism may have contributed to [J.T.]'s juvenile ALS. Nonetheless, it was our determination that the causal and/or contributing role of Gardasil in juvenile ALS should be examined in additional studies.

Pet. Ex. 11 at 1.

e. ALS

There is no disagreement about whether J.T. suffered from ALS, and indeed, the parties stipulate to that fact. ALS, also known as Lou Gehrig's disease, is a "devastating and universally fatal neurodegenerative disorder," that "primarily affects motor neurons ("MNs") and has no effective treatment." Pet. Ex. 62 at 1. ALS is a "progressive degenerative disease of the motor systems." Resp. Ex. F4 at 1. The disease is characterized by a "progressive loss of motor neurons," and ultimately leads to paralysis. Tr. 19, 243. Upper motor neurons are those "in [the] brain or brain stem that feed to [ ] other motor neurons and both excite and inhibit them. Id. at 244. Lower motor neurons are those in "the spinal cord that actually project right out to the muscles themselves." Id. ALS results in death or degeneration of these motor neurons. Id. There can be both upper and lower motor neuron involvement. Resp. Ex. F4 at 271. The disease typically presents as muscle atrophy which progresses to upper motor neuron involvement and respiratory insufficiency. Id. at 274.

There is no cure for ALS, and while disease progression can be slowed, patients eventually succumb to respiratory failure. Resp. Ex. F4 at 274-75. Fifty percent of patients die within three years of diagnosis, though the time frame may be altered based on age of onset. Id. at 271. While the disease is typically seen in older individuals, ALS which occurs prior to age 25 is defined as "juvenile ALS," or "JALS." Tr. 244. There is no specific laboratory test for ALS, which makes diagnosis challenging, especially early in the disease course. Resp. Ex. F4 at 272. Typically, denervation and decreased response to nerve stimuli are seen in patients with ALS. Id. Additionally, many patients present with wasting of the hand muscles. Id.

Approximately ten percent of ALS is associated with genetic mutations. Tr. 257. One of these mutations is the fused in sarcoma ("FUS") mutation. This mutation was first identified through its association with cancer, specifically sarcoma, where it escalates growth of cancer cells. Id. at 255. The mutation is now found in a variety of diseases. Resp. Ex. D at 4. As it relates to ALS, FUS mutations cause protein to build up in the cytoplasm of cells, instead of being properly localized in the nucleus. Tr. 257. The protein that builds up in the cytoplasm is believed to adversely impact protein synthesis. Id. at 246-48.

With regard to JALS, over 50 mutations have been found to be associated with the disease. One of these is FUS P525L, the mutation identified in J.T. Tr. 263-64; 260-61. This specific

mutation and its association with JALS was first referenced in the literature in 2009. See Resp. Ex. D6;[14] Resp. Ex. E6.[15] "Patients with the FUS P525L mutation, most of whom are female, reportedly display a specific ALS phenotype characterized by a severe course, early disease onset, rapid disease onset, rapid disease progression, multiple system degeneration and the presence of basophilic inclusions." Pet. Ex. 62 at 7. In the P525L mutation, the 525th amino acid, a proline, is changed to a leucine due to an altered base pair. Resp. Ex. D at 4. This causes the FUS protein to misfold and mislocalize. Tr. at 107. Rather than being in the nucleus, it is instead found in the cytoplasm of a cell. Id. It has been hypothesized that the misfolded FUS proteins "inhibit normal RNA and protein synthesis and thereby suppress[] neuronal functions and survival," resulting in neuron cell death, which is characteristic of the disease. Resp. Ex. F at 8; Tr. 107.

f. ADEM

In contrast, "[a]cute disseminated encephalomyelitis ("ADEM") is an immune-mediated inflammatory demyelinating disease of the CNS, which is typically transitory and self-limited." Resp. Ex. F at 3. "It is characterized by an acute or subacute encephalopathy … and MRI evidence of widespread demyelination that predominantly involves the white matter of the brain and spinal cord. It is presumed to be secondary to an immune response following a viral infection or vaccination." Id. Initial findings of ADEM usually begin within two days to four weeks after the exposure to the inciting event. Id. "It often presents with systemic symptoms such as fever, malaise, headache, and vomiting which occur shortly before the appearance of neurological symptoms and signs. The clinical course is rapidly progressive, developing maximum deficits within a few days (mean 4.5 days)." Id. "A wide variety of neurological deficits have been described in children with ADEM including obtundation and depressed consciousness; long tract signs; ataxia;[16] spinal cord involvement; visual involvement; [and] speech impairment or aphasia. Focal motor seizures have been reported." Id. MRI is the most sensitive marker of acute demyelination, showing lesions. Id.

Recovery from ADEM is usually complete, especially in children. Resp. Ex. F at 4. The clinical criteria for the diagnosis of ADEM are: (1) an acute or subacute encephalopathy with polyfocal deficits and widespread hyperintense lesions (seen on MRI) affecting the CNS white matter; (2) "no evidence of previous destructive white matter changes … present on MRI[;]" and (3) "no history of a previous clinical episode with features of a demyelinating event." Id.

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[14] Caroline Vance, et al., *Mutation in FUS, an RNA Processing Protein, Cause Familial Amyotrophic Lateral Sclerosis Type 6*, 323 SCI 1208 (2009) [Resp. Ex. D6].

[15] T.J. Kwiatkowski, Jr., et al., *Mutations in the FUS/TLS Gene on Chromosome 16 Cause Familial Amyotrophic Lateral Sclerosis*, 323 SCIENCE 1205 (2011) [Resp. Ex. E6].

[16] Ataxia is "the failure of muscular coordination," or "irregularity of muscular action." Dorland's at 170.

V. Expert Qualifications

a. Petitioners' Experts

i. Dr. Lawrence Steinman

Dr. Steinman is a board certified neurologist and serves as a professor of neurology and pediatrics at Stanford University, where he has been an attending physician and neurologist for the past 33 years. Pet. Exs. 20 at 1; Pet. Ex. 14 at 3. Dr. Steinman received his M.D. from Harvard University and completed his residency at Stanford University Hospital. Pet. Ex. 48 at 1. He served as the chair of the interdepartmental program in neuro-immunology at Stanford from 2002 to 2011 and has been awarded numerous accolades and patents related to his work in neurology. Pet. Ex. 14 at 3. Additionally, Dr. Steinman works as an editor for multiple journals in addition to publishing extensively on his work. Pet. Ex. 48 at 3-45. Dr. Steinman currently sees both adult and pediatric patients in his practice. Pet. Ex. 14 at 3. Dr. Steinman has seen many patients with ADEM and ALS, though he did not specify how many. Tr. 9.

ii. Dr. Paul Utz

Dr. Utz is a professor of medicine at Stanford University and is board certified in both immunology and rheumatology. Pet. Ex. 21 at 1. He obtained his M.D. from Stanford University and completed his residency at Brigham and Women's Hospital in Boston, Massachusetts. Prior to teaching at Stanford, Dr. Utz also taught at Harvard Medical School. Id. He served as the director of Stanford's Center for Clinical Immunology from June 2007 until November 2008. Pet. Ex. 49 at 2. Dr. Utz received a grant from the National Institutes of Health ("NIH") to study the immune system's response to the influenza vaccine. Pet. Ex. 21 at 2. He was involved in vaccine development for both multiple sclerosis and juvenile arthritis and is well-published in the areas of immunology and rheumatology. Id. at 1-2. Dr. Utz routinely sees patients with a variety of neuroinfectious and neuroimmunological diseases, and he has cared for patients with ADEM and ADEM-like illnesses. Resp. Ex. E at 1; Tr. 147. Because Dr. Utz specializes in immunology and rheumatology, he is very familiar with the diagnosis of ALS, as he often rules it out as a diagnosis from other systemic rheumatic diseases. Tr. 147. While he typically does not treat patients for ALS, he has seen patients who have the disease.

b. Respondent's Experts

i. Dr. Gerald Raymond

Dr. Gerald Raymond is a pediatric neurologist who specializes in neuropathology and genetics. He attended medical school at the University of Connecticut. Resp. Ex. O at 1. After medical school, Dr. Raymond completed residencies in pediatrics and neurology fellowships in developmental neuropathology, genetics and teratology. Id. Dr. Raymond is board-certified in pediatrics, clinical genetics, and neurology, with special competency in child neurology. Id. at 15. He has taught at numerous institutions including Université Catholique de Louvain in Brussels, Belgium, Johns Hopkins School of Medicine in Baltimore, Maryland, and is currently a professor of neurology at the University of Minnesota School of Medicine. Id. at 2 and 14. Dr. Raymond has served as a peer reviewer and published numerous articles in these fields as well. See id. at 2–9 and

16. He has treated over 100 patients with ADEM over the course of his professional career, and he has also seen patients with ALS. Tr. 241.

ii. Dr. Arun Venkatesan

Dr. Venkatesan completed both a Ph.D. in microbiology and immunology and an M.D. at the University of California, Los Angeles. Resp. Ex. E at 1. His residency in neurology was completed at Johns Hopkins University in Baltimore, Maryland, where he joined the teaching staff at the medical school. Id. Since 2009, he has served as the director of the Johns Hopkins Encephalitis Center where he sees both adult and pediatric patients. Id.; Resp. Ex. P at 1. He is also active with the Johns Hopkins Multiple Sclerosis Center and Transverse Myelitis Center. Resp. Ex. E at 1. Dr. Venkatesan has published numerous articles related to neuroinflammatory and neuroinfectious diseases. Resp. Ex. P at 1-3. He is currently receiving funding from NIH to further his research on encephalitis. Id. at 4. In the last five or six years, Dr. Venkatesan has seen over 100 patients with ADEM, and he also sees and diagnoses patients with ALS and other motor neuron disorders. Tr. 382-83.

VI. Discussion

a. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. §300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Human Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioners' burden of proof is by a preponderance of the evidence. §300aa-13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, petitioners must prove that that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." §300aa-13(a)(1)(B).

b. Legal Framework

To receive compensation under the Program, petitioners must prove either: (1) that J.T. suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table— corresponding to a vaccine that she received, or (2) that J.T. suffered an injury that was actually caused by a vaccination. See§§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Petitioners 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." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because petitioners do not allege that J.T. suffered a Table injury, they must prove that the vaccine J.T. received caused her death. To do so, they must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and her injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for her injury ("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and her injury ("Althen Prong Three"). §300aa–13(a)(1); Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

The causation theory must relate to the injury alleged. Thus, petitioners must provide a reputable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioners cannot establish entitlement to compensation based solely on their assertions. Rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 300aa-13(a)(1). In determining whether petitioners are entitled to compensation, the special master shall consider all material contained in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 300aa-13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' offered experts and rule in petitioners' favor when the evidence weighs in their favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence"); Althen, 418 F.3d at 1280 ("close calls" are resolved in petitioner's favor).

Another important aspect of the causation-in-fact case law under the Vaccine Act concerns the factors that a special master should consider in evaluating the reliability of expert testimony and other scientific evidence relating to causation issues. In Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579 (1993), the United States Supreme Court listed certain factors that federal trial courts should utilize in evaluating proposed expert testimony concerning scientific issues. In Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999), the Federal Circuit ruled that it is appropriate for special masters to utilize Daubert's factors as a framework for evaluating the reliability of causation-in-fact theories actually presented in Program cases.

The Daubert factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." Terran, 195 F.3d at 1316, n.2 (citing Daubert, 509 U.S. at 592-95). In addition, where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357, 1362 (Fed.Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 743 (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 146 (1997)).

c. Expert Opinions

i. Petitioners' Expert, Dr. Lawrence Steinman

1. Diagnosis

Dr. Steinman emphasized that an immune response in the form of widespread inflammation in J.T.'s spinal cord was found outside of the areas that ALS affects, placing the pathology outside of ALS alone and indicating the presence of a secondary condition, ADEM. Pet. Ex. 20 at 1, 14. He opined, "ALS does not explain how lymphocytes infiltrated far outside the boundaries seen in ALS. The mutation does not explain why the pathologists … considered … ADEM as the leading [diagnosis]." Id. at 15. For these reasons, Dr. Steinman believes that J.T.'s correct diagnosis is both ADEM and ALS.

a. Autopsy

Dr. Steinman's opinion, in large part, turns on the neuropathology findings consistent with inflammation, and the comparison to ADEM, an immune-mediated condition. More specifically, Dr. Steinman opined that the finding of "macrophage infiltrates, lymphocytic infiltrates, and severe astrogliosis," as well as lesions appearing to be the same age, is "hallmark" for ADEM. Tr. 32 (citing Pet. Ex. 6 at 7). Dr. Steinman agrees that the loss of neurons and basophilic inclusions described in the autopsy report are due to the FUS P525L mutation and not ADEM. Tr. 129

b. Clinical Course

Dr. Steinman was a consultant on the team of doctors who cared for J.T. during her hospitalization in February 2008. Tr. 12-14. At that time, the physicians believed that J.T. had a neuroinflammatory disease, an inflammatory neuropathy, and possibly a motor neuron disease like ALS.[17] Tr. 100. Chronic inflammatory demyelinating polyneuropathy ("CIDP") was considered as a differential diagnosis. Id. at 23-24. Although a neuroinflammatory disease was also considered, Dr. Steinman conceded that no one ever diagnosed J.T. with ADEM at any time during her hospital course. In fact, Dr. Steinman agreed that no one diagnosed J.T. with ADEM while she was alive. Id. at 25. The only encephalopathic manifestation that J.T. had was a seizure. Tr. 83-84. Dr. Steinman did not attribute J.T.'s seizure to inflammation. Id. at 24. Moreover, J.T.'s seizure (or seizures) did not lead her physicians to a differential diagnosis of ADEM. Id. at 84. Instead, she was diagnosed with ALS. Id. at 25.

As for diagnostic tests, Dr. Steinman conceded that J.T.'s EMG did not reveal findings consistent with ADEM, but it did show motor and axonal involvement consistent with ALS. Tr. 101-03. Similarly, J.T.'s cerebrospinal fluid did not show increased protein, which could be seen in ADEM, and thus, the results were more consistent with ALS. Id. 105. MRIs of J.T.'s brain and spine were also consistent with ALS, and not ADEM. Id. at 105-06; 110-11. Moreover, J.T. did not have the response to steroids, IVIG, or plasmapheresis Dr. Steinman would have anticipated if she had ADEM; he would have expected a better response with improvement in her condition. Id. at 112-14.

[17] The attending physician during this admission was Dr. Ching Wang. Tr. 101.

2. Causation Theory

Dr. Steinman proposed a causation theory best explained in several steps.[18] First, he opined that the HPV vaccine triggered J.T.'s ADEM via the mechanism of molecular mimicry. Pet. Ex. 20 at 1, 30; Tr. 16, 19. The description of the lesions being the same age indicates a "thunderclap" event, or trigger, which Dr. Steinman believed to be the vaccine. Tr. 32-33.

The second part of Dr. Steinman's theory relates to how ADEM caused J.T.'s ALS, and he also discussed the role of the FUS mutation in causing ALS. Dr. Steinman testified that J.T.'s FUS mutation "made her motor neurons vulnerable to injury." Tr. 469. He opined that the Gardasil vaccine likely caused damage to the motor neurons, which were already vulnerable from the FUS mutation. Tr. 469-71. The ADEM in turn triggered J.T.'s "fulminant course" of ALS. Pet. Ex. 20 at 1; Tr. 16. According to Dr. Steinman, this theory is supported both by the medical literature and by J.T.'s autopsy report. Pet. Ex. 20 at 1. Scientific literature has "strong support … for how [HPV vaccine] can induce ADEM." Id.

Dr. Steinman also testified regarding the temporal association between J.T.'s receipt of the Gardasil vaccination and her subsequent alleged development of ADEM and then ALS.

a. Gardasil Vaccination Triggered ADEM via Molecular Mimicry

Molecular mimicry occurs when there is structural similarity between a self-protein and a foreign-protein triggering an immune response that attacks the body's own cells. Pet. Ex. 14 at 6-7; Tr. 39. This structural similarity is due to homologous amino acid sequences located at the binding site of the protein, the portion of the protein that triggers T-cell recognition. Pet. Ex. 14 at 6, 9. Foreign proteins, "presented by the [human leukocyte antigen] molecules[21] of the immune system," "provoke[] the T cells to attack body tissues that contain the self-antigens. Pet. Ex. 18C at 109.[22] Specifically, Dr. Steinman asserts that the HPV vaccine has been shown to have structural similarity to myelin basic protein ("MBP") as well as aquaporin type 4 ("AQP4"). Pet. Ex. 14 at 9 and 13.

i. Myelin Basic Protein ("MBP")

Dr. Steinman opines that there is sufficient homology between the Gardasil vaccine and "the main constituents of the myelin sheath [i.e. MBP] to trigger a neuroinflammatory condition like

[18] Dr. Steinman briefly testified as to a possible second theory, that the aluminum adjuvant in the vaccine "stirred up" J.T.'s immune system and "push[ed] things over the edge." Tr. 472. This potential theory was not well developed by petitioners. To the extent that petitioners offer this as another causal theory, I find it unsupported by preponderant evidence.

[21] Leukocyte antigens are "a group of glycoproteins, antigenically similar but of different molecular weights, found on B cells, T cells, thymocytes, and leukopoietic cells." Dorland's at 105.

[22] For a more detailed explanation of the theory of molecular mimicry, see Pet. Ex. 32G and Resp. Ex. R.

ADEM." Tr. 17. He cites an article by Wucherpfennig et al.[23] showing that HPV, like many other viruses, shares "molecular similarities" with MBP between amino acids 82 and 98. Pet. Ex. 20 at 5. The study demonstrates that MBP shares an amino acid sequence with HPV types 7 and 13.[24] Pet. Ex. 14 at 10-11.

Dr. Steinman also described alleged key sequences of MBP and HPV type 11 that have homologies. Pet. Ex. 31 at 6. Within a 12 amino acid sequence, there is a three sequential amino acid homology and two isolated single amino acid homologies. Id. For HPV type 18, Dr. Steinman asserted "there are two matches, one with [three] amino acids and a second region with [three] consecutive amino acids." Id. at 7. In comparison, there is only a two amino acid homology, phenylalanine and lysine, between MBP and the L1 protein of HPV type 16. Pet. Ex. 20 at 7-8. But, Dr. Steinman explains, these amino acids are "the key anchors to the HLA molecule and to the T cell receptors." Id. at 8; Pet. Ex. 18B.

While Wucherpfennig examined the amino acid sequence necessary to cause antibodies to attack the brain, not the spinal cord, Dr. Steinman hypothesized that the process would work identically in the spinal cord. Tr. 41. Other studies cited by Dr. Steinman demonstrate that five or six amino acids were adequate to induce the animal model of ADEM in mice.[27] Dr. Steinman concedes, however, that no one can "say with absolute certainty… that the vaccine has enough [homology] to cause ADEM in a human." Id.

Because of the cross-reactivity shown in his submitted literature, Dr. Steinman believes "[a]n immunization to Gardasil could thus… trigger brain inflammation." Pet. Ex. 20 at 6. He also introduced a study by Pohl-Kappe et al.[28] describing "immunity to myelin basic protein in ADEM." Pet. Ex. 20 at 13. He opined that "[m]olecular mimicry is the scientific concept that best explains how Gardasil can trigger ADEM." Pet. Ex. 20 at 9.

ii. Aquaporin Type 4 ("AQP4")

AQP4 is a water channel found in the astrocytes of the blood-brain barrier ("BBB"). Pet. Ex. 14 at 13; Pet. Ex. 18G at 1991. Dr. Steinman opines that changes to astrocytes and the BBB are

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[23] Kai W. Wucherpfennig et al., *Recognition of the Immunodominant Myelin Basic Protein Peptide by Autoantibodies and HLA-DR2-restricted T Cell Clones from Multiple Sclerosis Patients*, 100 (5) J. CLINICAL INVESTIGATION 1114 (1997) [Pet. Ex. 24H].

[24] The quadrivalent Gardasil vaccine that J.T. received contains the L1 proteins of HPV types 6, 11, 16, and 18. Pet. Ex. 14 at 13 (citing Pet. Ex. 18H).

[27] Anand M. Guatam et al., *A Viral Peptide with Limited Homology to a Self Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis*, 161 J. IMMUNOLOGY 60 (1998); Anand M. Guatam et al., *Minimum structural requirements for peptide presentation by major histocompatibility complex class II molecules: Implications in induction of autoimmunity*, 91 PROC. NAT'L. ACAD. SCI. 767 (1994) [Pet. Ex. 35H].

[28] Anette Pohl-Koppe et al., *Myelin basic protein reactive Th2 T cells are found in acute disseminated encephalomyelitis*, 91 J. NEUROIMMUNOLOGY 19 (1998) [Pet. Ex. 24N].

linked to dysfunction and death of motor neurons. See Pet. Ex. 18G at 1. Dr. Steinman believes that homology to the self-proteins in AQP4 "trigger[ed] a neuroinflammatory condition." Tr. 17.

In support of this opinion, Dr. Steinman cited a study performed by Menge et al[29] showing three homologous amino acid sequences between AQP4 and HPV types 16 and 18. Pet. Ex. 14 at 13 (citing Pet. Ex. 18H). Dr. Steinman believes there is "striking cross-reactivity" between AQP4 and the protein in HPV type 16. Pet. Ex. 20 at 12.

Dr. Steinman cited another study, performed by Bataveljic et al.,[30] in support of the significance of AQP4 in ALS. Pet. Ex. 14 at 18. The study found that there was increased expression of AQP4 in the brainstem and cortex of rats with the SOD1 gene mutation[31] model of ALS. Pet. Ex. 18G at 1991. The authors of the study hypothesized that the changes in AQP4 channels could affect the BBB "disturbing the neuronal microenvironment, and causing motor neuronal dysfunction and death." Id. However, the authors did not discuss homology between HPV, or the HPV vaccine, and AQP4, or draw any conclusions about whether impairment in the BBB may contribute to the cause of ALS. Moreover, they cautioned against attributing too much significance to AQP4 alone in the impairment of the BBB. Pet. Ex. 18G at 2001.

Dr. Steinman testified about his concern that Dr. Huang, the neuropathologist for J.T.'s autopsy, never addressed the autopsy findings consistent with ADEM in the paper he later published.[32] Tr. 51. The suggestion of an immune-mediated condition referenced in J.T.'s autopsy is not discussed in Dr. Huang's article. Id. 51-52. Instead, Dr. Huang's article focuses on the finding of basophilic inclusions. Id. at 52. Dr. Steinman believes that the ADEM findings are too important to be ignored in any discussion of J.T.'s pathology. Id. at 55. He also believes it is significant that no other paper that discusses FUS/ALS mentions ADEM-like pathological findings. Id. at 50, 56-57. He argues that since the literature regarding juvenile ALS in the context of FUS P525L gene mutations does not discuss ADEM-like findings, the pathology in J.T.'s case is even "more unusual." For these reasons he is persuaded that "[J.T.] suffered from a two-hit scenario … involving ADEM and ALS." Pet. Ex. 31 at 2.

b. J.T.'s ADEM Triggered Her ALS

Dr. Steinman opined that ADEM "was the trigger" that "either provoked or worsened the course of [J.T.'s] ALS." Pet. Ex. 20 at 1. He posited that "ALS was triggered from an autoimmune

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[29] Til Menge et al., *Neuromyelitis optica following human papillomavirus vaccination*, 79 NEUROLOGY 285 (2012) [Pet. Ex. 18H].

[30] Danijela Bataveljic et al., *Changes in the Astrocytic Aquaporin-4 and Inwardly Rectifying Potassium Channel Expression in the Brain of the Amyotrophic Lateral Sclerosis SOD1^{G93A} Rat Model*, 60 GLIA 1991 (2012) [Pet. Ex. 18G].

[31] The SOD1 gene produces superoxide dismutase 1 ("SOD1"). ALS can be caused by autosomal dominant inheritance of SOD1. Pet. Ex. 18G at 1991.

[32] Huang et al., 20 BRAIN PATHOLOGY 1 [Pet. Ex. 9].

response involving both the innate and adaptive immune system." Id. at 2. In mounting a response to the Gardasil vaccine, Dr. Steinman testified that a "cascade of events" occurred in J.T.'s immune system which led to "the immune destruction of [J.T.'s] motor neuron system." Id. at 2. He also opined that "[t]here is striking cross-reactivity between AQP4 and the L1 protein of HPV type 16," which is found in the Gardasil vaccine. Id. at 12. He thus posited that "Vaccination with Gardasil triggered immunity to … AQP4 and this led to the triggering of ALS and ADEM…" Id.

Dr. Steinman testified that "Aquaporin-4 is involved in the pathogenesis of ALS." Pet. Ex. 14 at 18. He cited studies by Appel, Gussoni, and Panzara,[33] which suggest evidence of adaptive immunity in the spinal cord fluid of patients with ALS. While those findings suggest that immunological processes may play a role in the etiology or progression of ALS, they fail to provide persuasive evidence that the HPV vaccine or ADEM, either alone, or in concert, cause ALS or worsen its course. See Pet. Ex. 20 at 14-15.

For example, in Panzara, a study cited by Dr. Steinman which describes autopsies of patients who succumbed to ALS, the authors found inflammatory infiltrates in the spinal cord, raising the possibility of an immune-mediated process in motor neuron degeneration. Pet. Ex. 18A at 392. But the authors drew no conclusions, instead recommending further studies to determine the role of autoimmunity in the pathogenesis of ALS. Id. at 403.

c. The Role of the FUS Mutation in J.T.'s Development of ALS

Dr. Steinman readily conceded that J.T. had ALS and that she was born with the FUS P525L mutation. Tr. 72. And while he opined that the HPV vaccine triggered J.T.'s ALS, he did not offer an opinion on whether J.T. would have lived longer had she not been vaccinated. Id. at 77-78. Rather, he "explicitly [doesn't] know whether it hastened her course or not." Id. at 88. He cited a case by Sproviero[34] describing a patient with the P525L FUS mutation who did not develop ALS until age 44, after a battle with MS. Id. at 476. He opined that other patients with the P525L FUS mutation may have had a trigger for their ALS, but he suggests that since the articles describing them were mainly focused on the mutation itself, a trigger was never discussed. Id. at 478. Dr. Steinman also testified that insufficient numbers of people have been tested to determine whether a person can have the FUS mutation and not have ALS. Id. at 59-60. He would prefer to see genetic test results from "a few million people" to feel comfortable definitively concluding that the FUS P525L mutation will always cause ALS. Tr. 483-84. He dismissed the fact that the mutation has never been found in a healthy individual. Id. at 482-83. Dr. Steinman ultimately conceded, however, that there is no evidence to date that FUS is present in healthy people. Id. at 77.

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[33] Nathan P. Staff & Stanley H. Appel, *The Immune System Continues to Knock at the ALS Door, editorial in* 26 NEUROMUSCULAR DISORDERS 335 (2016) [Pet. Ex. 37]; Emanuela Gussoni et al., *Specific T-Cell Receptor Gene Rearrangements at the Site of Muscle Degeneration in Duchenne Muscular Dystrophy,* 153 J. IMMUNOL. 4798 (1994) [Pet. Ex. 24E]; Michael A. Panzara et al., *T Cell Receptor BV Gene Rearrangements in the Spinal Cords and Cerebrospinal Fluid of Patients with Amyotrophic Lateral Sclerosis*, 6 NEUROBIOLOGY OF DISEASE 392 (1999) [Pet. Ex. 18A].

[34] William Sproviero, et al., *FUS Mutations in Sporadic Amyotrophic Lateral Sclerosis: Clinical and Genetic Analysis*, 33 NEUROBIOLOGY AGING 837.e1 (2012) [Pet. Ex. 53].

Dr. Steinman also conceded that there is no medical literature to support an association between ADEM and FUS ALS. He did introduce articles by Graves et al.[35] and Hooten et al.,[36] showing the presence of neuroinflammation in patients with ALS. Pet. Ex. 14 at 14-15 (citing Pet. Ex. 18K). While the presence of neuroinflammation is not debated, Dr. Steinman agreed it was unclear from the current medical literature whether the inflammation initiates or is a consequence of neuron death seen in ALS. Tr. 108.

In Graves, the authors noted inflammation in the spinal cord and brain, suggesting mediation by activated macrophages, mast cells, and T cells. Citing Hayashi,[37] the authors suggest that "macrophages, present in ALS tissue [may] function as [ ] phagocytes,[38] removing myelin debris, left as axons degenerate…" Pet. Ex. 36 at 335. They conclude that "[f]urther studies are needed to investigate the initiating cause of inflammation." Id. at 336.

Hooten and colleagues suggested that there are two stages of neuroinflammation in ALS, the first being protective and the second neurotoxic. Pet. Ex. 39. A more recent article by Staff and Appel[39] summarized the consensus of the literature regarding neuroinflammation in ALS. The authors stated that "It is unclear at this point how and when the immune system impacts the course of disease in ALS patients." Pet. Ex. 37 at 335.

Dr. Steinman also submitted evidence of the innate immune system's response to the Gardasil vaccine. Pet. Ex. 14 at 14-15. After vaccination with Gardasil, participants in a study demonstrated increased expression of immune system receptors. Id. at 14 (citing Pet. Ex. 18I). This increased expression is the desired effect since it means the immune system is creating antibodies to defend against HPV. Id. Dr. Steinman believes that innate immune system activation is notable because it has been shown in patients with ALS. Id. (citing Pet. Exs. 18A, 18J). However, Dr. Steinman did not cite or submit any literature to support the idea that the FUS P525L mutation can be triggered by an immune stimulus. Tr. 75.

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[35] Michael C Graves et al., *Inflammation in Amyotrophic Lateral Sclerosis Spinal Cord and Brain is Mediated by Activated Macrophages, Mast Cells and T Cells*, 5 AMYOTROPH. LATERAL SCLER. OTHER MOTOR NEURON DISORD 213 (2004) [Pet. Ex. 36].

[36] Christopher G. Hooten, et al., *Protective and Toxic Neuroinflammation in Amyotrophic Lateral Sclerosis*, 12 NEUROTHERAPEUTICS 364 (2015) [Pet. Ex. 32].

[37] S. Hayashi et al., *Pathological Study of the Diffuse Myelin Pallor in the Anterolateral Columns of the Spinal Cord in Amyotrophic Lateral Sclerosis*, 188 J. NEUROL. SCI. 3 (2001) (cited in Pet. Ex. 36).

[38] A phagocyte is "any cell capable of ingesting particulate matter, such as a microphage, macrophage, or monocyte. Such cells ingest microorganisms and other particulate antigens that are opsonized (coated with antibody or complement), a process mediated by specific cell-surface receptors." Dorland's at 1423.

[39] Staff & Appel, NEUROMUSCULAR DISORDERS 335 [Pet Ex. 37].

Dr. Steinman agreed that the P525L mutation is seen in early-onset JALS cases and that it is one of the most aggressive forms of ALS. Tr. 75. The time frame from J.T.'s first symptom of ALS until her death was 22 months. Id. at 77. Finally, Dr. Steinman conceded that J.T.'s FUS P525L mutation could have caused her ALS without any vaccine trigger, and that J.T. would have eventually had ALS, although he could not say when. Id. at 140-41.[40]

d. Onset

Dr. Steinman opined that the temporal interval between J.T.'s vaccination, on March 1, 2007, and the onset of motor weakness nearly three months after vaccination, when she had a hurdling injury on May 24, 2007, is appropriate. Pet. Ex. 14 at 16; Pet Ex. 33 at 1. While it can be difficult to cite the specific onset of "something you're born with," Dr. Steinman stated that J.T.'s track accident was an appropriate indicator for both the onset of ADEM and ALS. Tr. 80-81, 83.

Dr. Steinman referenced an article by Menge et al.[41] describing three cases in which neuromyelitis optica ("NMO")[42] occurred between four and five months after HPV vaccination. Pet. Ex. 33 at 2. Thus, a three month interval, as seen in J.T.'s case, would be well within the time frame for the onset of a CNS degenerative disorder after vaccination. Pet. Ex. 33 at 2.

ii. Petitioners' Expert, Dr. Paul Utz

1. Diagnosis

Similar to Dr. Steinman, Dr. Utz opined that J.T. suffered from two neurological diseases: (1) a sudden onset autoimmune demyelinating syndrome[43] and (2) an inherited form of ALS. Pet. Ex. 21 at 2. Dr. Utz believes J.T. had an autoimmune demyelinating condition for two reasons. First, J.T. had a previous history of another autoimmune disorder, pityriasis,[44] which increased her risk of developing another autoimmune disease. Pet. Ex. 21 at 6. Second, Dr. Utz stated that that J.T.'s autopsy results indicate an autoimmune demyelinating event, specifically with regard to the

[40] Dr. Steinman later testified, however, that he did not believe J.T.'s ALS would have occurred without a "second-hit." Tr. 476.

[41] Til Menge et al., *Neuromyelitis Optica Following Human Papillomavirus Vaccination,* 79 NEUROLOGY 285 [Pet. Ex. 18h; Resp. Ex. F22].

[42] Menge explains, however, that NMO is an autoimmune demyelinating condition, like ADEM. See Pet. Ex. 18H at 287. However, ALS is a motor neuron disorder, not a demyelinating disorder like NMO.

[43] Unlike Dr. Steinman, Dr. Utz did not specify which specific autoimmune inflammatory condition he believed J.T. had but testified that these conditions include "ADEM, CIDP, vasculitis, transverse myelitis," and others. Tr. 158. He conceded there was no reference to ADEM in J.T.'s medical record. Id. at 163.

[44] Pityriasis is a skin disease that is characterized by the formation of fine, branny scales. Dorland's at 1451. "Branny" means "resembling bran; rough, scaly, dry." Id. at 248.

lesions of the same age and the evidence of widespread involvement of the CNS. Id. Dr. Utz based his opinions in part on test results and autopsy findings.

a. Test Results

Dr. Utz testified that J.T. had low titer antinuclear antibodies[45] ("ANA") with a speckled pattern, a positive antiphospholipid test,[46] and an elevated erythrocyte sedimentation rate[47] ("ESR"), all of which indicate an autoimmune/inflammatory condition. Pet. Ex. 21 at 10. Specifically, the ANA, while only "weakly positive," was "more consistent with diseases caused by inflammation," and "often seen in autoimmune diseases." Tr. 161. Dr. Utz also testified that J.T.'s antiphospholipid test was positive at least twice, and possibly three times, in the "moderately abnormal range." Id. at 162. He noted that while the ESR is a "relatively nonspecific test that's elevated when there is inflammation in general," it was elevated even while J.T. was receiving immunosuppressive drugs that should have decreased any inflammation. Id. at 159-60, 162. Dr. Utz opined that the physicians who treated J.T. concluded from the test results that she had an inflammatory condition, which Dr. Utz testified is consistent with his proposition. Id. at 159. Since the only trigger he could find in her records was the Gardasil vaccine, he concluded that the vaccine was the triggering event of the demyelinating disease that eventually resulted in J.T.'s death. Pet. Ex. 21 at 11.

b. Autopsy Results

Dr. Utz testified that J.T.'s autopsy further supports his opinion because it indicated that she suffered from an autoimmune demyelinating disorder while also showing "many inconsistencies… for FUS-related ALS." Tr. 164. In his opinion, the fact that the lesions visualized were all of the same age indicated a "discrete, single, inciting event…much more typical for ADEM… [and] not described in… FUS/ALS." Pet. Ex. 21 at 7; Tr. 167.

Additionally, T-cell infiltration seen in J.T.'s autopsy has been shown in animal models to cause destruction of the myelin surrounding axon sheaths. Pet. Ex. 21 at 7. Dr. Utz agreed, however, that lymphocytes are found in the central nervous system ("CNS") in both ADEM and ALS. Tr. 164-65. The fact that the pathologists did a second stain to differentiate between T cells

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[45] Antinuclear antibodies are "antibodies directed against nuclear antigens." Dorland's at 101.

[46] An antiphospholipid test is used to detect the presence of antiphospholipid autoantibodies, which are "primary markers for antiphospholipid antibody syndrome [and] are linked to increase risk of thrombosis … [and] thrombocytopenia." Julius M. Cruse & Robert E. Lewis, Illustrated Dictionary of Immunology, (3rd Ed. (2009)), at 572. The autoantibodies include "those specific for cardiolipin, phosphatidylserine, and lupus," and they are "present in individuals with antiphospholipid antibody syndrome and systemic lupus erythematosus, drug-induced disorders, and infectious and neurological diseases." Id.

[47] ESR is the "rate at which erythrocytes precipitate out from a well-mixed specimen of venous blood, measured by the distance the top of the column of erythrocytes falls in a given time interval under specified conditions; an increase in rate is usually due to elevated levels of plasma proteins …. It is increased in … active inflammatory disease." Dorland's at 1594.

and B cells, however, suggested to Dr. Utz that the pathologists saw something "abnormal" and "atypical for ALS." Id. at 165. Dr. Utz also found significant the macrophagic and lymphocytic infiltrates surrounding blood vessels (perivascular cuffing). Id. at 166. He testified that these are areas where the infiltrates are leaving the blood vessels and crossing the BBB to enter the CNS, indicates a process usually associated with ADEM. Id. at 166-67. He further testified that there is no mention of perivascular cuffing in any other FUS-related ALS case. Id. at 167.

2. Causation Theory

a. Molecular Mimicry and Stress[48]

Dr. Utz posited a two-part theory based on molecular mimicry and stress. He testified that self-antigens activated by the Gardasil vaccine triggered ADEM and also targeted the motor neurons affected in ALS. Tr. 205-06. The Gardasil vaccine "activate[d] preexisting autoreactive T and B cells through a process of molecular mimicry." Id. at 512. Those T and B cells became inflammatory and crossed the blood-brain barrier to reach the CNS. Id. Once in the CNS, they caused ADEM while also attacking the myelin sheath of neurons. Id. at 512-13. J.T.'s existing FUS mutation "stressed" her neurons, making them "poised to be pushed over the edge to develop ALS." Id. at 514. As the myelin containing cells were attacked by the self-antigens, the myelin was destroyed. Id. at 216. This demyelination killed the axons being protected by the myelin, and this axon death was "the ALS part of it." Tr. 216. Dr. Utz acknowledged that there is no literature to support his stress theory,[49] which is "speculative." Id. at 211. He opined that even without previously stressed cells, ADEM can still trigger ALS. Id. at 211-32. Dr. Utz believes the vaccine and subsequent ADEM caused J.T. to develop ALS sooner than she would have otherwise, if she even developed it at all. Id. at 220, 228.

As support for the theory that inflammation can trigger ALS, Dr. Utz cited three studies: Panzara et al., Casula et al., and Zhao et al.[50] Tr. 222-23; 228-29. These studies generally discuss evidence that an "inflammatory responses could play a critical role in the pathogenesis of motor neuron injuries in [ALS]." Pet. Ex. 18J at 233. In Zhao, however, the authors note that neuroinflammation is "[a] prominent pathological finding in ALS," and that "[t]he key question," is whether "neuroinflammation is a consequence of motor neuron injury," or causes it. Pet. Ex. 38 at 890. The authors' findings suggest a dynamic immune response designed to "promote neuroprotection or neurotoxicity at different stages of disease." Id. In the early stages of ALS, the immune system reacts to "signals from injured motor neurons to rescue and repair damaged tissue." Id. As the disease progresses, "a shift occurs from beneficial immune responses … to deleterious

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[48] Dr. Utz also testified that it is possible that the adjuvant in the vaccine opened the BBB allowing harmful cells to enter the CNS and cause ADEM. Tr. 204. As he stated that this theory was only possible, and not probable, I do not find preponderant evidence to support it.

[49] Dr. Utz also referred to "stress bodies or stress granules." See Tr. 231.

[50] Panzara et al., 6 NEUROBIOLOGY OF DISEASE 392 [Pet. Ex. 18A], discussed earlier; M. Casula et al., *Toll-Like Receptor Signaling in Amyotrophic Lateral Sclerosis Spinal Cord Tissue*, 179 NEUROSCI. 233 (2011) [Pet. Ex. 18J]; Zhao et al., 8 J. NEUROIMMUNO. PHARMACOLOGY 888 [Pet Ex. 38].

immune responses." Id. While "activation of immune pathways may contribute to the progression of inflammation, resulting in motor neuron injury … future studies … will be important to achieve a better understanding." Pet. Ex. 18J at 233.

In addition to molecular mimicry to MBP and AQP4, Dr. Utz opined that the HPV vaccine might also have triggered cross reactions with other myelin constituents. Pet. Ex. 21 at 7. While he believes that there is sufficient homology between AQP4 and HPV16 to "represent biologically-relevant T cell epitopes,[51] he admitted that there is no evidence of auto-reactivity to MBP or AQP4. Pet. Ex. 21 at 10.

Dr. Utz also posited that the disease may have been triggered by HPV antigens produced as a result of J.T.'s prior vaccinations. Pet. Ex. 21 at 7. He noted that J.T. had a history of warts which, while caused by a different HPV strain, may have enough protein similarities to components of Gardasil to allow the pre-existing antigens to react. Id. at 7-8.

Lastly, Dr. Utz opined that adjuvants "activate[d] toll-like receptors, … [which] are [ ] inflammatory." Tr. 182. Dr. Utz conceded, however, that his opinion as to adjuvants was derived from animal studies that tested Freund's adjuvant[52] and not the "proprietary alum[inum]-based adjuvant[s]" in Gardasil. Id. at 202.

b. The Role of the FUS Mutation

While Dr. Utz agreed that J.T. had the FUS P525L mutation, he believes that her ALS developed as a response to her immune reaction to Gardasil. Pet. Ex. 21 at 9; Tr. 158. He pointed out that it is unknown whether there are individuals with this specific FUS mutation living normal lives. Pet. Ex. 21 at 11. He conceded that none of the other FUS cases described in the literature discussed another patient receiving the Gardasil vaccine prior to developing ALS, nor did they discuss a trigger for the disease. Tr. 169. He pointed out, however, that the lesions noted on autopsy were of the same age, "strongly" indicating "an inciting event," since typical ALS lesions are of differing ages. Pet. Ex. 21 at 9. He also disagreed with the assertion of respondent's expert, Dr. Raymond, that the basophilic inclusions examined on autopsy were in fact FUS proteins. Id. Dr. Utz believed this claim was invalid since the Huang study never tested for FUS proteins when examining the inclusions.[53] Id.

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[51] An epitope is an "antigenic determinant," and is "the simplest form or smallest structural area on a complex antigen molecule that can combine with an antibody or form the major histocompatibility complex (MHC)-binding peptide recognized by T lymphocyte receptors." Illustrated Dictionary of Immunology at 253. "T cell epitopes are comprised of a complex of antigenic peptide linked to either MHC class I or class II molecules." Id.

[52] In the context of immunology, an adjuvant is "a nonspecific stimulator of the immune response." Dorland's at 32. Freund's adjuvant is "a water in oil emulsion incorporating antigen, in the aqueous phase, into lightweight paraffin oil with the aid of an emulsifying agent. On injection, this mixture induces strong persistent antibody formation." Id. at 32-33.

[53] Dr. Utz appears to be incorrect, as Huang et al. did stain the inclusions for FUS, and they had "intense positive staining." Pet. Ex. 9 at 3.

Dr. Utz further contended that the FUS mutation may not have significantly influenced the course of the disease because a study by Vance et al.[54] shows diffuse ubiquitination in the neurons, while J.T. had only rare ubiquitination.[55] Pet. Ex. 21 at 8. Additionally, other FUS patients did not display perivascular inflammation as was seen in J.T. Pet. Ex. 21 at 9. Dr. Utz also introduced evidence of two autoimmune diseases that are known to be associated with genetic mutations and activated by environmental triggers: systemic lupus erythematosus[56] and rheumatoid arthritis.[57] Tr. 509-10.

Dr. Utz does not believe that the FUS P525L mutation alone was sufficient to have caused J.T.'s ALS, or, at least, he believes it is unknown if J.T. "would have gone on to develop ALS from the mutation alone." Tr. 173, 497.[58] He noted that there are individuals with other FUS mutations who are living healthy, normal lives though he does concede that has not yet been observed with the P525L mutation. Id. at 173, 498. He also mentioned a study performed by Sharma et al.[59] in which the FUS gene was "knocked out" in mice but the animals neither died nor developed any ALS-like disease. Dr. Utz, like Dr. Steinman, concluded that an insufficient number of healthy individuals have been tested to conclude that P525L is a disease-causing mutation. Id. at 498. Lastly, Dr. Utz mentioned that there are mutations in other genes that have been associated with other diseases but not everyone with the mutation goes on to develop the disease. Id. at 498-99.

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[54] Vance et al., 23 SCI. 1208 [Resp. Ex. D6].

[55] Ubiquitination occurs when an ubiquitin protein is attached to another protein during "intracellular proteolysis," which is "the splitting of proteins by hydrolysis of the peptide bonds with formation of smaller polypeptides." Dorland's at 1535, 1997. J.T.'s autopsy showed "very rare neurons stained for ubiquitin." One of the subjects in the Vance paper had "diffuse ubiquitin positivity in nuclei in the patient's tissue but not control tissue, suggesting that one or more nuclear proteins are misfolded." Pet. Ex. 21 at 8. Although Dr. Utz points out that J.T. had rare ubiquitination, he does not explain the significance of this finding, except to contrast it with the findings in Vance. Even if significant, however, petitioners have not provided preponderant evidence to show that rare ubiquitination alone would change the outcome of my decision.

[56] Systemic lupus erythematosus is a systemic disease of the connective tissue which predominantly affects women. Tr. 509. According to Dr. Utz, a number of known genetic mutations, as well as environmental triggers, are associated with the disease. Id. at 509-10.

[57] Rheumatoid arthritis is a "chronic systemic disease primarily of the joints, usually polyarticular, marked by inflammatory changes in the synovial membranes and articular structures and by muscle atrophy and rarefaction of the bones." Dorland's at 157. "Rarefaction" means "diminution in density and weight." Id. at 1593.

[58] Dr. Utz gave inconsistent testimony on this point. Elsewhere, he testified that more likely than not, J.T. would have had ALS even if she had not received the vaccine. Tr. 218. Later, he changed his opinion, testifying that this was an unknown. See id. at 497-98, 505.

[59] Aarti Sharma, et al., *ALS-associated mutant FUS Induces Selective Motor Neuron Degeneration Through Toxic Gain of Function*, 7 NATURE COMMC'NS, No. 10465 (2016) [Resp. Ex. K]. The Sharma article actually states, "These findings demonstrate that FUS-dependent motor degeneration is not due to loss of FUS function, but to the gain of toxic properties conferred by ALS mutations." Resp. Ex K at 10465. This is in agreement with the finding of misfolded FUS proteins on autopsy.

Overall, while J.T.'s ALS was particularly aggressive, Dr. Utz testified that the literature does not support the supposition that her FUS P525L mutation caused her ALS. Tr. 179. Dr. Utz listed a series of papers to support his conclusion that the FUS mutation alone could not have caused the specific case of J.T.'s ALS, including Fecto & Siddique, Brown et al., Yan et al., Sproviero et al., Ito et al., Chio et al., and Mochizuki et al.[60] Id. at 501-02, 506. Dr. Utz opined that J.T.'s pathologic presentation of the disease was not consistent with others who had the same mutation. Id. at 179.

Fecto and Siddique reviewed publications assessing the various genes at play in the etiology of ALS and compared how these different genetic mutations lead to similar ALS symptoms and disease progression. Pet. Ex. 50 at 644. The authors observed that FUS mutations make up approximately four to five percent of ALS cases, and that the FUS mutation has been linked to earlier disease onset. Id. at 666-67. They note that "[a]t least three other reports have described FUS mutations in patients with rapidly progressive sporadic or familial [juvenile] ALS with basophilic inclusions, suggesting that basophilia due to nucleic acid accumulation is a hallmark of pathology in FUS-linked [juvenile] ALS." Id. at 666. While additional studies are needed to better understand the causative role of FUS mutations in the etiology of ALS, Fecto and Siddique report that several studies have observed that FUS mutations are involved in the development of ALS. Id.

Yan et al. studied the array of FUS mutations present in patients with familial ALS by sequencing the exons of the FUS gene of 476 patients with familial ALS and 726 control patients without ALS. Pet. Ex. 61 at 807. The results of the study identified 17 different FUS mutations which occurred in 22 different families. Id. Yan also observed that "[p]atients with FUS mutations appeared to have earlier symptom onset, a higher rate of bulbar onset, and shorter duration of symptoms that those with SOD1 mutations." Id. Patients with the mutation make up 4.79 percent of all cases of familial ALS, suggesting that "FUS mutations may be a globally distributed genetic cause of familial ALS in patients of different genetic backgrounds." Id. at 812. Yan et al. further posited that other factors, including environmental exposure and/or genetic background, could affect the clinical course of the disease. Id.

Chio et al. studied 52 Italian patients with familial ALS and 280 matched controls and performed mutational screening of the FUS gene, finding two distinct mutations associated with

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[60] Faisal Fecto & Teepu Siddique, *Making Connections: Pathology and Genetics Link Amyotrophic Lateral Sclerosis with Frontotemporal Lobe Dementia*, 45 J. MOLECULAR NEUROSCI. 663 (2011) [Pet. Ex. 50]; Jeffrey A. Brown, et al., *SOD1, ANG, TARDBP and FUS Mutations in Amyotrophic Lateral Sclerosis: A United States Clinical Testing Lab Experience*, 13 AMYOTROPHIC LATERAL SCLEROSIS 217 (2012) [Pet. Ex. 51]; J. Yan, et al., *Frameshift and Novel Mutations in FUS in Familial Amyotrophic Lateral Sclerosis and ALS/Dementia*, 75 NEUROLOGY 807 (2010) [Pet. Ex. 61]; Sproviero et al., 33 NEUROBIOLOGY AGING 837.e1 [Pet. Ex. 53]; Hidefumi Ito et al., *Optineurin is Co-Localized with FUS in Basophilic Inclusions of ALS with FUS Mutation and in Basophilic Inclusion Body Disease*, 121 ACTA NEUROPATHOLOGICA 555 (2011) [Pet. Ex. 52]; Adriano Chio et al., *Two Italian Kindreds with Familial Amyotrophic Lateral Sclerosis due to FUS Mutation*, 30 NEUROBIOLOGY AGING 1272 (2009) [Pet. Ex. 59]; and Yoko Mochizuki et al., *Familial ALS with FUS P525L Mutation: Two Japanese Sisters with Multiple Systems Involvement*, 323 J. NEUROLOGICAL SCIS. 85 (2012) [Pet. Ex. 54].

ALS. One of the families was found to have the FUS P525L mutation, the same mutation that J.T. had. Pet. Ex 59 at 2. The researchers also found a second, similar mutation in the FUS gene, also located in exon 15, known as the PR514S mutation. Id. at 2. The patient with the FUS P525L mutation was 21 years old and had a three month history of rapidly progressive bulbar dysfunction. Id. at 3. The patient died within one year of her diagnosis. Id. Although it was not possible for Chio et al. to analyze DNA from any of the patient's family members, the researchers note that "the [FUS] mutations were not found in 280 control samples." Id. at 2.

Finally, Dr. Utz cites the Mochizuki et al. study in support of his assertion that the FUS P525L mutation alone could not have caused J.T.'s development of ALS. The researchers stated that "much is unknown about the clinicopathology of ALS with the FUS P525L mutation." Pet. Ex. 54 at 85. However, the authors performed autopsies on two Japanese sisters, both of whom suffered from familial ALS, and were able to map disease progression by comparing the sisters' clinical courses and genetic makeup. The elder sister had an FUS P525L mutation with an onset of ALS at age 13 in the form of right and left leg weakness and eventual quadriparesis. Id. at 86. The initial clinical feature was a possible polyneuropathy. Id. With the assistance of a mechanical ventilator, she survived to the age of 40, over 26 years after her diagnosis. Id. Her younger sister began exhibiting symptoms of ALS at age 25, began using a mechanical ventilator approximately one year later, and died of pneumonia at age 27. Id. Their mother died at age 35 within six months of her diagnosis of progressive bulbar palsy. Id. While the eldest sibling was found to have P525L mutation, neither the DNA of the younger sibling nor their mother was analyzed. Id. at 89.

Mochizuki et al. noted that "All three patients in the family … developed limb weakness followed by bulbar palsy at a young age with very rapid progression …. [I]t seems likely that they had the same FUS mutation." Pet. Ex. 54 at 89. Notably, the elder sister, who had the FUS P525L mutation, like J.T., had a similar age of onset and disease manifestation as J.T. Pet. Ex. 1 at 193. And like J.T., the eldest sister in the Mochizuki study was thought to have a type of polyneuropathy prior to being diagnosed with ALS. Pet. Ex. 7 at 33.

Contrary to the testimony of Dr. Utz, these articles demonstrate that patients with ALS have been found to have similar mutations in the FUS gene and that certain mutations on the FUS gene, including P525L, are associated with a rapid onset of ALS symptoms at a young age. See Pet. Ex. 59 at 3.

c. Onset

Dr. Utz opined that the timeline from vaccination to initial symptoms presented in the medical records is consistent with an immune-mediated condition. Tr. 180. Due to the nature of these types of diseases, he believes the disease process began earlier than the accident J.T. had at the track but did not outwardly present itself until that time. Id. at 180-81.

iii. Respondent's Expert, Dr. Gerald Raymond

1. Diagnosis

Dr. Raymond opined that J.T. suffered only from ALS, eventually resulting in her death. Resp. Ex. D at 6. He opined that J.T.'s symptoms were consistent with JALS, which unlike adult onset ALS typically has either greater upper or lower motor neuron issues rather than both equally.

Resp. Ex. H at 5. In ALS, it is common to see symptoms begin in one limb before involving others. Id. J.T. never responded to immunosuppressants. While ALS has some amount of immune involvement, immunosuppressants have not been shown to be effective in treatment. Id. J.T.'s manner of death, respiratory failure, is also consistent with ALS. Id.

Dr. Raymond testified that the FUS P525L mutation which J.T. had alters protein function and occurs in a region of known essential function. Tr. 260-61. Further, it is not observed in controlled populations. J.T.'s mutation was de novo, meaning it was not present in her parents. Id. at 261. It has been identified in multiple patients with juvenile onset ALS. Id.

Dr. Raymond summarized several case studies of P525L mutation, where patients had rapid progression of disease. In Conte,[61] an eleven year old girl with the P525L mutation and ALS had progressive limb weakness with active and chronic denervation. Tr. 280-81; Resp. Ex. F13. The authors concluded that "this mutation is consistently associated with a specific phenotype characterized by juvenile onset, [and] severe course." Resp. Ex. D9 at 73. In Zou, [62] the authors described a young woman with progressive muscle atrophy and weakness with acute and chronic neurogenic changes. Tr. 286; Resp. Ex. E11. Finally, in Ozoguz,[63] the authors described a 14 year old boy with a de novo P525L mutation who had a rapid onset and progression of the disease. Tr. 291; Resp. Ex. H1. In Baumer,[64] two patients with a de novo P525L mutation had "a more aggressive earl[y] onset." Tr. 277-79. Both patients had lower motor neuron signs and progressive muscle weakness similar to J.T. Id. at 278-79.

Dr. Raymond also cited Baumer to describe neuropathological autopsy findings specific to P525L FUS mutation in ALS patients.[65] Tr. 294. The authors concluded that JALS "with basophilic inclusions is a form of ALS characterized by protein deposits in motor neurons that are morphologically and tinctorially distinct from those of classic sporadic ALS." Resp. Ex. D3 at 611. They identified these cases as "rapidly progressive FUS proteinopathy," which should be classified

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[61] Amelia Conte, et al., *P525L FUS Mutation is Consistently Associated with a Severe Form of Juvenile Amyotrophic Lateral Sclerosis*, 21 NEUROMUSCULAR DISORDERS 73 (2012) [Resp. Ex. F13].

[62] Zhang-Yu Zou, et al., *De Novo FUS Gene Mutations are Associated with Juvenile-Onset Sporadic Amyotrophic Lateral Sclerosis in China*, 34 NEUROBIOLOGY AGING 1312 (2013) [Resp. Ex. E11].

[63] Ashhan Ozoguz, et al., *The Distinct Genetic Pattern of ALS in Turkey and Novel Mutations*, 36 NEUROBIOLOGY AGING 1764.e9 (2015) [Resp. Ex. H1].

[64] D. Baumer, et al., *Juvenile ALS with Basophilic Inclusions is a FUS Proteinopathy with FUS Mutations*, 75 NEUROLOGY 611 (2010) [Resp. Exs. E2 and D3].

[65] Baumer et al., 75 NEUROLOGY 611 [Resp. Exs. E2 and D3]. Dr. Raymond testified that the literature discusses autopsies in probably three P525L mutation cases, disagreeing with Dr. Utz's testimony that there were 18 such reported autopsies. Tr. 292. Based on my review of the submitted literature, Dr. Raymond's testimony on the number of reported autopsies in P525L mutations appears to be more accurate. See id. at 292-300.

as ALS-FUS. Id. at 612. The autopsies showed cytoplasmic basophilic inclusions and corticospinal tract but not dorsal column degeneration. Id. Dr. Raymond opined that these findings are consistent with J.T.'s autopsy results. Tr. 296.

Dr. Raymond opined that J.T. did not meet the clinical criteria for ADEM because she did not have encephalopathy, her MRI was not consistent with a demyelinating condition, and she did not respond to immunosuppressants. Resp. Ex. F at 5; Tr. 312-13. J.T.'s MRIs did not show any indication of ADEM lesions, and her EMGs showed only a motor neuron disease. Tr. 309. Additionally, Dr. Raymond emphasized that none of J.T.'s treating physicians ever suggested the diagnosis of ADEM, a fact which Dr. Steinman also conceded. Resp. Ex. F at 5.

Dr. Raymond summarized the juvenile FUS P525L/ALS cases cited in the literature by referencing the following table from Zou et al. Resp. Ex. E11 at 1312.e6. The highlighted cases at the bottom of the table are the P525L cases.


Disease dur
Key: ALS, a
trophic late

Resp. Ex. E11 at 1312.e7.

Of these eleven patients, eight were female, age range eleven to 22, with disease duration of six to 24 months. Id. Dr. Raymond testified that J.T.'s onset was typical of other P525L patients, and that her 22 month clinical course was consistent, but perhaps a little longer, than others. Tr. 330.

Moreover, Dr. Raymond believes J.T.'s autopsy was consistent with ALS, and he offered reasonable explanations for any perceived inconsistent findings. Tr. 318-20. He explained that

relatively little information is known about J.T.'s type of genetically mediated ALS. Resp. Ex. F at 6. The genetic test revealing the P525L mutation was not completed until after the autopsy, leaving the pathologists with incomplete information at the time of autopsy. Id. at 5.

As for inflammatory changes and demyelination described on J.T.'s autopsy, Dr. Raymond opined that in "ALS, the spinal cord shows secondary loss of myelin due to the loss of neuronal axons," and that "[t]hese changes are associated with variable astrocytic gliosis and the accumulation of macrophages and lymphocytes." Resp. Ex. F at 2. Loss of neurons in the motor cortex leads to "severe myelin loss [which] can be traced up through the brainstem into the cerebral hemispheres." Id. This caused the "characteristic pallor" that can be seen on cross-sections of the spinal cord. Id.

Dr. Raymond explained that due to the progression of the disease, most motor neuron damage in ALS is typically seen in the corticospinal and other motor pathways. Resp. Ex. F at 2. However, in familial and genetic ALS, demyelination has also been demonstrated in other tracts. Id. Dr. Raymond referenced studies done by Hirano et al. and Tandan and Bradley, [66] which show demyelination in the posterior columns, spinocerebellar tracts, and Clarke's nucleus[67] of patients with familial ALS. Resp. Ex. F at 2. Respondent also cited other studies about neuroinflammation in ALS.[68] Dr. Raymond further explained that "evidence of inflammation is seen in both sporadic and familial ALS with the presences of macrophages, T cells, and B cells." Id. at 3. Macrophages are "presumed to be involved in the phagocytosis, or 'cleaning up' of the dying motor neurons, axons, and myelination debris. Lymphocytes are also seen[,] and there is often perivascular infiltration." Id.

In support of his opinions, Dr. Raymond also cited Troost et al.,[69] wherein the authors studied "the prevalence and extent of lymphocytic infiltration" by examining spinal cords from 48

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[66] Asao Hirano et al., *Familial Amyotrophic Lateral Sclerosis: A Subgroup Characterized by Posterior and Spinocerebellar Tract Involvement and Hyaline Inclusions in the Anterior Horn Cells*, 16 ARCHIVES OF NEUROLOGY 232 (1967) [Resp. Ex. F3]; Rup Tandan & Walter G. Bradley, *Amyotrophic Lateral Sclerosis: Part 1. Clinical Features, Pathology, and Ethical Issues in Management*, 18 ANN. NEUROLOGY 271 (1985) [Resp. Ex. F4].

[67] Clarke's nucleus is another name for the posterior thoracic nucleus. Dorland's at 1296.

[68] For example, in Philips & Robberecht, the authors discuss reactive microglial cells, and neuroinflammatory reactions in neurodegenerative diseases like ALS. Thomas Philip & Wim Robberecht, *Neuroinflammation in Amyotrophic Lateral Sclerosis: Role of Glial Activation in Motor Neuron Disease*, 10 LANCET NEUROL. 253 (2011) [Resp. Ex. E8]. The authors conclude that the "inflammatory reaction, which is supposed to combat the precipitating factor, is believed to turn into a hazardous process and contribute to neuronal damage." Id. at 254.

[69] D. Troost et al., *Lymphocytic infiltration in the spinal cord of patients with amyotrophic lateral sclerosis*, 8 CLINICAL NEUROPATHOLOGY 289 (1989) [Resp. Ex. F27]. Petitioners cited a number of more recent studies, including Graves (2003) [Pet. Ex. 36], Hooten (2015) [Pet. Ex. 32]; and Staff & Appel (2016) [Pet. Ex. 37], all of which support Dr. Raymond's opinion that macrophages and lymphocytic infiltrations may provide a "cleaning up" function, or have immunoprotective, followed by neurotoxic, roles.

cases of ALS. Resp. Ex. F27 at 289. They found lymphocytic infiltration in 44 percent (21 cases), and the "infiltrates were localized as small cuffs around the blood vessels." Id. at 292. Further, "lymphocytic infiltration … was not restricted to the damaged parts of the pyramidal tracts …. [but was also] observed in [ ] normal areas of the brain stem." Id.

Dr. Raymond believes that the autopsy finding that "[a]ll of the lesions in the spinal cord appear to be the same age," means that the disease was so far progressed that the motor neurons had died and thus the pathology was "at an end stage." Tr. 320. The analogy he gave was an empty cup; there is "no information about when I drank the water in the cup or when these neurons died. They're now all gone." Id. The "severe loss of motor neurons," caused "loss of exons [and] … demyelination." Id at 321. He stated that there is no evidence J.T. suffered that loss of neurons at one specific time. Instead, "[J.T.'s] disease became evident, and then [became] progressively worse until her death." Id. at 322. Additionally, the autopsy noted "rare cortical neurons with amorphous cytoplasmic inclusions" in the right frontal lobe and midbrain. Id. at 329. This finding indicates "early stage" neuronal loss in that section of the brain. This finding suggests that the pathology at issue did not occur at "one point in time." Id. Moreover, J.T.'s progressive course does not support the conclusion that she had complete loss of her neurons in her spinal cord at one time. Tr. 322.

In summary, Dr. Raymond believes that J.T.'s "symptoms, entire clinical picture, and pathology are all consistent with a genetically mediated ALS." Resp. Ex. F at 5; Tr. 331.

2. Causation Theory

Dr. Raymond opined that J.T. had a "serious alteration in the FUS gene that resulted in juvenile ALS and was the direct and sole cause of her disease and death." Resp. Ex. D at 6. "There is no evidence that this was caused or aggravated by the vaccine she received." Id. Dr. Raymond emphasized that the P525L mutation has not been seen in normal individuals, as supported by the emails Dr. Steinman received from Drs. Sapp and Brown.[70] Resp. Ex. F at 7-8. Dr. Raymond attached significance to their assertion that "[t]his is certainly the most aggressive form of ALS any of us here have seen – aggressive both in age of onset and in rate of progression." Id. at 8. Dr. Raymond believes that the P525L mutation is "a disease causing mutation that presents early and is clinically aggressive." Id. at 9.

[70] On January 30, 2014, petitioners filed Dr. Steinman's emails from Dr. Robert Brown and Dr. Peter Sapp as Exhibits 25 and 26. Dr. Steinman testified that Dr. Brown is "one of the foremost experts in ALS." Tr. 73-74. Dr. Brown is a professor at the University of Massachusetts Medical School and a co-discoverer of the FUS mutation. Id. at 59-60. He was also an author of the Huang article (Pet. Ex. 9). Id. at 63. In an email from Dr. Brown to Dr. Steinman dated April 11, 2013, Dr. Brown stated that "[w]e have seen the P525L mutation [ ] in at least three early onset (juvenile) cases …. More generally, others have described FUS mutations (including P525L) in juvenile ALS as well – often basophilic inclusions, of uncertain significance." Pet. Ex. 25 at 1. In an email dated April 12, 2013, Dr. Sapp reported to Dr. Steinman that the P525L mutation is not seen "in controls[,] and the ALS online database … does not report any instances from other publication[s]…" Pet. Ex. 26 at 1.

Dr. Raymond references a paper written by Niu et al. [71] in which researchers demonstrated that mutations in the FUS protein interfered with its ability to be transported from the cytoplasm back into the nucleus. Tr. 261-62. This mislocalization interfered with transcription and RNA processing. Id. at 257. He also pointed out that this mutation is present from the moment of conception, and that it is always present and active in an affected individual. Id. at 265. Dr. Raymond testified that the Sharma article demonstrates that any affected individual will eventually develop motor neuron loss.[72] Id. at 267-69. In fact, mice affected with a P525L mutation analog were more quickly and severely affected than mice with another FUS mutation. Id. at 268. Additionally, the mice required no environmental trigger for the motor neuron loss to begin; it occurred solely as a result of the mutation. Id. at 269. Dr. Raymond also introduced a paper authored by Jackel et al.,[73] in which a fruit fly model with the P525L mutation was found to have cytoplasmic accumulation of the FUS protein, nervous system changes, and local motor activity changes. Tr. 275-76.

In surveying the literature submitted by both petitioners and respondent, Dr. Raymond found more than 2,000 control patients, not one of which had the P525L mutation, supporting his opinion that the mutation is found only in affected individuals. Tr. 272-74.

Dr. Raymond rejected petitioners' theory of molecular mimicry as applied to the facts here. Dr. Steinman stated that T cells could recognize both HPV and MBP, because HPV has homology with a region of MBP and is therefore able to cross-react, basing his opinion largely on the Wucherfennig paper. However, Wucherfennig warned that the paper did not find cross reactivity in the HPV types found in Gardasil. Resp. Ex. F at 8 (ref. Pet. Ex. 24H). Wucherfennig stated that the epitope required a region of 13-15 proteins, and that the critical conserved region was FFK, not simply FK. Cross-reactivity with HPV was strain-specific to types 7 and 13. Id. Gardasil contains types 6, 11, 16, and 18. Id. Dr. Raymond also disagreed with Dr. Steinman's revised opinion to require FK with three other amino acids, in which case, almost any exposure could have been a trigger. Resp. Ex. H at 2. Dr. Steinman provided no evidence that the HFFK-like motif in HPV is a component of Gardasil, a recombinant vaccine. Id.

Dr. Raymond also disagreed with Dr. Steinman's assertions regarding cross reactivity between AQP4 and HPV, which were based on the Menge article, a report of four cases of NMO in the VAERS database following HPV immunization. Resp. Ex. F at 9. While the authors question the role of HPV, this does not establish a pathogenic link. Id. In addition, the link between AQP4 and ALS is not clear. There is no evidence that AQP4 interacts with FUS. Resp. Ex. D at 4. Further, there is no evidence that J.T. ever developed an antibody to AQP4 or had NMO. Id.

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[71] Chunyan Niu et al., *FUS-NLS/Tranportin 1 Complex Structure Provides Insights into the Nuclear Targeting Mechanism of FUS and the Implications in ALS*, 7 PLOS ONE e47056 (2012) [Resp. Ex. J].

[72] Sharma et al., 7 NATURE COMMC'NS (2016) [Resp. Ex. K].

[73] Sandra Jackel et al., *Nuclear Import Factor Transportin and Arginine Methyltransferase 1 Modify FUS Neurotoxicity in Drosphila*, 74 NEUROBIOLOGY DISEASE 76 (2015) [Resp. Ex. H2].

In summary, Dr. Raymond concluded that "[t]here have been no reports in the literature of ALS or interaction between HPV vaccine and progressive neuromotor diseases like ALS. There is no evidence that HPV vaccine can result in widespread alterations of DNA and no evidence that it interacts in any way with the FUS protein." Resp. Ex. D at 4.

Lastly, Dr. Raymond cited to the discussion of mechanistic evidence from the Institute of Medicine ("IOM"), in relation to the Huang study, quoted in pertinent part as follows: "Based on the genetic analysis and neuropathology, the authors [of Huang] did not attribute the rapidly progressive form of [JALS] in the patient to vaccination against HPV." Resp. Ex. L at 4. A footnote attributed the above quoted information to a "personal communication with Dr. Lomen-Hoerth, ALS Center, University of California, San Francisco." Id., note 1. Dr. Lomen-Hoerth is the specialist in ALS who treated J.T. from April 2008 until her death in March 2009; she also performed her autopsy. Tr. 545, 547.

iv. Respondent's Expert, Dr. Arun Venkatesan

1. Diagnosis

a. ALS is the Correct Diagnosis

Dr. Venkatesan opined that J.T. "suffered from juvenile-onset ALS caused by the FUS P525L gene mutation," unrelated to the Gardasil vaccine. Resp. Ex. E at 3. He based this conclusion on J.T.'s clinical course and diagnostic tests, which were all consistent with FUS P525L ALS. Tr. 386-88.

While petitioners propose that there was "an inciting autoimmune component" (i.e. vaccine-triggered ADEM), to J.T.'s ALS, Dr. Venkatesan does not believe that there is any evidence to support this position. Resp. Ex. E at 3. As support for his opinion, he referenced the fact that immunosuppressants had little benefit in treating J.T., nor have they been successful in other trials for the treatment of ALS. Id. Rather, he stated that in ALS, "the observed inflammatory response is predominantly a reaction to the degeneration of neurons and axons." Id. He cited studies performed by Hosmane et al., Viviana et al., and Philips and Robberecht.[74] Id.; Tr. 412-13. In particular, Philips and Robberecht explain that both inflammation and T cells are commonly seen in ALS. Id. at 413; Resp. Ex. E8. As the disease stage progresses, increased numbers of activated microglia and astrocytes are seen indicating an "activation of these immune cells." Tr. 414. Dr. Venkatesan concluded that as immunosuppressants have largely been proven ineffective at treating ALS, the inflammation is likely a result, and not a cause, of the disease. Id. at 415-16.

[74] Suneil Hosmane et al., *Toll/Interleukin-1 Receptor Domain-Containing Adapter Inducing Interferon-B Mediates Microglial Phagocytosis of Degenerating Axons*, 32(22) J. NEUROSCIENCE 7745 (2012) [Resp. Ex. E4]; Barbara Viviani et al., *Dying Neural Cells Activate Glia Through the Release of a Protease Product*, 32 GLIA 84 (2000) [Resp. Ex. E10]; Philips & Robberecht, 10 LANCET NEUROLOGY 253 [Resp. Ex. E8].

b. J.T. Did Not Have ADEM

i. Clinical Course

Dr. Venkatesan does not believe that J.T. ever had ADEM, as she did not exhibit any of the criteria for the condition. Resp. Ex. G at 1. He referenced a book chapter written by Silvia N. Tenembaum detailing the symptoms and diagnostic criteria for ADEM.[75] Tr. 387, 394; Resp. Ex. F6 at 1253. "Rapid onset encephalopathy (behavioral change or altered consciousness)" is a central feature of ADEM. Id. at 1254. Patients generally develop symptoms rapidly, with the most severe symptoms occurring one to two weeks after initial presentation. Id. at 392. After that time, patients usually begin to improve. Id. Dr. Venkatesan noted that J.T. did not "have any signs or symptoms of encephalopathy at the onset of her neurologic presentation," and her initial symptom was exclusively leg weakness. Resp. Ex. G at 1..

In ADEM, MRI is "the most sensitive paraclinical marker of acute demyelination," showing multiple white matter lesions in the brain and spinal cord. Resp. Ex. F6 at 1254. J.T. did not have an MRI or a lumbar puncture during her initial presentation, two tests essential to diagnose ADEM. Resp. Ex. G at 1. During the acute phase, ADEM appears on MRI as "multiple areas of signal abnormality," representing "dissemination of inflammatory lesions in the nervous system." Tr. 393. Even months later, after a patient is no longer symptomatic, the MRI will still show "evidence that there had been a prior injury to the nervous system." Id. An MRI performed approximately one year after J.T.'s initial symptoms showed no evidence that she ever had ADEM. Id. at 396-97.

Dr. Venkatesan also disagreed with Dr. Utz's assertion that J.T.'s lab tests demonstrated evidence of ADEM. Dr. Utz cited a weakly positive ANA, elevated ESR, and positive antiphospholipid antibodies as evidence that J.T. had ADEM. Tr. 400-01. Dr. Venkatesan disagreed with this conclusion. Id. at 401. Because comparison tests were not performed prior to vaccine administration, Dr. Venkatesan testified that there is no way to conclude those results were related to the vaccine. Id. He also does not believe those results were specific to or conclusive of ADEM, nor "[did] they point to any evidence for inflammation in the nervous system." Id.

ii. Autopsy

Dr. Venkatesan asserted that because ADEM is a clinical syndrome, it can be diagnosed only clinically, when the patient is alive. Tr. 397-98. Pathology seen on autopsy may be used to support the diagnosis, but ADEM cannot be diagnosed based on pathology after death. Id. He opined that the spinal cord inflammation observed on J.T.'s autopsy is not indicative of ADEM despite the assertions of Drs. Steinman and Utz. Resp. Ex. G at 1. While ADEM does cause inflammation, it is a monophasic disease, meaning that the inflammation is acute and resolves in a few weeks. Id. Additionally, Dr. Venkatesan opined that ALS can cause inflammation, and he cited an article authored by Philips and Robberecht[76] summarizing the "state of understanding of inflammation in ALS." Tr. 411-12. He also cited articles by Panzara et al., Casula et al., and Zhao

[75] Silvia N. Tenembaum, *Acute Disseminated Encephalomyelitis, in* 112 HANDBOOK OF CLINICAL NEUROLOGY: PEDIATRIC NEUROLOGY PART II (O. Dulac et al., eds., 3rd series 2013) [Resp. Ex. F6].

[76] Philips & Robberecht, 10 LANCET NEUROLOGY 253 [Resp. Ex. E8].

et al.[77] (also cited by Dr. Utz) as evidence that ALS caused inflammation. Id. at 416-20. As noted earlier, taken as a whole, these articles emphasize that inflammation is present in ALS, but "there is no data to suggest that inflammation can propagate ALS." Id. at 417.

Dr. Venkatesan also noted other issues on J.T.'s autopsy that precluded the diagnosis of ADEM. Tr. at 398. On autopsy, J.T. had "demyelination in the anterior and lateral columns of the spinal cord with what appears to be sparing of the posterior columns." Tr. 399. Dr. Venkatesan stated that it was difficult to imagine "a situation in which one would have ADEM… where there is extensive demyelination that is only along the motor tracts, but does not involve the sensory tracts, the dorsal columns." Id. Dr. Vankatesan emphasized that "the inflammatory cells were almost exclusively found in the anterior portion of the [spinal] cord, corresponding to areas that degenerate in ALS. This pattern is consistent with ALS," and not ADEM. Resp. Ex. T at 1. He further opined that the location of J.T.'s lesions was not "compatible" with ADEM. Tr. 399. Also, if the lesions all occurred at the same time, as Dr. Steinman hypothesized, Dr. Venkatesan opined that J.T. would have been "neurologically devastated…. reflected in extreme weakness, potentially paralysis," affecting not just one leg but rather her whole body at the time of initial presentation. Id. at 400. Dr. Venkatesan would also have expected to see evidence of such devastation on her MRIs. Id.

2. Causation Theory

Dr. Venkatesan opined that J.T.'s juvenile ALS was caused by the FUS P525L mutation, and he cited multiple case studies in support of his opinion. Articles by Vance et al. and Kwiatkowski et al.[78] show that FUS mutations are causally related to ALS. Resp. Ex. E at 5. Additional studies by Conte et al., Mackenzie et al., and Baumer et al.[79] demonstrate an association between the FUS P525L mutation with "juvenile onset, an aggressive clinical course, and predominantly a lower motor neuron disorder." Id. Dr. Venkatesan stated that J.T. was "described as having a 'pure lower motor neuron syndrome.'" Id. Zou et al. report the age of onset for genetically-mediated JALS is 11 to 22 years of age and the duration of illness is six months to two years.[80] Id. J.T.'s age of onset, 13 years old, and the duration of her illness, 22 months, fall within these ranges. Id. Additionally, Dr. Venkatesan noted that in his study, Dr. Huang concluded that J.T. had "'rapidly progressive juvenile ALS.'" Id.

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[77] Panzara et al., 6 NEUROBIOLOGY OF DISEASE 392 [Pet. Ex. 18A]; Casula et al., 179 NEUROSCIENCE 233 [Pet. Ex. 18J]; Zhou et al., 34 NEUROBIOLOGY AGING 1312 [Resp. Ex. E11].

[78] Caroline Vance, et al., *ALS mutant FUS Disrupts Nuclear Localization and Sequesters Wild-Type FUS Within Cytoplasmic Stress Granules*, 22 HUM. MOL. GENETICS 2676 (2013) [Resp. Ex. F10]; T.J. Kwiatkowski Jr., et al., *Mutations in the FUS/TLS Gene on Chromosome 16 Cause Familial Amyotrophic Lateral Sclerosis*, 323 SCI. 1205 (2009) [Resp. Ex. D5].

[79] Conte et al., 21 Neuromuscular Disorders 73 [Resp. Ex. F13]; Ian R.A. Mackenzie et al., *Pathological Heterogeneity in Amyotrophic Lateral Sclerosis with FUS Mutations: Two Distinct Patterns Correlating with Disease Severity and Mutation*, 122 ACTA NEUROPATHOL. 87 (2011) [Resp. Ex. E7]; Baumer et al., 75 NEUROLOGY 611 [Resp. Ex. E2].

[80] Zou et al., 34 NEUROBIOLOGY AGING 1312 [Resp. Ex. E11].

When analyzing Dr. Steinman's assertions, Dr. Venkatesan noted that, although Dr. Steinman believes the ADEM was caused by molecular mimicry to MBP or AQP4, there is no evidence of immunoreactivity to either of these molecules in J.T. Resp. Ex. E at 3. Additionally, Dr. Venkatesan disagreed with Dr. Steinman's reliance on the Menge et al.[81] article demonstrating increased AQP4 mRNA expression in SOD1 rats as proof for the involvement of AQP4 in ALS. Id.; Tr. 402-03. Dr. Venkatesan stated that an increase in mRNA does not necessarily mean an increase in the protein, nor does it explicitly indicate a role in ALS. Resp. Ex. E at 3. Furthermore, the SOD1 rate has not been proven to be a reliable representation of the FUS P525L mutation, or even FUS mutations in general. Id. Nor did Dr. Venkatesan believe that cross-reactivity has been demonstrated between HPV proteins and AQP4, as Dr. Steinman asserts. Id.; Tr. 402-03.

Dr. Venkatesan opined that the proposed mechanism of molecular mimicry between HPV proteins and MBP is tenuous. Resp. Ex. I at 1. He stated that the argument for molecular mimicry between HPV proteins and MBP "rests on limited sequence homology and a substantial reliance on degeneracy[,] and Dr. Steinman has not produced evidence that this proposed sequence can actually induce mimicry." Id. Dr. Venkatesan referenced a study performed by Silvanovich et al.,[82] in which researchers examined the odds of two molecules having a similar amino acid sequence. Tr. 407-10. Using the math demonstrated in that article, Dr. Venkatesan opined that there is actually a one in five chance that MBP has the HFF amino acid sequence that Dr. Steinman testified is so critical. Id. at 408-09. Thus, "when one is looking for evidence of similarity [ ] between amino acids," it is important to remember that it "can occur just by random chance." Id. at 406.

Dr. Venkatesan also disagreed with Dr. Utz's opinion that ADEM resulted in stress bodies or stress granules which may have played a causal role in J.T.'s ALS. Dr. Venkatesan emphasized that Dr. Utz's opinion as to ADEM, stress granules, and ALS is "quite tenuous and not supported by reliable evidence." Resp. Ex. T at 1. Citing a paper by Dr. Wang, Dr. Venkatesan explained that "while stress granules have been observed in ALS," it is not known whether they play a role in "disease pathogenesis" or if they serve "a protective function." Id. at 2 (referencing Resp. Ex. T1).

While on the longer side of what is acceptable, Dr. Venkatesan agrees with Dr. Steinman that the time period between vaccination and clinical presentation of symptoms is reasonable for an autoimmune response. Tr. 446; Resp. Ex. E at 4. However, Dr. Venkatesan believes J.T.'s ALS was caused by the FUS P525L mutation and not the Gardasil vaccine. Resp. Ex. I at 2.

VII. Analysis

Petitioners must establish that J.T. had the alleged diagnosis of ADEM, as "identifying the injury is a prerequisite to the analysis" of causation. Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1346 (Fed. Cir. 2010). The Federal Circuit has made clear that it is a petitioner's burden "to make a showing of at least one defined and recognized injury." Lombardi v. Sec'y of Health & Human Servs., 656 F.3d 1343, 1353 (Fed. Cir. 2011) (affirming the special master's decision to dismiss the petition when petitioner could not establish any of the alleged diagnoses).

[81] Menge et al., 79 NEUROLOGY 285 [Pet. Ex. 18h; Resp. Ex. F22].

[82] Andre Silvanovich et al., *The Value of Short Amino Acid Sequence Matches for Prediction of Protein Allergenicity*, 90 TOXICOLOGICAL SCIS. 252 (2006) [Resp. Ex. R].

The Federal Circuit has made clear that "identifying [the petitioner's] injury is a prerequisite" to the Althen analysis. Broekelschen, 618 F.3d at 1346. However, it is not necessary to diagnose an exact condition. In Lombardi, the Federal Circuit explained, "The function of a special master is not to 'diagnose' vaccine-related injuries, but instead to determine 'based on the record evidence as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the petitioner's injury.'" Lombardi v. Sec'y of Health & Human Servs., 656 F.3d 1343, 1351 (Fed. Cir. 2011) (citing Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1382 (Fed. Cir. 2009)).

In deciding the issues in this case, I have considered the record as a whole. § 13(a)(1). I reviewed and relied on statements in the medical records, as medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. Cucuras v. Sec'y of Health & Human Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). In addition, the treating physicians' opinions are "quite probative," as treating physicians are in the "best position" to evaluate the vaccinee's condition. Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1326 (Fed. Cir. 2006). However, no treating physician's views bind the special master, per se; rather, their views should be carefully considered and evaluated. § 300aa-13(b)(1); Snyder, 88 Fed. Cl. at 745 n.67. Each opinion from a treating physician should be weighed against other, contrary evidence present in the record – including conflicting opinions from other treating physicians. Hibbard v. Sec'y of Health & Human Servs., 100 Fed. Cl. 742, 749 (Fed. Cl. 2011), aff'd, 698 F.3d 1355 (Fed. Cir. 2012); Caves v. Sec'y of Health & Human Servs., 100 Fed. Cl. 119, 136 (Fed. Cl. 2011), aff'd, 463 Fed. Appx. 932 (Fed. Cir. 2012); Veryzer v. Sec'y of Health & Human Servs., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), aff'd, 100 Fed. Cl. 344 (2011).

a. J.T.'s Correct Diagnosis is ALS

The parties stipulated that J.T. had the P525L mutation and ALS, and thus her diagnosis of ALS is not in question. Therefore, I must decide whether J.T. had ADEM. I find that respondent's experts are more persuasive in concluding that J.T. did not suffer ADEM and that she suffered only from ALS. My reasons for this finding include that her clinical course was consistent with ALS but inconsistent with ADEM; her EMG and other diagnostic testing was consistent with a motor neuron disease and inconsistent with ADEM; she did not respond to immunosuppresive therapy; none of her treating doctors ever diagnosed her with ADEM; and the findings on autopsy were inconsistent with ADEM but consistent with ALS. Moreover, J.T.'s course is consistent with current medical knowledge of the FUS P525L mutation. Each of these reasons is discussed more fully below.

J.T.'s clinical course was not consistent with a monophasic illness such as ADEM but was instead consistent with a rapidly progressive, aggressive motor neuron condition like ALS. The initial manifestation of her illness occurred on May 24, 2007, when she fell while attempting to jump a hurdle. By June 2007, she had weakness and pain in her left leg, and by August 2007, she was walking with a limp. She was referred to physical therapy, but returned to the orthopedist in October 2007, due to the worsening of her condition. At that time, the orthopedist noted that J.T.'s limp was significantly worse and the muscles in her legs had atrophied. By November 2007, she had wasting of her hands and atrophy of the muscles in her thigh and calf. She was referred to a pediatric neurologist. On November 13, 2007, the orthopedist described asymmetric muscle weakness and wasting of her limbs. Pet. Ex. 7 at 33. The duration of J.T.'s illness was

approximately 22 months. As described by Dr. Raymond, J.T.'s aggressive course and her symptoms are consistent with ALS, not ADEM. Tr. 304-07.

J.T.'s EMG testing was not consistent with ADEM, but it was consistent with motor neuron disease, or ALS. EMGs performed in November 2007 showed acute and chronic denervation of the motor system with sparing of the sensory system, suggesting a motor neuron disease. While hospitalized, EMG revealed "pure motor neurogenic disorder with axonal features predominating." Pet. Ex. 2 at 822.

Moreover, J.T.'s diagnostic testing was not consistent with ADEM, but was consistent with ALS. The classic diagnostic test for ADEM is the MRI of the brain. Dr. Steinman agreed that J.T.'s MRI did not show ADEM-like demyelinating lesions, and therefore, it was not consistent with ADEM. Tr. 105, 308. Dr. Steinman testified that the MRI of J.T.'s spine showed a loss of cervical and lumbar enlargements, evidence of degenerative changes consistent with ALS, not ADEM. Id. at 106, 110-11. Dr. Steinman also testified that J.T.'s EMG showed motor and axonal involvement and injury to the anterior horn cells, which is consistent with ALS. Id. at 103. He further stated that the EMG did not reveal any findings consistent with ADEM. Id. at 101.

Dr. Steinman also testified that J.T.'s CSF did not show increased protein, which would have been expected in ADEM, and thus was more consistent with ALS. Tr. 105. She also tested negative for oligoclonal bands, which would be expected with multiple sclerosis, and her muscle and nerve biopsy was also consistent with neurogenic muscular pathology. Id. at 308.

J.T.'s illness did not respond to immunosuppressive medication or treatment such as IVIG, steroids, or plasmapheresis, which are generally effective against neuroinflammatory and immune-mediated conditions like ADEM. Even Dr. Steinman agreed that he would have expected a better response to IVIG if J.T. had ADEM. Tr. 112.

Further, none of J.T.'s treating physicians ever diagnosed her with ADEM. See Tr. 24-25. While her initial diagnosis was unclear, after her disease progressed and she was seen by an ALS specialist, she was diagnosed with a motor neuron disease (ALS). Dr. Steinman testified that he and the other physicians who saw J.T. during her hospitalization in February 2008 thought she had an "inflammatory neuropathy," such as CIDP, but they did not consider ADEM as a differential diagnosis. Id. at 22-24. During her February 2008 admission at Lucile Packard Children's Hospital, J.T. was diagnosed with a possible motor neuron disease. By March 2008, J.T.'s neurologist diagnosed her with a motor neuropathy of unknown cause, and the differential diagnosis included ALS. In April 2008, Dr. Lomen-Hoerth opined that J.T. had a lower motor neuron syndrome. Pet. Ex. 1 at 128. J.T. died on March 15, 2009, of "atypical [ ] ALS-like motor neuron disease." Pet. Ex. 6 at 1.

The findings in J.T.'s autopsy also provide evidence to support the diagnosis of ALS and not ADEM. There were three principle findings: extensive macrophage and lymphocytic infiltrates and severe astrogliosis of the spinal cord, severe loss of motor neurons, and cytoplasmic inclusions in neurons in the brain and spinal cord. The pathologists attributed the loss of motor neurons and the cytoplasmic basophilic inclusions to ALS. At the time of J.T.'s autopsy, severe loss of motor neurons and cytoplasmic basophilic inclusions had been reported in juvenile ALS in several case

studies.[83] That finding was not questioned by the pathologists or disputed by the parties. However, the significance of the findings of extensive demyelination and the extensive macrophage and lymphocytic infiltrates are strongly contested. The disagreement has its origins in the discussion portion of the autopsy report, where the pathologists question the "histological feature of the demyelination" which "appeared to be of the same age," and the suggestion that J.T. had a "progressive neurological disease [] mediated by immune responses leading to extensive demyelination in the spinal cord." Pet. Ex. 6 at 8. MS and ADEM are cited as two examples of such conditions. But the pathologists did not diagnose J.T. with either MS or ADEM. Instead, they distinguish J.T.'s clinical course from that of MS, because MS is rarely seen in patients under 15 years of age and most MS patients have a "remitting-relapsing" clinical course, not a progressively worsening course like J.T. As for ADEM, the pathologists note that while "astrogliosis can be detected in ADEM…[it is] usually not as robust as that seen in chronic MS lesions." Pet. Ex. 6 at 9.

In contrast, Dr. Raymond cited to literature which described evidence of demyelination in ALS cases, characterized as lymphocytic infiltration of the spinal cord. Troost examined 48 ALS spinal cords, and described myelin pallor, macrophages, and lymphocytic infiltration in 21 of the patients (44%). Resp. Ex. F27 at 291. The lymphocytic infiltrates "were localized as small cuffs around the blood vessels (perivascular cuffing)." Id. at 292. The lymphocytic infiltration was seen in damaged areas, as well as "histologically normal areas of the brain stem, particularly in the pyramidal tract." Id. Troost concluded that lymphocytic infiltration is a common phenomenon in ALS patients. Id. Dr. Raymond also cited literature detailing the findings of myelin pallor and "[l]oss of myelin from the cerebrospinal tracts and posterior columns…particularly in familial cases." Resp. Ex. F30 at 382. Thus, based on all of the literature referenced by the pathologists who performed the autopsy, as well as the experts for both parties, there appear to be pathological findings common to both ADEM and ALS.

What was meant by the pathologists and Dr. Huang, the neuropathologist, when they wrote in the autopsy report that "the histological features of the demyelination appeared to be of the same age" is not entirely clear. Dr. Steinman and Dr. Raymond debated the meaning of this reference at length. For Dr. Steinman, the reference to the lesions being the same age is fundamental to his opinion that J.T. had ADEM. He testified that this finding signified a "thunderclap" event, a hallmark for ADEM. Dr. Raymond disagreed, testifying that it meant the lesions were at an end-stage. He argued that if the lesions had occurred at one time, J.T. would have been paralyzed, inconsistent with her progressive decline as described in the records. While I cannot resolve this debate, it does not alter the fact that J.T.'s autopsy findings are consistent with pathology seen in ALS cases, and specifically FUS P525L ALS cases reported in the literature.

Juvenile ALS is a rare disease. In 2007 when J.T. first became ill, her mutation was not even known, and it was not reported in the literature until 2009. J.T.'s presentation and diagnosis may not have been clear until her condition worsened and she was seen by ALS specialists. Further, because ALS is a terrible and fatal condition, the physicians appear to have been reluctant to make the diagnosis. While initially J.T.'s condition may have been attributed to an inflammatory

[83] In 1992, Matsumoto and others reported two cases of juvenile ALS with basophilic inclusions. S. Matsumoto et al., *Basophilic Inclusions in Sporadic Juvenile Amyotrophic Lateral Sclerosis: An Immunocytochemical and Ultrastructural Study*, 83 ACTA NEUROPATHOL. 579 (1992) [Resp. Ex. D2]. In 2009, Kwiatkowski (one case) and Vance (three cases) both reported report cytoplasmic inclusions in postmortem studies of cases with FUS ALS. Resp. Ex. D5; Resp. Ex. E9.

neuropathy, when she had diagnostic testing and was seen by ALS specialists, she was diagnosed with ALS and only ALS. Her clinical course and the timeline of her diagnosis reflect the growing body of knowledge about the geneotype-phenotype of FUS P525L ALS.

Based on J.T.'s clinical course, the opinions and diagnoses of her treating physicians, her autopsy results, and the current body of medical knowledge as described by the experts and set forth in their respective medical literature, I find by a preponderance of the evidence that J.T. did not have ADEM and that she had only ALS.

b. Althen Analysis

i. Althen Prong One: Petitioners' Medical Theory

Under Althen Prong One, petitioners must set forth a medical theory explaining how the HPV could have caused J.T.'s ALS, leading to her eventual death. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009); Pafford, 451 F.3d at 1355-56. Petitioners' theory of causation must be informed by a "sound and reliable medical or scientific explanation." Knudsen, 35 F.3d at 548; see also Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 300aa- 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioners rely upon a medical opinion to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen, 618 F.3d at 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it.") (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980)).

1. Evaluation of the Evidence

I find that petitioners have failed to show preponderant evidence of Althen Prong One for four reasons. First, petitioners' causal theory is built on the assumption that J.T. had ADEM. Both Drs. Steinman and Utz opined that the first step of their theories is that the HPV vaccine caused J.T. to develop ADEM. Since I do not find that J.T. ever had ADEM, there is no longer a foundational premise for their mechanistic theory.

Second, assuming that petitioners are alleging that HPV caused J.T.'s ALS (even if she did not have ADEM), they failed to provide preponderant evidence. Dr. Utz opined that the self-antigens activated by the HPV vaccine also targeted motor neurons affected in ALS. While petitioners did provide some evidence of homology between the HPV vaccine, MPB, and AQP4, they did not provide preponderant evidence of homology between HPV and motor neurons, the destruction of which causes ALS.

Similarly, petitioners did not explain or provide evidence to support Dr. Steinman's theory that the HPV vaccine damaged motor neurons which were already vulnerable due to the FUS mutation. Dr. Steinman suggested that the HPV vaccine, via homology with AQP4, resulted in changes to the BBB, which disturbed the neuronal microenvironment, contributing to the death of motor neurons. The premise for this theory appears to come from the Bataveljic article. However,

the authors of that article did not discuss homology between HPV and AQP4 or draw any conclusions about whether impairment in the BBB may contribute to the cause of ALS. Moreover, they cautioned against attributing too much significance to AQP4 alone with regard to impairment of the BBB. See Pet. Ex. 18G at 2001.

Dr. Steinman cited studies by Appel, Gossoni, and Panzara,[84] which suggest evidence of adaptive immunity in the spinal cord fluid of patients with ALS. Pet. Ex. 20 at 14-15. While those findings suggest that immunological processes may play a role in the etiology or progression of ALS, they fail to provide persuasive evidence that the HPV vaccine or ADEM, either alone, or in concert, cause ALS, or worsen its course.

Third, petitioners emphasize the finding of neuroinflammation on autopsy and the references to ADEM and MS in the autopsy report as evidence of an immune-mediated condition related to HPV. Dr. Steinman introduced evidence showing the presence of neuroinflammation in patients with ALS. Pet. Ex. 14 at 14-15 (citing Pet. Ex. 18K). But while the presence of neuroinflammation is not debated, Dr. Steinman conceded it was unclear from the current medical literature whether the inflammation initiates or is a consequence of neuron death seen in ALS. Tr. 108. In Panzara,[85] a study examining autopsies of patients who succumbed to ALS, the authors found inflammatory infiltrates in the spinal cord, raising the possibility of an immune-mediated process in motor neuron degeneration. Pet. Ex. 18A at 392. But they drew no conclusions, instead recommending further studies to determine the role of autoimmunity in the pathogenesis of ALS. Id. at 404. Similarly, in Graves,[86] the authors concluded that "[f]urther studies are needed to investigate the initiating cause of [ ] inflammation." Pet. Ex. 36 at 6. I find the literature and Dr. Raymond's testimony to be most persuasive on the significance of the inflammation. As best summarized by Staff and Appel, it is "unclear at this point how and when the immune system impacts the course of disease in ALS patients." Pet. Ex. 37 at 335.

Fourth, I find petitioners' theories regarding stress and vaccine adjuvants to be speculative. Dr. Utz acknowledged that his theory that J.T.'s existing FUS mutation stressed her neurons, making them susceptible to ALS was speculative. While he did not concede that his theory based on adjuvants was speculative, Dr. Utz's testimony about this theory during the hearing was not persuasive. Moreover, this theory assumes that adjuvants activate toll-like receptors, which cause inflammation. Again, the role of inflammation in the etiology of ALS is simply unknown at this time, and thus, I do not find any theory based on this premise to be persuasive.

ii. Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, petitioners must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the

[84] Staff & Appel, 26 NEUROMUSCULAR DISORDERS 335 [Pet. Ex. 37]; Gussoni, E., et al., 153 J. Immunol. 4798 [Pet. Ex. 24E]; Panzara et al., 6 NEUROBIOLOGY OF DISEASE 392 (1999) [Pet. Ex. 18A].

[85] Panzara et al., 6 NEUROBIOLOGY OF DISEASE 392 (1999) [Pet. Ex. 18A].

[86] Graves, et al., 5 AMYOTROPH. LATERAL SCLER. OTHER MOTOR NEURON DISORD. 213 [Pet. Ex. 36].

injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner[s] must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (citations omitted).

1. Evaluation of the Evidence

I find that petitioners failed to prove by preponderant evidence that the vaccine was the "but for" cause of J.T.'s ALS for the following reasons. Petitioners agreed and both of their experts conceded that J.T. had ALS and was born with the FUS P525L mutation. However, petitioners' experts were equivocal and gave contradictory evidence about whether J.T. would have developed ALS if she had not received the vaccine. Initially, Dr. Steinman testified that J.T.'s mutation could have caused her ALS without any vaccine trigger. However, later during the hearing, he recanted his earlier testimony and testified that he did not believe that her ALS would have developed without a trigger, such as the vaccine. Similarly, Dr. Utz initially testified that more likely than not, J.T. would have had ALS even if she had not received the vaccine. Tr. 218. However, he later testified that it was unknown whether J.T. would have developed ALS if she had not received the vaccine. Id. at 497-98, 505. In contrast, respondent's experts put forth a persuasive explanation that J.T.'s serious genetic mutation caused her ALS and death and that the vaccine played no role in the development or progression of her disease. Further, Dr. Lomen-Hoerth, an ALS specialist and J.T.'s treating physician, did not attribute J.T.'s ALS to the HPV vaccine. I find the equivocation by petitioners' experts to be telling, and Dr. Loemen-Hoerth and respondent's experts to be more persuasive on this point.

I also find that petitioners failed to establish by preponderant evidence that the HPV vaccine may have worsened J.T.'s condition or that it otherwise affected the course of her illness. Petitioners put forth no evidence to support their position on this issue. In contrast, Dr. Raymond provided literature showing the reported cases of FUS P525L ALS, and these cases illustrate that J.T.'s age at onset, clinical course, duration of illness, and severity of illness were consistent with the reported cases. Further, there are no known instances of disease free individuals who have the P525L mutation. For these reasons, I find that petitioners failed to provide preponderant evidence of Althen Prong Two.

iii. Althen Prong Three: Proximate Temporal Relationship

Under Althen Prong Three, petitioners must provide "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." De Bazan, 539 F.3d at 1352. The acceptable temporal association will vary according to the particular medical theory advanced in the case. See Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 356 (2011) (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting the vaccine and injury").

1. Evaluation of the Evidence

Petitioners' experts opined that the temporal interval between J.T.'s vaccinations on March 1, 2007, and the onset of motor weakness evidenced by her fall when jumping a hurdle on May 24,

2007, (84-85 days) is appropriate. Respondent's expert, Dr. Venkatesan, testified that this time frame is "a little long" for onset given an immune response or molecular mimicry mechanism. Tr. 446. However, Dr. Venkatesan stated that it was very difficult to say when J.T.'s symptoms began, and that it was "very likely" that her symptoms started earlier than the hurdle event.

Dr. Steinman testified that the onset of both J.T.'s alleged ADEM and her ALS occurred on May 24, 2007, the day of her track accident, and he also testified that J.T.'s alleged ADEM in turn triggered her ALS. Tr. 80-81, 83. Generally, cause and effect takes time to develop. For example, when a person is exposed to a virus, there is a time period between exposure and the development of symptoms, also known as the "incubation period."[89] In other words, symptom manifestation is not instantaneous following exposure. Petitioners state in their prehearing submission that J.T.'s alleged ADEM "eventually triggered her ALS-like condition." Pet. Prehearing Sub. at 16. Dr. Steinman's testimony as to the onset of ADEM and ALS is thus inconsistent. Moreover, Dr. Steinman did not provide a plausible explanation of how or why the initial manifestation of both the alleged ADEM and the ALS occurred at the same time, in light of his theory that ADEM caused ALS.[90]

Even assuming, *arguendo*, that petitioners could satisfy Althen Prong Three by preponderantly proving a medically appropriate onset, a temporal relationship alone does not constitute preponderant evidence of vaccine causation. Petitioners failed to establish Althen Prongs One and Two by preponderant evidence, and therefore, they failed to meet their burden of proof as to causation.

c. Alternative Causation

Because petitioners did not meet their burden of proof on causation, respondent does not have the burden of establishing that a factor unrelated to the vaccination caused J.T.'s injuries. See Doe v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1358 (Fed. Cir. 2010) ("[petitioner] Doe never established a prima facie case, so the burden (and attendant restrictions on what 'factors unrelated' the government could argue) never shifted"). Nevertheless, respondent has identified an alternative cause of J.T.'s injuries: the FUS P525L ALS gene mutation. Pursuant to the Vaccine Act, compensation shall be awarded where the petitioner demonstrates the requirements set forth under the Act by a preponderance of the evidence, and "there is not a preponderance of the evidence that the . . . injury . . . is due to factors unrelated to the administration of the vaccine." § 300aa-13(a)(1)(A)-(B). The Vaccine Act provides that "factors unrelated to the administration of the vaccine," are those "which are shown to have been the agent . . . principally responsible for causing the petitioner's illness, disability, injury, condition or death." Id. § 13(a)(2)(B).

Thus, even if petitioners had established their case by a preponderance of the evidence, their arguments fail because respondent has proven by preponderant evidence that the FUS P525L ALS

[89] "Incubation period" is defined as "the interval between receipt of infection … and the first symptoms of illness." Dorland's at 1415.

[90] In Sproviero, a case relied on by Dr. Steinman, the patient had MS and at some later date developed ALS. Pet. Ex. 53. Thus, Sproviero does not support Dr. Steinman's opinion that the onset of ADEM and ALS occurred at the same time.

mutation—a factor unrelated to the administration of the vaccine—is responsible for causing J.T.'s JALS and her death.

i. Althen Prong One: Respondent's Medical Theory

To prove Althen Prong One establishing alternative causation, respondent is required to set forth a medical theory explaining how a factor unrelated to the vaccine caused the injury at issue. Respondent's expert, Dr. Raymond, explained the causal theory underlying FUS P525L ALS, as follows: "FUS is a nucleoprotein that functions in DNA and RNA metabolism, including DNA repair, and the regulation of transcription, RNA splicing, and export to the cytoplasm." Resp. Ex. D at 3. "In neurons, FUS is predominantly localized to the nucleus. []Neuropathological analysis of brain and spinal cord of ALS patients carrying FUS mutations show[] cytoplasmic retention and the formation of FUS…aggregates." Resp. Ex. H at 3. The P525L mutation has been "identified as a disease causing mutation …. seen primarily in sporadic cases of juvenile ALS .... [I]ndividuals with [this] mutation have an earlier age of onset and a rapid progression" than seen in other types of ALS." Id.

While it is not exactly clear how the FUS P525L mutation causes neuronal degeneration or why it affects younger patients, literature cited by respondent reveals "mislocalization of mutant FUS proteins in neuronal cytoplasm with abnormal FUS protein aggregates that are associated with markedly disorganize[d] intracellular organelles, including endoplasmic reticulum and mitochondria," which has led to the hypothesis that "mutant FUS proteins [] inhibit normal RNA and protein synthesis, thereby suppressing neuronal functions and survival." Resp. Ex. F at 7.

Dr. Raymond cites an article by Blokhuis[91] in support of this theory. In Blokhuis, the authors discuss "ALS causing gene defects," including the FUS mutation. Resp. Ex. D8 at 777. "FUS mediates a wide range of cellular processes including DNA repair, transcription, splicing and mRNA processing. The protein shuttles between the nucleus and the cytoplasm to function in the transport of mRNA." Id. at 782. The authors suggests several molecular mechanisms whereby protein aggregation, which occurs due to the mutation, affects neuronal function and causes disease. While the mechanism is not clear,[92] the authors agree that "the fact that mutations in the genes encoding these proteins [FUS] segregate with disease in [familial ALS] supports the idea that their dysfunction is linked to motor neuron degeneration and disease pathogenesis." Id. at 788.

Thus, although the exact mechanism is not understood, there appears to be a consensus by those who have studied the FUS mutation and its association with ALS that FUS mutations adversely affect motor neurons and lead to ALS. More specifically, the FUS P525L mutation has been associated with neuropathological abnormalities, basophilic inclusions and FUS protein aggregates, which have been linked to motor neuron degeneration. Therefore, I find by a preponderance of the evidence that respondent has satisfied Althen Prong One.

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[91] Anna M. Blokhius et al., *Protein Aggregation in Amyotrophic Lateral Sclerosis*, 125 ACTA NEUROPATHOL. 777 (2013) [Resp. Ex. D8].

[92] In an animal study published in 2015, Sharma and colleagues demonstrated that "FUS-dependent motor degeneration [was] not due to loss of FUS function, but to the gain of toxic properties conferred by ALS mutations." Resp. Ex. K at 1.

ii. Althen Prong Two: A Logical Sequence of Cause and Effect

The second prong of Althen requires proof of a "logical sequence of cause and effect," showing that factors unrelated to the administration of the vaccine are responsible for causing J.T.'s JALS and subsequent death.

Dr. Raymond set forth a logical sequence of cause and effect showing that the FUS P525L mutation caused J.T.'s juvenile ALS. First, J.T.'s clinical course was consistent with ALS and the rapid and aggressive course of P525L FUS described in other cases. Resp. Ex. H at 4. J.T. had a rapidly progressive decline, characterized by muscular weakness and wasting in her limbs, which is consistent with ALS. She did not respond to immunosuppressive therapy. EMGs and nerve conduction tests showed findings consistent with ALS, and J.T. was diagnosed with ALS. J.T.'s autopsy showed neuropathological findings consistent with and specific to FUS P525L ALS. Genetic testing revealed that she had the FUS-P525L genetic mutation. This mutation has not been seen in healthy individuals. J.T. had the genotype-phenotype consistent with other case reports. Dr. Raymond testified that it is not necessary to invoke the vaccination as a trigger to explain J.T.'s condition. I agree and find by a preponderance of the evidence that respondent has satisfied Althen Prong Two.

iii. Althen Prong Three: Timing

The last element of causation is proof of a proximate temporal relationship between the gene mutation and the injury. Althen, 418 F. 3d at 1278. The initial manifestation of J.T.'s ALS was age 13. The age range for juvenile cases of FUS P525L includes children as young as 11 up to age 22. J.T.'s onset occurred at age 13, within this age range. Resp. Ex. H at 4. The duration of her illness, approximately 22 months, was also consistent with FUS P525L ALS. Therefore, I find that respondent has satisfied Althen Prong Three.

VIII. Conclusion

It is clear from the medical records that petitioners have greatly suffered as a result of their daughter's illness and tragic death, and I wish to extend my deepest sympathy to petitioners for the loss of their child. However, I cannot decide this case based upon my sympathy for petitioners but rather by my analysis of the evidence.

For all of the reasons discussed above, I find that petitioners have not established entitlement to compensation and their petition must be dismissed. In the absence of a timely filed motion for review pursuant to Vaccine Rule 23, the Clerk of the Court **SHALL ENTER JUDGMENT** in accordance with this Decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Chief Special Master