In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: August 8, 2024

MARY MULLINS, on behalf of K.M.,	*	PUBLISHED
Petitioner,	*	No. 19-320V
v.	*	Special Master Nora Beth Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Ruling on Entitlement; Haemophilius Influenzae Type B ("Hib") Vaccine; Pneumococcal Conjugate ("Prevnar") Vaccine; Acute Disseminated Encephalomyelitis ("ADEM").
Respondent.	*	

Brian L. Cinelli, Schiffmacher Cinelli Adoff LLP, Buffalo, NY, for Petitioner.
Elizabeth Andary, U.S. Department of Justice, Washington, DC, for Respondent.

RULING ON ENTITLEMENT[1]

On February 28, 2019, Mary Mullins ("Petitioner"), on behalf of K.M., filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10 et seq. (2018),[2] alleging that K.M. suffered acute disseminated encephalomyelitis ("ADEM") or "other demyelinating disorder/inflammatory response, seizure disorder, and other sequalae" as a result of receiving a haemophilius influenzae type B ("Hib") vaccine and/or a pneumococcal conjugate ("Prevnar") vaccine on February 29, 2016. Petition at Preamble (ECF No. 1). Respondent argued against compensation, stating "this case is not

[1] Because this Ruling contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Ruling will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[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 (2018) ("Vaccine Act" or "the Act"). All citations in this Ruling to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

appropriate for compensation under the terms of the Vaccine Act." Respondent's Report ("Resp. Rept.") at 2 (ECF No. 10).

After carefully analyzing and weighing the evidence presented in accordance with the applicable legal standards, the undersigned finds Petitioner has provided preponderant evidence that the Hib and/or Prevnar vaccines K.M. received on February 29, 2016 caused her to develop ADEM, satisfying Petitioner's burden of proof under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Accordingly, Petitioner is entitled to compensation.

I. ISSUES TO BE DECIDED

The parties dispute two factual issues: diagnosis and onset. Joint Prehearing Submission, filed Jan. 29, 2024, at 1-2 (ECF No. 106). Regarding diagnosis, Petitioner contends K.M.'s proper diagnosis is ADEM, and Respondent argues K.M.'s diagnosis is not ADEM and remains unclear. Petitioner's Initial Pre-Hearing Brief ("Pet. Br."), filed Jan. 8, 2024, at 25-44 (ECF No. 98); Resp. Prehearing Br. ("Resp. Br."), filed Jan. 29, 2024, at 20-24 (ECF No. 103). And for onset, Respondent argues K.M.'s onset was April 22, 2016, and Petitioner argues onset was prior to April 22. Pet. Br. at 60-63; Resp. Br. at 34-35.

Causation is also in dispute. Joint Prehearing Submission at 1-2. Specifically, all three Althen prongs are in dispute: (1) "[w]hether the Hib and/or [Prevnar] vaccine can cause K.M.'s alleged injury;" (2) "[w]hether K.M.'s condition was caused by her receipt of the Hib and/or [Prevnar] vaccines on February 29, 2016; and (3) "[w]hether the onset of K.M.'s condition began within a timeframe for which it is medically acceptable to infer causation in fact." Id. at 2.

II. BACKGROUND

A. Procedural History

Petitioner filed her petition on February 28, 2019, followed by medical records, affidavits, and photographs in March 2019. Petition; Pet. Exhibits ("Exs.") 1-24. Respondent filed his Rule 4(c) Report on July 31, 2019, arguing against compensation. Resp. Rept. at 2.

This case was reassigned to the undersigned on October 3, 2019. Notice of Reassignment dated Oct. 3, 2019 (ECF No. 12). Petitioner filed genetic testing in January 2020 and imaging films in July and August 2020. Pet. Exs. 25, 27-28. From July 2020 to March 2022, Petitioner filed expert reports from Dr. Robert Shuman and Dr. Lawrence Steinman and Respondent filed expert reports from Dr. Andrew MacGinnitie and Dr. Michael Kruer. Pet. Exs. 26, 29-31; Resp. Exs. A, C, E-F.

Thereafter, the undersigned held a status conference on May 10, 2022, after which an entitlement hearing was set to begin in February 2024. Order dated May 10, 2022 (ECF No. 70); Prehearing Order dated July 5, 2022 (ECF No. 74). Prior to the hearing, Petitioner filed updated medical records and updated medical literature. Pet. Exs. 32-48.

An entitlement hearing was held from February 27, 2024 to March 1, 2024. Order dated Mar. 1, 2024 (ECF No. 112). Petitioner, Mr. Daniel Mullins ("Mr. Mullins"), Dr. Steinman, Dr. Shuman, Dr. Kruer, and Dr. MacGinnitie testified. Transcript ("Tr.") 3, 181, 411. Thereafter, both parties filed additional records. Pet. Exs. 49-59; Resp. Exs. I-L.

This matter is now ripe for adjudication.

B. Medical Terminology

1. Acute Disseminated Encephalomyelitis

ADEM "is an immune-mediated inflammatory demyelinating disorder of the central nervous system (CNS)." Resp. Ex. C, Tab 1 at 1.[3] The National Institute of Neurological Disorders and Stroke ("NINDS") defines ADEM as "a brief but widespread attack of inflammation in the brain and spinal cord that damages myelin—the protective covering nerve fibers." Pet. Ex. 29-2 at 1.[4] According to NINDS, ADEM symptoms

> appear rapidly, beginning with encephalitis-like symptoms such as fever, fatigue, headache, nausea and vomiting, and in the most severe cases, seizures and coma. ADEM typically damages white matter (brain tissue . . .), leading to neurological symptoms such as visual loss (due to inflammation of the optic nerve) in one or both eyes, weakness even to the point of paralysis, and difficulty coordinating voluntary muscle movements (such as those used in walking). . . . Children are more likely than adults to have ADEM . . . . In addition, ADEM usually consists of a single episode or attack of widespread myelin damage . . . . Doctors will often use imaging techniques, such as MRI (magnetic resonance imaging), to search for other and new lesions (areas of damage) on the brain.

Id.; see also Resp. Ex. C, Tab 1 at 1 (noting MRI scans show "widespread subcortical and central white matter lesions").

The International Pediatric Multiple Sclerosis ("MS") Study Group proposed the following criteria for diagnosing pediatric ADEM:

- A first polyfocal clinical CNS event with presumed inflammatory demyelinating cause

[3] Karen L.O. Burton et al., Long-Term Neuropsychological Outcomes of Childhood Onset Acute Disseminated Encephalomyelitis (ADEM): A Meta-Analysis, 27 Neuropsychology Rev. 124 (2017).

[4] Acute Disseminated Encephalomyelitis Information Page, Nat'l Inst. of Neurological Disorders & Stroke, https://www.ninds.nih.gov/health-information/disorders/acute-disseminated-encephalomyelitis (last modified June 15, 2018).

- Encephalopathy[5] that cannot be explained by fever
- No new clinical and MRI findings emerge three months or more after the onset
- Brain MRI is abnormal during the acute (three-month) phase
- Typically on brain MRI:
  - Diffuse, poorly demarcated, large (>1-2 cm) lesions involving predominantly the cerebral white matter
  - T1 hypointense lesions in the white matter are rare
  - Deep grey matter lesions (e.g. thalamus or basal ganglia) can be present

Resp. Ex. F, Tab 3 at 2, 6 app. 2.[6] All criteria are required for diagnosis. Id. at 2. The International Pediatric MS Study Group noted "clinical symptoms and radiologic findings of ADEM can fluctuate in severity and evolve in the first three months following disease onset." Id. at 3. However, their definition requires "[n]o new symptoms, signs[,] or MRI findings after three months of the incident ADEM." Id. at 6 app. 2. Additionally, "[CSF] oligoclonal bands are only rarely observed." Id. at 3; see also Pet. Ex. 30-4 at 4 ("In children with ADEM[,] oligoclonal band frequency is reported in between 3-29% of cases . . . . Transient appearance of oligoclonal bands is not uncommon in ADEM . . . .").[7]

ADEM often occurs following infection and vaccination. See, e.g., Pet. Ex. 26-38 at 3;[8] Pet. Ex. 29-2 at 1; Pet. Ex. 30-17 at 1-2, 6;[9] Pet. Ex. 46 at 2;[10] Resp. Ex. C, Tab 1 at 1.

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[5] Encephalopathy was defined as "an alteration in consciousness (e.g. stupor, lethargy) or behavioral change unexplained by fever, systemic illness[,] or postictal symptoms." Resp. Ex. F, Tab 3 at 3 (Lauren B. Krupp et al., International Pediatric Multiple Sclerosis Study Group Criteria for Pediatric Multiple Sclerosis and Immune-Mediated Central Nervous System Demyelinating Disorders: Revisions to the 2007 Definitions, 19 Multiple Sclerosis J. 1261 (2013).

[6] For the 2007 definitions, see Pet. Ex. 48 (Lauren B. Krupp et al., Consensus Definitions Proposed for Pediatric Multiple Sclerosis and Related Disorders, 68 Neurology S7 (2007)). Because the injury at issue in this matter took place in 2016, the undersigned uses the 2013 definitions.

[7] L. Bennetto & N. Scolding, Inflammatory/Post-Infectious Encephalomyelitis, 75 J. Neurology Neurosurgery & Psychiatry i22 (2004).

[8] Suvasini Sharma & Russell C. Dale, Acute Disseminated Encephalomyelitis, in Acute Encephalopathy and Encephalitis in Infancy and Its Related Disorders 133 (Hideo Yamanouchi et al. eds., 2018).

[9] Silvia Tenembaum et al., Acute Disseminated Encephalomyelitis: A Long-Term Follow-Up Study of 84 Pediatric Patients, 59 Neurology 1224 (2002).

[10] Jari Honkaniemi et al., Delayed MR Imaging Changes in Acute Disseminated Encephalomyelitis, 22 Am. J. Neuroradiology 117 (2001).

Treatment for ADEM includes anti-inflammatory drugs, including intravenous corticosteroids (methylprednisone), oral corticosteroids, plasmapheresis, and intravenous immunoglobulin ("IVIG"). Pet. Ex. 29-2 at 1. Most individuals recover within the first six months; however, some "may have mild to moderate lifelong impairment ranging from cognitive difficulties, weakness, loss of vision, or numbness." Id.; see also Pet. Ex. 26-38 at 8 (noting "[m]ortality has been reported in 1%-3% of affected patients," "[r]esidual severe disability is rare[] [and] reported in 7% of children," and "[a]bout 10%-40% of children are reported to experience residual cognitive impairment or changes in mood and behavior"); Pet. Ex. 46 at 2 ("ADEM is associated with a significant mortality of 10%-30%. About 20%-30% of patients who survive are left with neurologic sequelae.").

2. Leukodystrophy

Leukodystrophy refers to "various types of neurodegeneration involving disturbance of the white matter of the brain." Leukodystrophy, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=28066 (last visited May 31, 2024). "Leukodystrophies are heritable disorders affecting the white matter of the [CNS] with or without peripheral nervous system involvement." Resp. Ex. F, Tab 4 at 4.[11] MRIs in leukodystrophies show "T2 hyperintensity in the affected white matter" and variable T1 signal. Id. "Leukodystrophies do not include acquired CNS myelin disorders, such as [MS] and related acquired demyelinating processes, infectious and postinfectious white matter damage, toxic injuries[,] and non-genetic vascular insults." Id.

C. Summary of Medical Records[12]

K.M. was born at 37.3 weeks gestation on February 27, 2015 via Cesarean section delivery due to Petitioner's preeclampsia. Pet. Ex. 5 at 10, 47. K.M. had no apparent significant medical problems at birth. See id. at 23-45. She received a hepatitis B vaccine on February 27, 2015. Id. at 18. She was discharged home on March 1, 2015. Id. at 20, 86.

During her first year, K.M. had some early difficulties with breast feeding. Pet. Ex. 5 at 125, 245-50. K.M. was seen for routine health care visits during the first year of life. See Pet. Ex. 6 at 1-41. She received age-appropriate immunizations during this time. See id. She was noted to have mild intermittent asthma and recurrent acute otitis media,[13] but was otherwise noted to be a "well child" with normal growth and development. Id.

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[11] Adeline Vanderver et al., Case Definition and Classification of Leukodystrophies and Leukoencephalopathies, 114 Molecular Genetics & Metabolism 494 (2015).

[12] This summary of medical records is largely taken from the parties' briefs, as the undersigned finds they provided an accurate representation of the records. See Pet. Br. at 4-25; Resp. Br. at 2-15.

[13] Otitis media is "inflammation of the middle ear." Otitis Media, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=95455 (last visited May 31, 2024).

On February 29, 2016, K.M. was seen by her primary care pediatrician ("PCP"), Jiyeon Becker, M.D., for a one-year-old routine well child visit. Pet. Ex. 6 at 42-43. On physical examination, "scant serous fluid behind right [tympanic membrane]" was noted. Id. at 43. Neurologically, Dr. Becker noted "[g]ood tone and movement throughout. [Deep tendon reflexes] 2+ upper and lower extremities; sitting and pulling to stand; verbalizing; interacting appropriately with caregiver and provider." Id. Assessment was "[n]ormal growth" and "[n]ormal development. . . . Resolving [otitis media], then viral gastroenteritis over weekend. . . . [Okay] to receive vaccines today." Id. Unspecified viral infection was listed as a diagnosis. Id. K.M. received her fourth Hib vaccination and third Prevnar vaccination at this visit. Id.; Pet. Ex. 8 at 1.

K.M. returned to her pediatrician's office on March 7, 2016 and was seen by Heather Fedak, certified pediatric nurse practitioner ("CPNP"), for complaints of a fever. Pet. Ex. 6 at 44-45. Petitioner reported K.M. woke up screaming the night before and was very fussy. Id. at 44. Physical examination revealed inflammation in left ear and upper airway congestion. Id. She was diagnosed with otitis media of the left ear, unspecified fever, fussiness, and nasal congestion. Id. at 45. K.M. was given a prescription for oral amoxicillin. Id.

On March 30, 2016, K.M. was seen by Mary Callahan, M.D., at her pediatrician's office for complaints of an earache, runny nose, and a cough for one week. Pet. Ex. 6 at 46-47. She was diagnosed with bilateral otalgia[14] and an unspecified acute upper respiratory infection. Id. Dr. Callahan noted K.M.'s ears were not infected on examination but recommended insertion of pressure equalization ("PE") tubes in her ears. Id. at 47. On April 20, 2016, K.M. had tympanostomy tubes placed in her ears to help with her recurrent ear infections. Pet. Ex. 9 at 1.

On April 23, 2016, K.M.'s mother took her to Prime Care Urgent and Family Care. Pet. Ex. 9 at 1. Petitioner reported K.M. had congestion and was "overall not feeling well or acting herself." Id. Petitioner reported that K.M. had tympanostomy tubes placed three days prior, and for the past two days, K.M. had been less active and eating less than usual. Id. K.M. had a faint positive rapid strep test and was diagnosed acute pharyngitis and was prescribed oral amoxicillin. Id. at 3-4.

On April 25, 2016, Petitioner took K.M. to the Spotsylvania Emergency Department ("ED") for complaints of signs of weakness. Pet. Ex. 10 at 8. Upon arrival, registered nurse ("RN") Lori J. Sprouse documented that Petitioner reported K.M.

> had ear tubes placed Wed[nesday] of last week. Report[ed] Friday night [April 22, 2016] [K.M.] was not able to stand or sit up. Also report[ed] [K.M.] leaning to right side. Report[ed] seeing urgent care on Sat[urday] and told light faint strep positive. Was seen by PCP today and referred to work up. Report[ed] [K.M.] at time stiff and start[ed] crying as if something hurt[] intermittently. Report[ed] normal at daycare Friday nothing abnormal reported.

[14] Otalgia is "pain in the ear" also called earache. Otalgia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=35938 (last visited May 31, 2024).

Id. at 16 (emphasis omitted). Petitioner also reported K.M. was "not w[a]lking in her usual manner." Id. at 8. During triage, K.M. was noted to be leaning right. Id. at 16. K.M. had bloodwork performed and a head computed tomography ("CT") scan. Id. at 40, 44. Head CT was normal. Id. at 44. K.M. was diagnosed with weakness and strep throat. Id. at 32. She was discharged and instructed to follow up with her PCP in two days. Id.

Later that day, on April 25, 2016, K.M. presented to the VCU Health System ED ("VCU"). Pet. Ex. 7 at 36. Petitioner reported that K.M. was "very irritable [and] unable to bear weight," and her "balance [was] off" by Friday, April 22. Id. K.M. was also "acting out of it and slumping in her high chair." Id. at 178. ED personnel noted that K.M.'s PCP referred K.M. to VCU for a neurology consultation. Id. at 179. K.M.'s admitting physician at VCU, Hadi Anwar, M.D., indicated her presentation was concerning for a CNS infection, noting that K.M. had "fever, irritability, ?ataxia/hypotonicity, ? meningeal inflammation causing her not to bear weight or sit, [and] [cerebrospinal fluid ("CSF")] pleocytosis."[15] Id. at 180. Lab results, including her lymphocytic predominance and normal glucose levels, were more consistent with a viral infection, but K.M. had been previously treated with amoxicillin, which could have sterilized her CSF culture. Id. She was admitted to VCU to rule out the possibility of sepsis and to complete a meningitis workup. Id. at 114.

On the same day she was admitted, K.M. saw Christopher Woleben, M.D., and Cameron Ellis, M.D., for a neurological evaluation. Pet. Ex. 7 at 368. Differential diagnoses included meningitis, sepsis, bacteremia, and neurological insult. Id. at 369. Diagnosis was "[a]ltered mental status." Id. at 371-72. Dr. Woleben noted that K.M. presented with an "altered mental status concerning for partially treated meningitis versus encephalitis." Id. at 372. Full sepsis workup was ordered and performed, including urine, blood, and CSF cultures. Id. at 145, 369. Repeat CSF revealed mild leukocytosis (elevated white blood cells ("WBC")) with a lymphocyte (B cells) predominance, and all CSF cultures were negative. Id. at 145. A pathologist also noted that K.M.'s CSF had "increased lymphocytes, monocytes, and occasional eosinophils and basophils in the background of red blood cells," as well as "a few reactive lymphocytes and possible plasma cells." Id. at 396. Erythrocyte sedimentation rate ("ESR") was only mildly elevated to 14, and her C-reactive protein ("CRP") was normal. Id. at 145.

K.M. was also seen by Muhammad Bhatti, M.D., for a pediatric neurology consultation. Pet. Ex. 7 at 191. Dr. Bhatti noted that K.M. "presented [] with acute onset of irritability without any focal neurological symptoms." Id. at 194. His differential diagnosis was noted as "broad but include[d] [m]eningitis[] [and] [c]erebritis." Id.

K.M. also had an infectious disease consult with Beth Marshall, M.D. Pet. Ex. 7 at 320. Dr. Marshall noted that K.M. presented for a history of behavioral change and concern for neurologic pathology. Id. K.M.'s labs were "significant for a leukocytosis (WBC = 20)." Id. She further noted that K.M.'s "CSF [was] suggestive of inflammatory process given significant

[15] Pleocytosis refers to the "presence of a greater than normal number of cells in the [CSF]." Pleocytosis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=39556 (last visited May 31, 2024).

number of mononuclear cells, however normal protein and lactate [was] somewhat less suggestive of bacterial meningitis." Id. at 322. She commented that K.M. had been treated with oral antimicrobials, which may have had "some CNS penetration and only partially treated a CNS bacterial process." Id. She opined that it was most prudent to offer some course of therapy for bacterial meningitis, but she could not rule out aseptic or viral meningitis, and the possibility of encephalitis or cerebritis should also be considered. Id. at 322-23.

An April 26 electroencephalogram ("EEG") was abnormal due to "generalized delta activity, indicating bihemispheric dysfunction," and "[t]his finding could be seen in the setting of . . . encephalopathy." Pet. Ex. 7 at 196. Follow-up EEG was recommended if mental status did not improve. Id.

K.M. was seen by Dr. Marshall on April 27 following the EEG. Pet. Ex. 7 at 240. Dr. Marshall determined K.M.'s "clinical picture, as suggested by EEG, [was] more likely an encephalitis" and "MRI may assist with diagnosing ADEM or other such finding that may suggest etiology." Id. at 342.

Later that day, on April 27, 2016, K.M. underwent a brain MRI which showed "multiple asymmetric foci of parenchymal T2 signal hyperintensity, some of which are associated with T1 signal hypointensity." Pet. Ex. 7 at 197. Additionally, the foci were "visualized within the white matter of the cerebral hemispheres, within both cerebellar hemispheres . . . [and] thalami." Id. The findings were noted as "nonspecific[] and may be associated with viral encephalitis." Id.

K.M. had an otolaryngology consultation on April 29, 2016 and the otolaryngologist determined there was "[n]o evidence of otitis media" and tympanostomy tubes remained in place. Pet. Ex. 7 at 235-38.

On April 30, 2016, K.M. was seen by pediatric neurologist David J. Leszczyszyn, M.D., who noted that her family had observed clinical improvement in K.M. in the preceding 24 hours, with more eye contact, increased interaction and responsiveness, and decreased irritability. Pet. Ex. 7 at 231. He reviewed the brain MRI and lab tests, however, he was awaiting additional immune neurological test results. Id. He recommended a repeat brain MRI and additional spinal cord imaging before starting K.M. on high dose steroids or other immune therapy. Id. He noted that "ADEM remain[ed] a possibility[,] but she appear[ed] to be making positive, albeit slow, progress with antibiotics and supportive care." Id. Ammar Hussain, MBBS, further noted that K.M.'s "[c]linical picture and unrevealing work up so far raise[ed] suspicion for ADEM–autoimmune process. Neurological sequelae depend on the underlying etiology and can take weeks to months or even longer to improve." Id. at 234-35. Additionally, "if expected recovery [was] not seen soon, will consider repeat CSF testing, neuro axis imaging[,] and use of immunotherapy." Id. at 235.

K.M. had repeat MRIs on May 2, 2016. Pet. Ex. 7 at 330. The MRI of the brain again showed multiple lesions; however, "[s]ome of these lesions show[ed] enhancement, new since the prior study, . . . suggestive of an active inflammatory/demyelinating process." Id. The MRI was "compatible with ADEM or encephalitis." Id. MRIs of the cervical, thoracic, and lumbar spine were normal. Id. Repeat lumbar puncture revealed 11 oligoclonal bands in the CSF,

which were not detected in the serum sample. Id. at 388. CSF also revealed reactive lymphocytes and plasmoid lymphocytes. Id. at 395.

On May 3, 2016, K.M. was seen by Dr. Leszczyszyn, who noted that K.M. was initially treated for meningitis. Pet. Ex. 7 at 223. However, "the mild improvement seen a few days ago seem[ed] to have faded." Id. He felt strongly that because K.M. had been "fully treated for an infectious process," but did not have "clinical improvement and [had] new enhancement [on MRI], [] we should proceed with immune therapy for possible ADEM." Id. She was placed on five days of high dose steroids, in the form of intravenous methylprednisolone ("IVMP"), and five days of IVIG. Id. at 227. Dr. Leszczyszyn followed up on May 5 and noted that K.M. was undergoing active immune treatment, receiving high dose IVMP and IVIG infusions, for presumed ADEM. Id. at 215. He was recommending Ativan for the next several days. Id.

On May 9, 2016, a meeting was held with K.M.'s parents and her treating health care provider team, including child neurology, palliative care, infectious disease, and general pediatrics to discuss her case. Pet. Ex. 7 at 141. K.M.'s infectious workup and treatment history was discussed, and K.M.'s parents were informed that there was no identified infectious cause for K.M.'s symptoms. Id. Neurology discussed the workup leading to her presumed diagnosis of ADEM and explained that it was a "diagnosis of exclusion." Id. at 141-42. K.M.'s parents contacted Johns Hopkins for a second opinion. Id. at 142. K.M.'s parents also strongly desired to have ear tubes removed as well as further workup to determine whether K.M.'s symptoms were related to the ear tubes. Id. K.M. had an otolaryngology consultation on May 9, 2016 and the otolaryngologist determined "ear tube hypersensitivity is unlikely a cause of [K.M.'s] ADEM." Id. at 238. Ear tube removal was not recommended due to risks and complications. Id. at 242.

K.M. was discharged on May 11, 2016 with a diagnosis of "presumed" ADEM. Pet. Ex. 7 at 361. At discharge, it was noted that she had a full septic workup and a negative infectious workup. Id. at 362. K.M.'s discharge note stated that "[a]s patient had previously received amoxicillin, bacterial meningitis could not be ruled out despite negative cultures." Id. Neurologically, the discharge note documented her MRIs showed evolving lesions, for which she received IVMP and IVIG for her presumptive diagnosis of ADEM. Id.

On May 16, 2016, five days after her discharge from VCU, K.M. returned to her PCP for a follow-up appointment. Pet. Ex. 6 at 48. At that time, Dr. Becker noted that K.M. was still fussy and difficult to console, had lost purposeful gaze, and could not sit or stand independently. Id. He noted that K.M.'s parents preferred a transfer to Johns Hopkins Hospital if readmission was required. Id. at 49. K.M. returned to her pediatrician the following day for follow-up, and no improvement was noted. Id. at 50.

On May 21, 2016, K.M. presented to Johns Hopkins Hospital with worsening neurologic symptoms and neurologic regression. Pet. Ex. 11 at 1, 33, 38. "[K.M.] was admitted for evaluation of developmental regression with injury to the white matter of her brain." Id. at 1. Since her discharge from VCU, it was reported that K.M.'s symptoms continued to worsen. Id. at 38. She became more irritable, slept less, and had decreased oral intake. Id. She was having trouble swallowing, began to drool more, and had only been able to eat pureed foods. Id.

On May 22, 2016, K.M. was seen by Dana Kim Furstenau, M.D., who noted that K.M. "could have ADEM given her MRI results . . . , but she ha[d] not improved and ha[d] instead worsened after treatment." Pet. Ex. 11 at 41. She noted that "[b]ecause of [K.M.'s] continued and worsening symptoms, other causes, such as metabolic disorders or neurodegenerative disorders, must be considered." Id. K.M. was also seen by Ernesto Gonzalez-Giraldo, M.D., on May 22. Id. at 42. He concluded that given K.M.'s course and presentation, "ADEM seem[ed] less likely" and there were now concerns for a metabolic/genetic underlying condition. Id. at 42. He ordered a repeat brain MRI, lumbar puncture, EEG, and routine studies. Id. at 43. He also requested a consult for a leukodystrophy opinion and a neurogenetic recommendation. Id.

The following day, May 23, 2016, K.M. saw Matthew J. Erick, M.D., for an additional neurologic follow-up. Pet. Ex. 11 at 50-51. He indicated K.M.'s case was "concerning for a metabolic neurodegenerative process particularly leukodystrophies." Id. at 51. Dr. Erick noted he also would consider mitochondrial disorders as a potential etiology of her symptoms. Id.

Radiologist Christopher Trimble, M.D., was consulted to provide a second opinion on K.M.'s imaging performed at VCU. Pet. Ex. 11 at 305-16. Dr. Trimble's impression was "[m]ultifocal areas of T2 signal abnormality in the subcortical and periventricular white matter and bilateral thalami, some of which demonstrate increasing enhancement between examinations. These findings are most suggestive of an infectious encephalitis or inflammatory encephalitis such as [ADEM]." Id. at 316.

Additional MRIs of the entire spine and brain and a magnetic resonance ("MR") spectroscopy were performed on May 23, 2016. Pet. Ex. 11 at 296-304. The MRIs of the cervical, thoracic, and lumbar spine were normal. Id. at 303. The brain MRI demonstrated "interval development of moderate generalized brain parenchymal volume loss. There [were] now more confluent symmetric T2 FLAIR hyperintensity within the white matter of both cerebral hemispheres and cerebellar hemispheres whereas more discrete lesions were appreciable on prior [imaging]. There [were] no enhancing lesions present . . . ." Id. MR spectroscopy showed K.M.'s "right periventricular region [was] consistent with an inflammatory demyelinating lesion and associated neuroaxonal loss of dysfunction" and her left frontal region was normal. Id. at 296. Repeat lumbar puncture obtained the same day, May 23, revealed CSF with high glucose (86; range 50-75 mg/dL), high WBCs (9 and 10; range 0-5/cu mm), and pleocytosis. Id. at 117, 119, 147, 149. K.M. had "[i]ncreased levels of several amino acids including glutamine, serine, and glycine," and "[a]lthough not diagnostic, this pattern has been associated with mitochondrial dysfunction." Id. at 146. Additionally, no growth was seen on CSF cultures. Id. at 151.

On May 25, 2016, K.M. was seen by Jennifer Lauren Orthmann Murphy, M.D., for a neuroimmunology consult. Pet. Ex. 11 at 99. Dr. Orthmann Murphy concluded,

> It seems most likely that an infection (possibly post-op and related to bilateral PE placement) incited the CNS inflammation indicated by the pleocytosis that became more predominantly lymphocytic over the course of

> [three] lumbar punctures, as well as the briefly enhancing [white matter] lesions. . . .
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> . . . .
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> . . . [K.M.] initially presented . . . with leukocytosis, but has never had a fever, and infectious workup has been unremarkable to date. Therefore, ADEM is also a possibility, as the heterogeneous patchy appearance of [white matter] lesions, brief enhancement, and response of CNS inflammation to steroids is consistent. . . .
>
> Another possibility is that infection triggered an underlying metabolic disorder, including mitochondrial disorder, or leukodystrophy []. Vanishing [w]hite [m]atter disease can present after an episode of stress, as can metabolic disorders[] [and] mitochondrial disorders. Her serum amino acids suggest a mitochondrial disorder is possible. We agree with consultation to neurogenetics to work up this possibility . . . .

Id. at 104-05.

On May 26, 2016, Dr. Orthmann Murphy noted that neuroimmunology and neuroradiology had been consulted and no signs of infection arising from K.M.'s auditory canals appeared on any imaging. Pet. Ex. 11 at 106. The consensus was that K.M. had an "inflammatory encephalopathy, either ADEM or due to infection (without a good source of infection) along with underlying metabolic dysfunction." Id.

The same day, she was seen by resident Noura Al Dhaheri, M.D., and attending geneticist and pediatrician, Nara Sobreira, M.D., Ph.D., for a genetics consultation. Pet. Ex. 11 at 110-14; see also Pet. Ex. 25 at 8-15. The treating note stated that "[t]he team has taken into account ruling out infectious and possible auto-immune mediated process that could cause acute demy[e]lination," and "[f]rom a metabolic/neurogenetic standpoint, there are few metabolic conditions that could be triggered by illness and several neurogenetic condition[s] that could cause white matter demy[e]lination." Pet. Ex. 25 at 13. Dr. Dhaheri and Dr. Sobreira "agree[d] that leukodystrophy seems to be most consistent with patient clinical presentation and MRI findings, however the pleocytosis is somewhat out of proportion to what is seen in one of these leukodyst[r]ophy conditions: Aicardi [Goutières] syndrome."[16] Id. Additional comprehensive genetic workup, including whole exome sequencing ("WES") testing, was recommended and ordered. Id. at 13-14. The results of the WES testing were reviewed in June 2016 and were negative for any significant findings for causative variants. Id. at 47-53.

On May 27, 2016, K.M. was discharged to Kennedy Krieger Institute ("KKI") for inpatient therapy while awaiting the results of the genetic testing. Pet. Ex. 14 at 7; Pet. Ex. 11 at

[16] Genetic testing of the associated genes was negative. Pet. Ex. 11 at 778. For more information on Aicardi-Goutières syndrome, see Resp. Ex. F, Tab 5 (Françoise Goutières, Aicardi-Goutières Syndrome, 27 Brain & Development 201 (2005)).

2, 115-18. On discharge, Johns Hopkins noted that K.M.'s case had been reviewed by neurology, neuroimmunology, and neurogenetics. Pet. Ex. 11 at 117. "The general consensus was that the pattern on MRI imaging was most consistent with a genetic degenerative pattern such as a leukodystrophy. However, the CSF pleocytosis was atypical, possibly indicative of an infectious or inflammatory process as a triggering event." Id.

Upon admission at KKI, treating physicians noted that the "[e]tiology of [K.M.'s] illness [was] not currently known, and include[d] ADEM, viral or parainfectious encephalitis, metabolic neurodegenerative process such as leukodystrophies . . . , mitochondrial disorders, and organic acidemias." Pet. Ex. 14 at 7. K.M. remained in inpatient therapy at KKI until June 7, 2016, when she was readmitted to Johns Hopkins for three days of recurrent fevers. Id. at 102, 120. She was discharged from Johns Hopkins on June 13, 2016 and readmitted to KKI, where she remained in inpatient rehabilitation until July 14, 2016, when she was discharged home. Id. at 163, 169, 531-32.

On July 26, 2016, K.M. returned to her PCP for a follow-up appointment. Pet. Ex. 6 at 54. Petitioner reported K.M. was "doing much better" and had a gastrostomy tube placement scheduled for September 1, 2016. Id. On examination, K.M. "ha[d] improved affect and comfort level with more relaxed appearance from last visit." Id. K.M. was "[s]till unable to hold head independently," "[t]rack[ed] more to noise than sight," and was able to vocalize but did not form words. Id. K.M. had "truncal and [lower extremity] hypotonia. [Upper extremity] hypertonicity ha[d] improved but persist[ed], left greater than right." Id. at 55. Preventative health was discussed with the family and K.M. was given her fourth diphtheria-tetanus-acellular pertussis ("DTaP") vaccine and her fourth Prevnar vaccine. Id.; Pet. Ex. 8 at 1.

In August 2016, certified genetic counselor Christy Smith from Johns Hopkins informed Petitioner that mitochondrial genetic testing was negative and normal. Pet. Ex. 11 at 765. Ms. Smith explained that "at this point, all of the testing ha[d] been negative and [they] did not have an underlying genetic cause for [K.M.'s] symptoms." Id.

K.M. presented to her pediatrician for a pre-operative appointment on August 12, 2016. Pet. Ex. 6 at 56. K.M. did not appear acutely or chronically ill. Id. Her gaze and upper extremity movement was improving, although her truncal tone remained diminished. Id.

K.M. returned to Johns Hopkins on September 1, 2016 to have her gastrostomy tube placed and for a scheduled repeat brain MRI. Pet. Ex. 11 at 595, 602-04. Brain MRI revealed

> [r]edemonstration of patchy confluent symmetric FLAIR hyperintense signal along the subcortical and periventricular white matter of both cerebral hemispheres with progressive interval increase compared to multiple priors dating to MRI [April 27, 2016]. These findings [were] suspicious for a slowly progressive neurodegenerative disorder like e.g. [neuronal ceroid lipofuscinoses], folate transport deficiency[,] as well as mitochondrial disorders. ADEM appear[ed] less likely.

Id. at 294, 777.

On September 8, 2016, K.M. presented to the Leukodystrophy Clinic at The Children's Hospital of Philadelphia ("CHOP") for an EEG, which showed hypsarrhythmia.[17] Pet. Ex. 15 at 49. From September 12 to 15, 2016, K.M. was admitted to the CHOP Leukodystrophy Clinic for continued workup and evaluation. Id. at 23, 30. The neurology admission note detailed K.M.'s clinical course and noted the September 2016 MRI "showed worsening of her leukodystrophy and was also concerning for cerebral folate deficiency." Id. at 30. K.M. was noted to move all extremities, although with no purposeful movements, and have seizures. Id. There was a concern for Aicardi-Goutières syndrome,[18] for which a metabolic lumbar puncture and CT were ordered, and a concern for cerebral folic acid deficiency. Id. at 33. It was noted K.M. "continue[d] to have rapid progression of symptoms without a definite diagnosis." Id. at 34.

Head CT performed September 13, 2016 showed "[m]arked diffuse cerebral volume loss with extensive periventricular hypodensity, significantly progressed since [April 25, 2016] head CT, and in keeping with suspected leukodystrophy. No intracranial calcifications." Pet. Ex. 15 at 85-86. Petitioner believed K.M. was unable to see and requested an ophthalmology consultation, which occurred on September 13, 2016. Id. at 49-54. Physical examination revealed temporal pallor of both optic nerves and diminished visual responses. Id. at 53. Ophthalmology reviewed the September 1, 2016 MRI and September 13, 2016 head CT and determined "[t]he white matter in the optic nerves may [] be affected[] and [] account[ed] for the mild temporal pallor of both optic nerves. The temporal pallor seen [was] not commensurate with the amount of vision that [K.M.] display[ed]." Id. Ophthalmology concluded "there [was] likely an additive effect of cortical visual impairment, considering the marked cerebral volume loss noted on the head CT." Id.

K.M. was discharged from CHOP on September 15, 2016 with a diagnosis of hypsarrhythmia. Pet. Ex. 15 at 54, 62. She was placed on leucovorin (folinic acid) for treatment, and it was noted at discharge that a stronger dosage of leucovorin or initiation of Vigabatrin (an anticonvulsant) could be considered for additional treatment of her seizures, depending on how K.M. did after discharge. Id. at 57.

On September 29, 2016, K.M. followed up with KKI. Pet. Ex. 14 at 564-70. Neuropsychology assessed K.M.'s neurobehavioral status, which appeared stable. Id. at 564. Neuropsychology diagnosis was neurodegenerative disorder. Id. Physical Medicine and Rehabilitation documented the current working diagnosis as leukodystrophy versus folate transport deficiency. Id. at 569. K.M. had improvement in tone and was sleeping better, but continued to have poor trunk and neck control and remained the same cognitively. Id.

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[17] Hypsarrhythmia is "an electroencephalographic abnormality sometimes observed in infants, with random, high-voltage slow waves and spikes that arise from multiple foci and spread to all cortical areas. It is seen most commonly in cases of jackknife seizures." Hypsarrhythmia, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=24469 (last visited May 31, 2024).

[18] Again, genetic testing of the five associated genes for Aicardi-Goutières syndrome was negative. Pet. Ex. 11 at 778.

From November 2016 through 2017, K.M. continued to receive treatment at VCU, Johns Hopkins, and Children's National. See, e.g., Pet. Ex. 7 at 894, 924, 934, 971, 1001, 1012, 1017, 1033, 1038, 1053; Pet. Ex. 11 at 785-93; Pet. Ex. 16 at 1-29. In addition to routine treatment, diagnostic testing, and other care, K.M. also experienced some additional complications during this time. See, e.g., Pet. Ex. 17 at 13-16 (alopecia areata (hair loss)); Pet. Ex. 5 at 309-11 (pneumonia and acute respiratory failure); Pet. Ex. 7 at 1113 (aspiration pneumonia).

On January 7, 2017, K.M. had an abnormal EEG that was "indicative of a moderate encephalopathy with tendency towards seizures of a multifocal origin." Pet. Ex. 16 at 59. In March, K.M. returned to Children's National for 48-hour video EEG. Id. at 7, 10. EEG was abnormal in the awake and sleep states. Id. at 24. "From the findings, this EEG [was] compatible with hypsarrhythmia, which indicates severe encephalopathy or epileptic encephalopathy. The seizure semiology (clusters of spasms) and presence of hypsarrhythmia on EEG is consistent with a diagnosis of infantile spasms." Id. at 25. K.M. was assessed with intractable epilepsy and started on additional anticonvulsants. Id.

In May 2017, Petitioner reported to providers at VCU that K.M. was having "at least [five] seizures a day." Pet. Ex. 7 at 1006. At a visit regarding her gastrostomy tube in May, K.M. was noted to have "a history of questionable ADEM." Id. at 1007. In June, at a visit to VCU, Petitioner reported K.M. had "as many as 10 [seizures] a day," despite being on medication. Id. at 1017. Impression was "apparent ADEM and seizures with developmental delay." Id. at 1018.

In August 2017, K.M. underwent another brain MRI at Children's National that revealed "[m]ild-to-moderate diffuse gray and white matter cerebral, cerebellar, and brainstem volume loss" that "could represent atrophy or cerebral atrophy if [K.M.] [was] on or was recently administered corticosteroids." Pet. Ex. 16 at 30-31. The MRI also revealed "[c]onfluent, mildly heterogeneous deep and periventricular bilateral cerebral white matter signal abnormality." Id. at 31. This finding was "nonspecific and could represent leukoencephalopathy from prior insult versus underlying leukodystrophy depending on the clinical context."[19] Id.

K.M. has continued to receive treatment. See, e.g., Pet. Ex. 7 at 1471-2016; Pet. Ex. 35 at 2-99; Pet. Ex. 36; Pet. Ex. 43. In January 2018, K.M. presented to orthopedic surgeon Joanna Horstmann, M.D., for an evaluation of her hips and spine. Pet. Ex. 7 at 1471. History of present illness documented K.M. did "not currently have diagnosis other than [ADEM]." Id. On March 13, 2018, K.M. underwent bilateral osteotomy at VCU for treatment of hip dysplasia. Id. at 1613-14.

K.M.'s current treating pediatrician Jane R. Hull, M.D., authored a note dated April 21, 2023, which stated,

[19] The radiologist who interpreted this MRI does not appear to have had K.M.'s previous MRIs for comparison. See Pet. Ex. 16 at 30-31.

> [K.M.] has chronic medical conditions related to [ADEM]. She has brain atrophy as well as multiple lesions in the central white matter, thalami, and cerebellum.
>
> As a result of the above, [K.M.] can not hold her head up, swallow well, eat by mouth, sit up, roll over, crawl, walk, or talk. She also has cortical blindness as a result of her brain injury.
>
> [K.M.] requires 24/7 100% total care and is completely dependent on caregivers for all [activities of daily living] such as bathing, dressing, brushing teeth/hair, diaper changes, etc. She cannot move or do any tasks herself.

Pet. Ex. 42 at 137.

An assessment from a well child visit on June 14, 2023 noted K.M. had quadriplegic cerebral palsy. Pet. Ex. 42 at 43. A neurology appointment on May 5, 2023 indicated K.M. continued to experience multiple seizures on a daily basis and assessed K.M. with "severe neurodevelopmental abnormalities including intractable epilepsy, cerebral palsy with dysphagia, profound intellectual disability all secondary to an early life inflammatory event suggestive of hyperacute ADEM." Pet. Ex. 43 at 90.

D. Petitioner's Hearing Testimony and Affidavit[20]

Petitioner is the mother of K.M. Tr. 8. "For the first year of her life[,] K.M. was a healthy and completely normal child." Pet. Ex. 1 at ¶ 3. Although she had frequent ear infections, there were no other health concerns or issues. Tr. 13. "During [her] first year, K.M. met all of her developmental milestones, was walking and talking[,] and had a 10-15 word vocabulary." Pet. Ex. 1 at ¶ 4; see also Tr. 9-12. She went to daycare five days a week, and no issues were noted. Pet. Ex. 1 at ¶ 4; Tr. 9.

K.M. had her first birthday on February 27, 2016. Pet. Ex. 1 at ¶ 5. "Earlier that month[,] [K.M.] had been sick with a cold and what [was] thought [to be] an ear infection." Id. Petitioner remembered K.M. had a stomach bug on her birthday, although it was not diagnosed. Id.; Tr. 14. On February 29, 2016, K.M. saw her pediatrician and received the vaccinations at issue. Pet. Ex. 1 at ¶ 5. Petitioner averred K.M.'s stomach hurt on the day of this visit. Id.; Tr. 31-32.

One week later, on March 6, 2016, K.M. was fussy with a fever of 105°F. Pet. Ex. 1 at ¶ 7. The following morning at the pediatrician's office, they were told K.M. had inflammation in her left ear. Id. K.M. was given a 10-day course of amoxicillin. Tr. 16-17. Petitioner felt K.M. did not appear to be improving and Petitioner brought K.M. back to her pediatrician on March 30 for what was thought to be a persistent earache. Pet. Ex. 1 at ¶ 8; Tr. 17-18, 35. Petitioner

[20] Following the hearing, Petitioner submitted social media posts to support her contentions herein. See Pet. Exs. 53-59. Although the undersigned has reviewed all of the social media posts, for the sake of brevity this Ruling will not summarize the posts.

reported earache of one week. Tr. 18-19. Petitioner averred that during this time, K.M. "continued to act differently as she remained largely lethargic and was fussier than normal" and "[s]he was definitely not her normal self." Pet. Ex. 1 at ¶ 8; see also Tr. 15-18.

Petitioner testified that following the March 30 appointment, until April 20, 2016, the date in which K.M. had her ear tubes placed, K.M. continued to act in this manner. Tr. 20. K.M. was regressing in her ability to walk and not progressing in her speech. Tr. 21. K.M. was not using utensils and she was using her bottle to drink. Tr. 22-23. Given the continued fussiness during this time, Petitioner and Mr. Mullins had K.M. undergo ear tube placement on April 20. Tr. 38-39; Pet. Ex. 1 at ¶ 9.

On April 22, 2016, two days after her tube placement procedure, K.M. was "extremely fussy," "lethargic[,] and unhappy" at daycare. Tr. 24. That night, K.M. was "falling over to the side[] [and] couldn't sit up by herself." Id. During the night, she was screaming and rigid. Tr. 25. The following morning, April 23, K.M. was unable to sit up or hold her head up and "was [] completely limp." Id.

E. Mr. Mullins' Hearing Testimony and Affidavit

Mr. Mullins is the father of K.M. Pet. Ex. 2 at ¶ 1. Prior to the vaccinations at issue, "K.M. was a healthy, spunky[,] and strong child." Id. at ¶ 3; see also Tr. 52. K.M. "was like most kids." Pet. Ex. 2 at ¶ 3. She was walking and talking. Id. at ¶ 5; Tr. 54-55. She was using utensils, a sippy cup, and playing games like peek-a-boo with her family. Tr. 55-56. K.M. had repeated ear infections during her first year. Tr. 56. There were no health concerns or issues her pediatrician raised. Id.

Mr. Mullins recalled "K.M. was not feeling well" around her first birthday when she received the vaccinations at issue. Pet. Ex. 2 at ¶ 6; see also Tr. 57 ("She was ill . . . to the tune of a fever, along with vomit."). Following the vaccinations on February 29, 2016, K.M. "started acting differently." Pet. Ex. 2 at ¶ 7. K.M. woke up screaming, was fussy, and had a fever one week after the vaccinations. Id. K.M.'s fussiness continued to progress. Tr. 58. K.M. was prescribed amoxicillin on March 7, however, Mr. Mullins did not notice any improvement in K.M.'s demeanor or fussiness following the amoxicillin. Tr. 58-60.

He testified that around March 15 or March 20 he saw "a much more prominent regression." Tr. 78. Mr. Mullins testified that between March 30 and April 20, K.M. was constantly fussy and inconsolable, she needed assistance walking, she regressed in her vocabulary usage and use of utensils, and she was no longer playing games with her family. Tr. 61-65. Based on K.M.'s treating physician's recommendation, K.M. underwent ear tube placement procedure on April 20, 2016. Tr. 61. On April 22, 2016, K.M. began to lean to the right, was unable to sit up, and went limp. Tr. 65. That night, she was screaming and "stiff as a board." Tr. 66.

F. Expert Reports[21]

1. Petitioner's Expert, Dr. Lawrence Steinman[22]

a. Background and Qualifications

Dr. Steinman is board certified in neurology and has practiced neurology at Stanford University for over 40 years. Pet. Ex. 29 at 1-2. He received his B.A. from Dartmouth College in 1968 and his M.D. from Harvard University in 1973. Pet. Ex. 29-1 at 1. Thereafter, he completed a surgery internship, pediatrics residency, and pediatric and adult neurology residency at Stanford University Hospital, as well as three fellowships, including one in clinical immunology. Id. Dr. Steinman has worked as a Professor at Stanford University since 1980. Id. Dr. Steinman is "actively involved in patient care" and "ha[s] cared for hundreds of adults and children with various forms of neuroinflammatory diseases including transverse myelitis, Guillain Barr[é] Syndrome (GBS), chronic inflammatory neuropathy (CIDP), inflammatory neuropathy, [ADEM], neuromyelitis optica (NMO), autoimmune epilepsies[,] and [MS]." Pet. Ex. 29 at 1. He has authored or co-authored over 600 publications. Pet. Ex. 29-1 at 5-49. Dr. Steinman has authored papers on molecular mimicry, metabolic neuropathies, mitochondrial diseases, and the intersection of neuroinflammation and leukodystrophies. Id.; Pet. Ex. 29 at 2. One of Dr. Steinman's specialties is in the area of MS, and he has received a Charcot Prize for Lifetime Achievement due to his research in MS. Pet. Ex. 29 at 3. In 2015, he was elected to the National Academy of Sciences. Id. Dr. Steinman is also a member in the National Academy of Medicine. Id. Over the course of his 50 years as a treating physician, he has treated hundreds of patients with ADEM or ADEM-like injury. See Tr. 167.

b. Opinion

Dr. Steinman opined the Hib and Prevnar vaccines caused K.M. to develop ADEM via molecular mimicry. Tr. 91-92, 97.

i. Diagnosis

Dr. Steinman opined, more likely than not, K.M.'s diagnosis is ADEM. Tr. 91, 149-50; Pet. Ex. 29 at 6, 9. For support, he relied upon the NINDS definition of ADEM.[23] Pet. Ex. 29 at 6-7; see Pet. Ex. 29-2 at 1. He noted he does not use the International Pediatric MS Study Group criteria[24] when diagnosing ADEM. Tr. 150; see Resp. Ex. F, Tab 3.

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[21] Although the undersigned has reviewed all of the expert reports and expert testimony, for the sake of brevity this Ruling does not include every detail of the experts' opinions. Instead, the undersigned focuses on the experts' material opinions, as they relate to the relevant issues.

[22] Dr. Steinman submitted one expert report and testified at the hearing. Pet. Ex. 29; Tr. 3.

[23] See supra Section II.B.1.

[24] See supra Section II.B.1.

He explained K.M.'s pleocytosis, including inflammatory WBCs in the CSF, indicated she had a neuroinflammatory process at play. Pet. Ex. 29 at 6; Tr. 104. And although pleocytosis can be seen in leukodystrophy, it is more likely in ADEM, and therefore, he maintained the diagnosis of ADEM is more likely in K.M.'s case. Pet. Ex. 29 at 7.

An extensive workup for leukodystrophies and metabolic, genetic, and infectious causes was completed and these causes were all ruled out. Pet. Ex. 29 at 7; Tr. 92, 101-03, 169-70. Genetic testing was normal, indicating no underlying genetic cause of K.M.'s condition. Pet. Ex. 29 at 7-8; Tr. 107-09. Dr. Steinman noted specifically that K.M. had no identified form of leukodystrophy. Tr. 169-70. Given the extensive negative testing, Dr. Steinman opined leukodystrophy was "far below ADEM as a differential diagnosis." Pet. Ex. 29 at 8.

On cross-examination, Dr. Steinman opined that oligoclonal bands are seen in ADEM, although not in the majority of cases. Tr. 150. K.M. had 11 oligoclonal bands on May 2, 2016, which was significant to Dr. Steinman. Tr. 167. First, the presence of 11 oligoclonal bands demonstrated the existence of an inflammatory response in the CSF. Id. Second, antigens relating to Dr. Steinman's theories may have affected the large number of oligoclonal bands. Id. And third, he noted the presence of 11 oligoclonal bands suggested an infection or vaccine was at play in the development, and an infection was never identified while vaccines were identified. Tr. 167, 171-74.

Dr. Steinman agreed steroids and IVIG are classic treatments for ADEM and that K.M. did not respond to this treatment. Tr. 151. Dr. Steinman asserted, however, this treatment is not always effective. Id.

ii. Althen Prong One

Dr. Steinman opined the Prevnar vaccine and the tetanus toxoid component of the Hib vaccine can cause ADEM through molecular mimicry. Pet. Ex. 29 at 9-10, 40. He examined the components of the vaccines and presented three molecular mimics to show how the Prevnar vaccine and the tetanus toxoid component of the Hib vaccine can induce an immune response that can cause ADEM. Id. at 11.

1. Phosphoglycerol in Prevnar

Dr. Steinman's first theory involves phosphoglycerol[25] contained in the Prevnar vaccine. He opined that phosphoglycerol is attacked in CNS diseases, including MS and disseminated encephalomyelitis, and experimental autoimmune encephalomyelitis ("EAE"), the animal counterpart of ADEM. Pet. Ex. 29 at 11-12. Although an "imperfect model for ADEM," Dr. Steinman used MS literature in support of his theory, along with patents and documents from the

[25] Phospho- is a "prefix [] indicating the presence of phosphorus in a compound." Stedman's Medical Dictionary 1486 (28th ed. 2006). Glycerol is "[a] sweet viscous fluid obtained by the saponification of fats and fixed oils; used as a solvent, as a skin emollient, . . . and as a vehicle and sweetening agent." Stedman's at 820.

U.S. Food and Drug Administration ("FDA") and Centers for Disease Control and Prevention ("CDC"). Id. at 12, 15-19.

Based upon information obtained from the vaccine patent,[26] Dr. Steinman explained that the glycerol phosphate side chains in the vaccine are necessary for its immunogenicity.[27] Pet. Ex. 29 at 19-20; Tr. 115, 117. Dr. Steinman relied on Chang et al.,[28] who demonstrated "a phospholipid linkage is quite necessary for immunogenicity." Pet. Ex. 29 at 14 (citing Pet. Ex. 29-17). Dr. Steinman explained the phosphoglycerol component is preserved during the process of making the vaccine in order for the immunization to be effective. Id. at 14, 19; Tr. 115, 123-25, 699 (testifying phosphoglycerol must be present for a vaccine to be effective and antibodies to bind); Pet. Ex. 29-17 at 1 ("It is shown that glycerol-phosphate must be preserved for conserving adequate antigenicity of the 18C capsular polysaccharide.").

He explained phosphoglycerol is a three-carbon molecule with phosphate that is a building block of phospholipids[29] in the myelin sheath, which is attacked in ADEM, and a building block of sugars (18C and 23F) contained in the Prevnar vaccine. Tr. 113. Based on his own research, Dr. Steinman explained that "phospholipids are components of the myelin sheath in humans, and [] they are targeted by antibodies in neuroinflammation." Pet. Ex. 29 at 12.

For support, he cited Ho et al.,[30] an article in which he is a named author. Pet. Ex. 29 at 12 (citing Pet. Ex. 29-13). He explained Ho et al. showed "[l]ipids constitute 70% of the myelin sheath, and autoantibodies against lipids may contribute to the demyelination that characterizes [MS]." Id. at 12 (quoting Pet. Ex. 29-13 at 1). He also noted they showed that in the demyelinating disease of MS, autoantibodies primarily target a phosphoglycerol component of myelin. Id. at 13 (citing Pet. Ex. 29-13 at 9). Dr. Steinman acknowledged on cross-examination that Ho et al. studied MS, not ADEM. Tr. 153. He also confirmed Ho et al. did not find the administration of lipids induced autoimmunity. Tr. 155.

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[26] The patent is filed as Petitioner's Exhibit 29-20. The description of the glycerol phosphate side chain in 18C can be found at page 34, and a diagram of the chemical structure is at page 6.

[27] Immunogenicity is defined as "the property that endows a substance with the capacity to provoke an immune response, or the degree to which a substance possesses this property." Immunogenicity, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=24893 (last visited May 31, 2024).

[28] Janoi Chang et al., Relevance of O-acetyl and Phosphoglycerol Groups for the Antigenicity of the *Streptococcus pneumoniae* Serotype 18C Capsular Polysaccharide, 30 Vaccine 7090 (2012).

[29] Phospholipid is defined as "any lipid that contains phosphorus, including those with a glycerol backbone (phosphoglycerides and plasmalogens) . . . . Phospholipids are the major form of lipid in all cell membranes." Phospholipid, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=38759 (last visited May 31, 2024).

[30] Peggy P. Ho et al., Identification of Naturally Occurring Fatty Acids of the Myelin Sheath That Resolve Neuroinflammation, 4 Sci. Translational Med. 1 (2012).

Dr. Steinman also cited a study from Bryson et al.[31] regarding antibodies directed to serotype 23F from humans who received Pneumovax 23, another pneumococcal vaccine that contains 23F. Pet. Ex. 29 at 21-24 (citing Pet. Ex. 29-23 at 2); see also Tr. 116. He explained Bryson et al. showed X-rays of "human antibodies targeting serotype 23F." Pet. Ex. 29 at 22 (citing Pet. Ex. 29-23 at 2); see also Tr. 698-99. Dr. Steinman opined the X-rays demonstrate "the immune response to the phosphoglycerol in the polysaccharide capsule of serotype 23F is critical to the human immune response to serotype 23F." Pet. Ex. 29 at 23; see also Tr. 698-99. Dr. Steinman concluded that the "data from the Bryson [et al.] article demonstrate unequivocally that the immune response to the serotype 23F component of Pneumovax 23 targets the phosphoglycerol in serotype 23F." Pet. Ex. 29 at 24 (emphasis omitted). He concluded that "[s]ince the 23F and 18C components of Prevnar 13 also contain the phosphoglycerol moiety targeted by the antibodies generated by Pneumovax, it is very likely that the immune response to 23F and 18C components of Prevnar 13 vaccine also targets the phosphoglycerol moiety." Id. at 24-25.

Respondent's expert, Dr. MacGinnitie, took issue with Dr. Steinman's theory for three reasons. First, because phosphate is present across various components of cells, antibodies would be expected to target all phosphate-containing molecules. Resp. Ex. E at 2-3; Tr. 122. In response, Dr. Steinman discussed antiphospholipid syndrome,[32] for example, which is a syndrome that only manifests in certain organs or in certain scenarios, and argued that even though "[t]here are many molecules that are all over the body, . . . highly anatomic-specific disease[s]" still occur. Tr. 122-23, 699-700. Dr. Steinman agreed that the immune response is not always directed to phosphoglycerol, but noted it is the majority of time. Tr. 118.

Dr. MacGinnitie also argued the antigens in Prevnar are linked to carbohydrates and are not the same molecule as the phospholipids targeted in a demyelinating disease. Resp. Ex. E at 3; Tr. 124. In response Dr. Steinman cited Ho et al. and maintained phosphoglycerol is necessary for the immune response and it uses the same molecule. Tr. 124-25 (citing Pet. Ex. 29-13).

Third, Dr. MacGinnitie argued the presence of a phosphate molecule may be necessary but is not sufficient for targeting antibodies. Resp. Ex. E at 5; Tr. 125-26. Dr. Steinman did not disagree and testified that "Dr. MacGinnitie comment[ed] on the exception to the rule." Tr. 127-28 (citing Pet. Ex. 29-13 at 3).

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[31] Steve Bryson et al., Structures of Preferred Human IgV Genes–Based Protective Antibodies Identify How Conserved Residues Contact Diverse Antigens and Assign Source of Specificity to CDR3 Loop Variation, 196 J. Immunology 4723 (2016).

[32] Antiphospholipid syndrome is "a multisystem inflammatory disorder characterized by the presence of circulating antiphospholipid antibodies with thrombosis (including thrombotic microangiopathy), spontaneous abortion, thrombocytopenia, valvular heart disease, and other less frequent symptoms." Antiphospholipid Syndrome, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=110221 (last visited May 31, 2024).

In summary, Dr. Steinman explained that there is phosphoglycerol in Prevnar and myelin. Tr. 125. "[T]he immune response to serotypes 18C and 23F in Prevnar 13 targets the phosphoglycerol moiety in those serotypes," which can lead to ADEM. Pet. Ex. 29 at 25; see also Tr. 117, 124-25.

2. CRM_{197} in Prevnar

Dr. Steinman's second theory involves the diphtheria toxin and CRM_{197},[33] the protein carrier in the Prevnar vaccine, "cross-react[ing] with paranodal proteins in the myelin sheath[,] including with neurofascin,[34] that is associated with neuroinflammation in the [CNS], including ADEM." Pet. Ex. 29 at 25. For this theory, he focused on the mimicry between CRM_{197} and the paranodal protein neurofascin, located in the myelin sheath, due to the similarly between CRM_{197} and diphtheria toxin. Id, at 27.

Prevnar is a conjugate vaccine in which the individual polysaccharides of the capsular antigens of *Streptococcus pneumoniae* are linked to a non-toxic diphtheria CRM_{197} protein. Pet. Ex. 29 at 10-11 (citing Pet. Ex. 29-11 at 24). "CRM_{197} is a nontoxic variant of diphtheria toxin," used as a protein carrier which makes the vaccine more immunogenic. Id. at 10, 27 (quoting Pet. Ex. 29-11 at 24). CRM_{197} differs from diphtheria toxin by only one amino acid, "which reduces the toxin activity of the diphtheria toxin but retains the immunological properties of diphtheria toxin and/or the toxoid." Id. at 27; see also Pet. Ex. 29-26 at 1;[35] Pet. Ex. 29-27 at 3.[36]

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[33] Protein carrier "CRM_{197} is a nontoxic variant of diphtheria toxin isolated from cultures of *Corynebacterium diphtheriae* strain C7 (β197) grown in a casamino acids and yeast extract-based medium." Pet. Ex. 29-11 at 24 (Prevnar 13 package insert).

[34] Dr. Steinman testified that paranodal proteins are located along the axon and covered in a myelin sheath for protection. Tr. 131. Neurofascin is a paranodal protein at the nodes of Ranvier. Tr. 132; Pet. Ex. 29 at 25. The nodes of Ranvier are "constrictions occurring on myelinated nerve fibers at regular intervals of about [one] mm; at these sites the myelin sheath is absent and the axon is enclosed only by Schwann cell processes." Nodes of Ranvier, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=93095 (last visited May 31, 2024). Schwann cells are "large nucleated cells whose cell membrane spirally enwraps the axons of myelinated peripheral neurons and is the source of myelin; a single Schwann cell supplies the myelin sheath between two nodes of Ranvier." Schwann Cell, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=64407 (last visited May 31, 2024).

[35] Michael Bröker et al., Biochemical and Biological Characteristics of Cross-Reacting Material 197 (CRM_{197}), a Non-Toxic Mutant of Diphtheria Toxin: Use as a Conjugation Protein in Vaccines and Other Potential Clinical Applications, 39 Biologicals 195 (2011).

[36] Michael Bröker et al., Chemistry of a New Investigational Quadrivalent Meningococcal Conjugate Vaccine That Is Immunogenic At All Ages, 27 Vaccine 5574 (2009).

He explained that in cases of CNS inflammation, which is a hallmark to ADEM, antibodies to neurofascin are seen. Pet. Ex. 29 at 26. He cited a figure from Fehmi et al.[37] that illustrated the structure of the peripheral nervous system nodes, paranodes, and juxtaparanodes. Id. (citing Pet. Ex. 29-28 at 3 fig.1). Fehmi et al. wrote "[neurofascin] has been proposed as a candidate nodal antigen in inflammatory demyelinating diseases of [] the CNS." Pet. Ex. 29-28 at 7. Lanz et al.,[38] an article in which Dr. Steinman is a named author, also discussed paranodal proteins, including neurofascin, and noted "[a]ntibodies to paranodal proteins are found in MS." Pet. Ex. 38 at 3; see also Pet. Ex. 29-15.[39]

Dr. Steinman conducted a BLAST search[40] to determine whether there was homology between CRM_{197} in the vaccine and neurofascin. Pet. Ex. 29 at 28. His BLAST search was of neurofascin versus diphtheria toxoid, which he used because it is "nearly identical" to CRM_{197}. Id. at 31-33; see also Tr. 130, 132, 138. He determined the "YPGLTKVL epitope of diphtheria toxin shares [five] of [eight] identical amino acids with the YPGMTYTL epitope of neurofascin" and the YPGLTKVL epitope in diphtheria toxin is identical to the epitope in CRM_{197}. Pet. Ex. 29 at 33-34; see also Tr. 132-33.

Dr. Steinman opined this sequence was significant and cited a number of papers, including some that he authored or co-authored, to support his opinion that homology of just five amino acids can induce an immune response consistent with his theory here. Pet. Ex. 29 at 28-30. For example, in his 1993 paper, Dr. Steinman wrote that "[a]n autoimmune response can begin even if the molecular mimicry is not quite exact." Pet. Ex. 29-10 at 4.[41] He cited the Gautam et al. studies for the proposition that EAE could be induced with only five amino acids

[37] Janev Fehmi et al., Nodes, Paranodes and Neuropathies, 89 J. Neurology Neurosurgery & Psychiatry 61 (2018).

[38] Tobias V. Lanz et al., Roadmap for Understanding Mechanisms on How Epstein-Barr Virus Triggers Multiple Sclerosis and for Translating These Discoveries in Clinical Trials, 12 Clinical & Translational Immunology e1438 (2023).

[39] Emily K. Mathey et al., Neurofascin As a Novel Target for Autoantibody-Mediated Axonal Injury, 204 J. Experimental Med. 2363 (2007).

[40] A BLAST (Basic Local Alignment Search Tool) search "finds regions of similarity between biological sequences. The program compares nucleotide or protein sequences to sequence databases and calculates the statistical significance." BLAST, https://blast.ncbi.nlm.nih.gov/Blast.cgi (last visited May 31, 2024).

[41] Lawrence Steinman, Autoimmune Disease, 269 Sci. Am. 106 (1993).

identical to myelin basic protein. Pet. Ex. 29 at 28-30 (citing Pet. Ex. 29-30;[42] Pet. Ex. 29-31;[43] Pet. Ex. 29-32).[44] He also cited Root-Bernstein,[45] who also used a BLAST search in his study and wrote "[s]imilarities were considered to be significant if a sequence contained at least [five] identical amino acids in 10." Pet. Ex. 29-33 at 1.

Dr. Steinman explained EAE is "one of the best models of all animal models . . . for studying ADEM." Tr. 119-20; see also Pet. Ex. 29 at 29. Citing a Gautam et al. article, he noted EAE was induced when "[five] of 12 amino acids were identical between the virus and myelin basic protein, and only [three] were consecutive." Pet. Ex. 29 at 29 (citing Pet. Ex. 29-32 at 1, 3). The authors were "able to activate immunity to myelin basic protein and to induce clinical paralysis and neuroinflammation with the viral peptide that was a molecular mimic of [myelin basic protein]." Id. (citing Pet. Ex. 29-32 at 4-5). In another article from Gautam et al., "a six amino acid peptide with identity at [five] amino acids was sufficient to trigger neuroinflammation." Id. at 29 (citing Pet. Ex. 29-31 at 1, 3-4, 4 fig.3). And "a peptide with [four] of 11 amino acids induced neuroinflammation as frequently as a native 11 amino acid myelin peptide." Id. at 30 (citing Pet. Ex. 29-30 at 3-4 ("Since only four or five native residues in a peptide were able to induce EAE, it is conceivable that a pathogen (e.g., viral) with limited homology to self a few amino acid residues may trigger autoimmune disease.")).

In response to Dr. MacGinnitie's contentions that the Gautam et al. articles are not informative here, Dr. Steinman disagreed. Tr. 140-42. He testified these articles are "reproducible, sound[,] and reliable." Tr. 141. Dr. MacGinnitie took issue with the fact that complete Freund's adjuvant was given to mice in these studies, which is not an adjuvant given to humans. Resp. Ex. E at 6. However, Dr. Steinman maintained autoimmune disease can occur without Freund's adjuvant. Tr. 141-42, 160.

Although Silvanovich et al.[46] "provide[d] explanations that [] mimics are not uncommon," they noted "BLAST searches are still the preferred method for identifying mimics." Pet. Ex. 29 at 30 (citing Pet. Ex. 29-34 at 7 ("Thus, for large proteins and an expanding allergen

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[42] Anand M. Gautam et al., A Polyalanine Peptide with Only Five Native Myelin Basic Protein Residues Induces Autoimmune Encephalomyelitis, 176 J. Experimental Med. 605 (1992).

[43] Anand M. Gautam et al., Minimum Structural Requirements for Peptide Presentation by Major Histocompatibility Complex Class II Molecules: Implications in Induction of Autoimmunity, 91 Immunology 767 (1994).

[44] Anand M. Gautam 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).

[45] Robert Root-Bernstein, Rethinking Molecular Mimicry in Rheumatic Heart Disease and Autoimmune Myocarditis: Laminin, Collagen IV, CAR, and B1AR As Initial Targets of Disease, 2 Frontiers Pediatrics 1 (2014).

[46] Andre Silvanovich et al., The Value of Short Amino Acid Sequence Matches for Prediction of Protein Allergenicity, 90 Toxicological Scis. 252 (2006).

database, a FASTA or BLAST bioinformatics search appears to be the optimum method for identifying potential similarities between newly expressed proteins and known allergens.")); see also Tr. 161-62.

Dr. MacGinnitie also took issue with the expect value ("E-value")[47] with Dr. Steinman's BLAST searches. Resp. Ex. E at 6-7. Here, the E-value was as low as 0.21, which he did not find significant. Id.; Tr. 133; see Pet. Ex. 29 at 32-34. Dr. Steinman acknowledged that an E-value of 0.21 was "nowhere near as profound as an E value of zero," but asserted he showed more evidence than just the BLAST search to support his theory. Tr. 134.

Following his BLAST search, he used the Immune Epitope Database ("IEDB")[48] and Alignment Resource to determine if this mimic has been described in humans. Pet. Ex. 29 at 34. He found the YPGLTKVL epitope of diphtheria toxin in the IEDB, evidencing that "humans do make an immune response to that area." Id. at 35-36; Tr. 135-36.

For further support, he cited to Raju et al.,[49] which studied the regions of mimicry between neurofascin, diphtheria toxin, and CRM_{197}. Pet. Ex. 29 at 36 (citing Pet. Ex. 29-35). He noted Raju et al. stated "[h]umans have been shown to mount T cell responses to [] region[s] of the diphtheria toxin molecule." Id. (citing Pet. Ex. 29-35 at 5).

Dr. Steinman concluded that his BLAST search, IEDB search, and the literature (specifically, the Gautam et al. articles and Raju et al. article) are compelling evidence in support of a molecular mimicry theory showing how CRM_{197} in the Prevnar vaccine can cause ADEM. Pet. Ex. 29 at 37; Tr. 139-40.

3. Tetanus Toxoid in the Hib Vaccine

Dr. Steinman's third mimic, similar to the second involving CRM_{197} in Prevnar, concerns homology between the tetanus toxoid in the Hib vaccine[50] and neurofascin. Pet. Ex. 29 at 37. Antibodies to neurofascin are seen in CNS inflammation and ADEM is characterized by such inflammation. Id.

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[47] Expected value, or E-value, "in statistics, [is] the value of an estimate that is the mean of its sampling distribution." Expected Value, Dorland Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=116686 (last visited May 31, 2024).

[48] The IEDB "catalogs experimental data on antibody and T cell epitopes studied in humans and other animal species in the context of infectious disease, allergy, autoimmunity[,] and transplantation. The IEDB also hosts epitope prediction and analysis tools . . . ." IEDB, https://www.iedb.org/home_v3.php (last visited May 31, 2024); see also Pet. Ex. 29 at 35.

[49] Raghavanpillai Raju et al., Epitopes for Human CD4+ Cells on Diphtheria Toxin: Structural Features of Sequence Segments Forming Epitopes Recognized by Most Subjects, 25 Euro. J. Immunology 3207 (1995).

[50] See Pet. Ex. 29-12 at 12 (package insert).

Similar to above, a BLAST search revealed a sequence[51] of five of nine identical amino acids between tetanus toxoid and neurofascin. Pet. Ex. 29 at 39. He also noted this epitope was identified on IEDB as triggering an immune response in humans in two papers. Id. at 39-40 (citing Pet. Ex. 29-36;[52] Pet. Ex. 29-37).[53]

Dr. Steinman concluded that there is "compelling support for a theory that a molecular mimic in the [Hib] vaccine could trigger [] ADEM." Pet. Ex. 29 at 40.

4. Medical Literature

Dr. Steinman acknowledged there is no literature associating Hib and Prevnar with ADEM, nor is ADEM mentioned in the package inserts. Tr. 151-52. During the hearing, however, he cited to a Japanese article authored by Kira et al.[54] that reported a 73-year-old woman who developed ADEM 17 days after her second pneumococcal vaccination.[55] Tr. 168; Pet. Ex. 51 at 1. They noted post-vaccination ADEM may occur two to 30 days following various vaccinations, although "ADEM following pneumococcal vaccination ha[d] never been reported." Pet. Ex. 51 at 1. The authors diagnosed their patient with ADEM based on the 2013 International Pediatric MS Study Group criteria. Id. at 3 (citing Resp. Ex. F, Tab 3 at 2, 6 app. 2). They concluded their patient had "ADEM associated with pneumococcal vaccination" and highlighted the "risk of ADEM caused by unexpected immune activation following repeated administration of the vaccine." Id. at 1, 3.

Pellegrino et al.,[56] a study filed after the hearing, evaluated data from the Vaccine Adverse Event Reporting System ("VAERS") database and the EudraVigilance postauthorisation

[51] This sequence is DINNDIISD. Pet. Ex. 29 at 39. Again, Dr. Steinman was not deterred by the e-value of the BLAST search. See id. at 38-39; Tr. 130-42.

[52] Raghavanpillai Raju et al., Epitope Repertoire of Human CD4$^+$ Lines Propagated with Tetanus Toxoid or with Synthetic Tetanus Toxin Sequences, 9 J. Autoimmunity 79 (1996).

[53] Brenda M. Diethelm-Okita et al., Epitope Repertoire of Human CD4$^+$ T Cells on Tetanus Toxin: Identification of Immunodominant Sequence Segments, 175 J. Infectious Diseases 382 (1997).

[54] Yuu-ichi Kira et al., Acute Disseminated Encephalomyelitis in an Elderly Patient Following Pneumococcal Vaccination with Extremely High Cerebrospinal Fluid Interleukin-6, 13 Clinical & Experimental Neuroimmunology 336 (2022).

[55] K.M. did not receive this type of pneumococcal vaccine.

[56] Paolo Pellegrino et al., Acute Disseminated Encephalomyelitis Onset: Evaluation Based on Vaccine Adverse Events Reports Systems, 8 PLoS ONE e77766 (2013).

module ("EVPM")[57] to examine reports of ADEM following vaccinations. Pet. Ex. 52 at 1. The authors examined 404 cases, 199 from VAERS and 205 from EVPM. Id. at 1-2. They grouped together vaccines against diphtheria, pertussis, tetanus, polio, and Hib and concluded "this was the vaccine group most frequently associated with ADEM development in the VAERS database (21%)" and "less than 15% of the ADEM cases in the EVPM database." Id. at 3. For children under five years of age, pneumococcal conjugate vaccines were the second most commonly involved vaccines (11%). Id. at 4. As to timing between vaccination and ADEM onset, 121 (61%) of cases developed ADEM between two and 30 days post-vaccination and 37 (19%) developed ADEM more than 30 days post-vaccination.[58] Id. at 3 tbl.1. The authors acknowledged that "[s]ince these data arise from passive surveillances systems, we cannot draw conclusions on the possible differences in the risk of ADEM following a specific vaccine." Id. at 5.

iii. Althen Prong Two

Dr. Steinman opined that based on molecular mimicry, "there [was] a logical cause and effect relationship between [the] vaccines and the development of an inflammatory response in K.M.'s nervous system," namely ADEM. Tr. 145, 148; see also Pet. Ex. 29 at 42. He explained "[t]hese mimics were sufficient to trigger inflammation and pleocytosis in the [CNS]," based on his research of the vaccine components, patents, BLAST and IEDB searches, and peer-reviewed literature. Pet. Ex. 29 at 42.

To summarize, Dr. Steinman explained his data showed components of the vaccines "contained mimics of neurofascin, targeted in [CNS] neuroinflammation," and the literature and patents showed phosphoglycerol in Prevnar is targeted by the immune system. Pet. Ex. 29 at 42; see also Tr. 123 (testifying phosphoglycerol must be present for Prevnar to be effective). He also showed how the related CNS disease of MS also involves an immune response to phosphoglycerol. Pet. Ex. 29 at 42. He concluded "[b]oth the neurofascin mimic and the immune response to phosphoglycerol could provoke [CNS] inflammation in [K.M.], and did so." Id. (emphasis omitted). He testified that there was "an inflammatory eruption in K.M.'s brain which caused severe damage, and . . . the provocation was more likely than not due to the components of the actual vaccines that [K.M.] received, the Hib vaccine and the Prevnar [] vaccine." Tr. 91-92.

Dr. Steinman also argued the alum adjuvant in Prevnar strengthens the immune response to the sugars contained in the vaccine and enhances the immune response to CRM_{197}. Pet. Ex. 29 at 28. Due to the "extensive cross-reactivity" between CRM_{197} and diphtheria toxoid, a strong recall response to diphtheria toxoid following Prevnar vaccination existed where K.M. had diphtheria-containing vaccinations before the vaccinations at issue here. Id.

[57] EVMP is the VAERS European counterpart. See Tr. 657.

[58] This data was from only the VAERS cases, as this information was not available on the EVPM database. Pet. Ex. 52 at 3.

Dr. Steinman agreed K.M.'s treating physicians suspected K.M. suffered from infections between her vaccinations and onset of ADEM; however, she never tested positive for an infection. Tr. 163-64, 171-74. He testified that infections and vaccines can both cause ADEM, and that ADEM can result from the combined effect of an infection and an immune system that is primed by a vaccination. Tr. 110, 167-68, 171-72. He further explained that "if [K.M.] had a strep infection, it could have revved up the immune system so that there was even a more intensified response to those molecular mimics . . . in the vaccine." Tr. 171. There are "two arms of the immune system:" the adaptive ("antibodies and T cells") and the innate. Id. The infections "could have intensified the adaptive response to those molecular mimics." Tr. 171-72.

Dr. Steinman acknowledged none of the treating physicians attributed K.M.'s condition to her vaccinations. Tr. 164.

Lastly, Dr. Steinman opined non-vaccine causes were ruled out; "There was extensive laboratory work and imaging studies to rule out infectious causes, metabolic diseases[,] and other causes like leukodystrophy." Pet. Ex. 29 at 42.

iv. Althen Prong Three

As to Althen prong three, K.M. was vaccinated with Hib and Prevnar on February 29, 2016. Pet. Ex. 29 at 40. Dr. Steinman determined K.M.'s clinical symptoms were observed around April 22, 2016, 53 days after vaccination, when K.M. became irritable, was noted to lean to one side, was unable to sit up or hold her head up, and experienced stiffness in extremities. Id. (citing Pet. Ex. 14 at 126); Tr. 145. However, he opined onset was prior to April 22, "as early as the first few days of April." Tr. 145-46, 148.

For support, he first noted K.M.'s initial imaging and testing (clonal antibodies) support an onset prior to April 22. Tr. 145. Plasmacytoid cells, which are plasma cells that make clonal antibodies, were present in the April 25, 2016 CSF.[59] Tr. 106. Dr. Steinman explained that these cells take days to weeks to appear. Id. Here, he opined that the presence of plasmacytoid cells in K.M.'s CSF from April 25 indicated the inflammatory process was occurring for "at least [] a week but more likely a few weeks." Id.

He also opined K.M.'s behaviors evidenced an onset in early April. Tr. 145-46. K.M. was unable to communicate her symptoms clearly given her age, but was not acting as she normally would according to her parents. Id. K.M. was not playing with her brother, she was not walking well, and she seemed to be regressing. Id.; see Tr. 61-65.

[59] CSF from April 25, 2016 revealed "increased lymphocytes, monocytes, and occasional eosinophils and basophils in the background of red blood cells. In addition, a few reactive lymphocytes and possible plasma cells [were] seen." Pet. Ex. 7 at 396. The May 2 CSF revealed "[r]eactive lymphocytes" and "[p]lasmoid lymphocytes." Id. at 395.

To demonstrate such timing is appropriate, he cited Schonberger et al.[60] regarding GBS and influenza vaccination due to the paucity of literature on Hib and Prevnar and ADEM. Pet. Ex. 29 at 40-41 (citing Pet. Ex. 29-38); Tr. 146-48. Although Schonberger et al. does not discuss ADEM or the vaccines at issue here, Dr. Steinman opined it provides support due to the common mechanism of molecular mimicry. Pet. Ex. 29 at 40-41; Tr. 164-65. Schonberger et al. found "[t]he period of increased risk was concentrated primarily within the [five]-week period after vaccination, although it lasted [] approximately [nine] or 10 weeks." Pet. Ex. 29-38 at 1.

Kira et al. reported a case of ADEM that occurred 17 days after a pneumococcal vaccination. Pet. Ex. 51 at 1. The authors in Kira et al. also noted post-vaccination ADEM may occur two to 30 days following various vaccinations. Id. Pellegrino et al. also noted ADEM "commonly occurs within one month from antigenic challenge," which includes vaccination. Pet. Ex. 52 at 1. "The time interval ranged between 2-30 days from vaccination in 61% of the cases, while 37 patients (19%) developed ADEM after one month." Id. at 3, 3 tbl.1.

2. Petitioner's Expert, Dr. Robert M. Shuman[61]

a. Background and Qualifications

Dr. Shuman received his M.D. from Stanford University School of Medicine in 1968, followed by a pediatrics internship, pediatrics residency, pathology residency, neuropathology fellowship, neurology residency, and epilepsy "minifellowship." Pet. Ex. 26-1 at 1. He held various academic appointments from 1974 to 1991. Id. at 1-2; Tr. 287. From 1991 to 2006, Dr. Shuman worked in private practice as a child neurologist. Pet. Ex. 26-1 at 2. He has not worked with patients in a private practice setting since 2006, nor has he regularly seen patients since 2006. Tr. 298. Dr. Shuman has authored or co-authored almost 100 publications over the course of his career. Pet. Ex. 26-1 at 6-12. He is board certified in neurology with a special competence in child neurology, neuropathology, and neuroimaging. Tr. 186, 697; Pet. Ex. 26-1 at 2. At the hearing, Dr. Shuman was the only expert board certified in neuroimaging. Tr. 697.

[60] Lawrence B. Schonberger et al., Guillain-Barre Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-1997, 110 Am. J. Epidemiology (1979).

[61] Dr. Shuman submitted three expert reports and testified at the hearing. Pet. Exs. 26, 30-31; Tr. 181.

b. Opinion

i. Diagnosis[62]

Dr. Shuman opined K.M., more likely than not, has ADEM.[63] Tr. 189, 255, 355. In his expert reports, and at the hearing, he thoroughly examined K.M.'s medical records, including imaging and test results, and explained what aspects of her records support a diagnosis of ADEM. Dr. Shuman opined ADEM is generally monophasic and rapidly progressive without intervention. Tr. 303.

First, Dr. Shuman discussed K.M.'s symptoms that are consistent with ADEM. K.M. had encephalopathy, which he noted is a major criterion for the diagnosis of ADEM in children. Tr. 190. For support, he cited to medical records indicating K.M. had symptoms consistent with encephalopathy. Tr. 191. For example, on May 4, 2016, K.M. was noted to have "irritability, regression in development, including refusal to walk, found to likely have ADEM." Id. (quoting Pet. Ex. 7 at 69). He noted K.M. did not have a fever, and thus, a fever could not have caused her encephalopathy symptoms. Tr. 237-41 (citing Pet. Ex. 6 at 46; Pet. Ex. 9 at 1-3; Pet. Ex. 7 at 36, 182). ADEM can also affect a child's level of consciousness, and K.M. developed a decreased level of consciousness demonstrated by her difficulty to engage, increased sleep, and irritability when aroused. Tr. 198-99.

K.M. also presented with vision problems, including failure to fix and follow a face, which Dr. Shuman opined is also consistent with ADEM. Tr. 192-94 (citing Pet. Ex. 7 at 233 (noting "poor fixation, does not track through testing limited by irritability" on physical examination); Pet. Ex. 11 at 75-76 (indicating, on physical examination, that K.M. "does not fix on examiner's eyes, does not track")).

Dr. Shuman also noted ADEM can affect a child's ability to chew and swallow as well as their speech. Tr. 195, 197. K.M. presented with difficulty chewing and swallowing, necessitating a gastrostomy tube. Tr. 195-96. "K.M. [also] had ongoing impairments in her ability to produce speech[] due to her ongoing oral motor dysfunction . . . . Her repertoire of speech sounds remain[ed] limited . . . [and] [s]he was unable to produce any consonant sounds . . . . [T]he fluency of her speech could not be assessed . . . as she was nonverbal." Tr. 197-98 (citing Pet. Ex. 14 at 543). Given this, and the fact that K.M.'s parents reported observations of

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[62] For Dr. Shuman's discussions regarding pediatric autoimmune encephalitis, see Pet. Ex. 30 at 2; Tr. 228-32. He testified that ADEM falls under the broad category of autoimmune encephalitis. Tr. 333.

[63] For Dr. Shuman's discussion on mixed or combined ADEM, and how it relates to K.M.'s case specifically, see Tr. 243-50, 257-62, 334-37, 357-58; Pet. Ex. 31 at 40-43. The undersigned does not discuss these subtypes of ADEM or the colloquy between Dr. Shuman and Dr. Kruer about these questions. For Dr. Kruer's testimony about these issues, see Tr. 443-45, 495-96, 533-35. Whether K.M. had a mixed or combined form of ADEM is not outcome determinative here. The issue here is whether K.M. had ADEM or a neurodegenerative disease (leukodystrophy). See Pet. Br. at 25-44; Resp. Br. at 20-24.

speech prior to the vaccinations at issue here, he opined K.M. suffered a regression in speech. Tr. 198.

Further, Dr. Shuman opined ADEM can lead to seizures or difficulty with motor movement. Tr. 199-200. K.M. suffers from seizures and hypsarrhythmia, which he opined are due to her ADEM. Tr. 200-02. He also opined ADEM can lead to neuromuscular issues, like those seen in K.M., which is consistent with the opinions of her treating physicians. Tr. 150-52 (citing Pet. Ex. 43 at 90, 612).

On cross-examination, Dr. Shuman agreed these symptoms (vision issues, encephalopathy, seizures, speech regression) are not specific to ADEM and can be due to other conditions of the brain, including neurogenetic disorders. Tr. 324-25; Pet. Ex. 31 at 36. However, he maintained K.M.'s most likely diagnosis is ADEM. Tr. 255.

Next, Dr. Shuman discussed K.M.'s MRIs and opined they were consistent with ADEM.[64] Tr. 205-15; see also Pet. Ex. 26 at 115; Pet. Ex. 30 at 1. Her first MRI (April 27, 2016) showed lesions that he believed explained the symptoms and clinical observations in K.M. Tr. 205-07. The lesions were not equal in size, and therefore, were different ages, with the "younger" lesions being the smaller ones. Tr. 207-08. Dr. Shuman noted with ADEM, there are usually multiple lesions that are large, and K.M. had at least four large lesions seen on her first MRI. Tr. 208-09, 241-42. K.M.'s lesions were bilateral and asymmetric, which is also consistent with ADEM. Tr. 209-10, 317. Additionally, her lesions were diffuse and poorly demarcated. Tr. 241-42.

K.M. underwent subsequent MRIs on May 2, 2016, May 23, 2016, and September 1, 2016, as well as one about one year later on August 30, 2017. Tr. 210-11; see Pet. Ex. 49 at 1. Dr. Shuman examined each MRI and explained the progression of changes. Tr. 211-15; Pet. Ex. 26 at 111. K.M.'s MRIs showed extensive damage that can affect cognitive and motor function. Tr. 217. Over time, the ventricles increased in size while the white matter in the brain decreased. Tr. 212-13; see also Pet. Ex. 26 at 113-14. The May 2 MRI was consistent with an encephalomyelitis typical of ADEM and showed evidence of active disease. Tr. 213-14. The fourth MRI (September 2016) was consistent with "end-stage demyelination," showing "cerebral atrophy" and "virtually complete demyelination of [K.M.'s] cerebrum. Pet. Ex. 26 at 111-12. And the fifth MRI (August 2017) "confirm[ed] the lack of repair of her damaged myelin." Id. Dr. Shuman opined there was no new damage seen on the MRI in August 2017 "probably because there [was] little myelin left to damage." Id. at 112.

On cross-examination, Dr. Shuman agreed that K.M.'s 2016 MRIs revealed a progression from asymmetrical to more symmetrical lesions. Tr. 317. Even though asymmetrical lesions are consistent with ADEM, he opined the lesions became more symmetrical because they were increasing in size, leaving less room for normal tissue in the brain. Tr. 325-26, 358-59; Pet. Ex. 26 at 112.

[64] For the MRI images of the Dr. Shuman referenced at the hearing, see Pet. Ex. 49 at 1; Pet. Ex. 26 at 113-14.

Dr. Shuman also cited to records indicating K.M.'s treating physicians found her MRI findings consistent with ADEM. Tr. 215-16. For example, on May 9, 2016, history of present illness documented, "[c]linical status, other testing + MRI findings = presumptive ADEM." Pet. Ex. 7 at 354; see Tr. 215. On May 31, 2016, at KKI, a treating physician documented K.M.'s MRI "raised concern for ADEM." Tr. 216-17 (quoting Pet. Ex. 14 at 126).

Next, Dr. Shuman discussed K.M.'s CSF results and opined they are consistent with ADEM.[65] Tr. 228. In a patient with ADEM, a lumbar puncture would show mild elevation of protein (K.M.'s was "right at the top end of normal") and increased lymphocytes, macrophages, and WBCs. Tr. 222-24; see also Pet. Ex. 26 at 109 ("Monocytes, lymphocytes and plasma cells suggest . . . a chronic reactive autoimmune process."). K.M.'s CSF results from April 25, 2016 and May 2, 2016 showed elevated WBCs, lymphocytes, and monocytes.[66] Tr. 224-26 (citing Pet. Ex. 7 at 395). He also opined it was unusual for eosinophils to be present in K.M.'s CSF and their presence "connote[d] an allergic response." Pet. Ex. 26 at 108-09; Tr. 226 (citing Pet. Ex. 7 at 395). Dr. Shuman testified that the presence of oligoclonal bands is a sign of an immune response. Tr. 227. Oligoclonal bands can be found in cases of ADEM, although they are more typical in adults and unusual in children under the age of 12. Tr. 227-28. He maintained the presence of oligoclonal bands in K.M.'s CSF is further evidence that supports a diagnosis of ADEM. Tr. 355.

With regard to the International Pediatric MS Study Group criteria cited by Dr. Kruer, Dr. Shuman opined K.M. met its criteria for ADEM. Tr. 235-43, 308 (citing Resp. Ex. F at 2; Resp. Ex. F, Tab 3 at 2-3, 6 app. 2). However, on cross-examination he acknowledged that one criterion—"[n]o new clinical and MRI findings emerge three months or more after the onset"—was not met, testifying there were "certainly" new MRI findings. Tr. 326-27 (quoting Resp. Ex. F, Tab 3 at 2).

To explain why K.M.'s MRI findings are consistent with ADEM, Dr. Shuman cited a study by Armangue et al.[67] Tr. 219 (citing Pet. Ex. 26-2). The study examined 535 children with demyelinating syndromes, including ADEM, (239 children) and children with encephalitis other than ADEM (296 children). Pet. Ex. 26-2 at 1, 3, 10. Four of the ADEM patients had a "[l]eukodystrophy-like pattern" similar to K.M. Id. at 8 tbl.2; Tr. 219-22; Pet. Ex. 30 at 9-10. Each patient initially presented as ADEM with encephalopathy, like K.M. Tr. 221-22; Pet. Ex. 26-2 at 8 tbl.2, 10 fig.4. Follow-up MRIs, however, showed "[l]eukodystrophy-like patterns." Pet. Ex. 26-2 at 8 tbl.2. Dr. Shuman opined these patients required multiple rounds of treatment (i.e., with additional rounds of IVIG or steroids) or more extensive therapy to include

[65] For Dr. Shuman's table containing her CSF results, see Pet. Ex. 26 at 111.

[66] The monocytes were not marked as "high" on the medical records. See Pet. Ex. 7 at 395.

[67] Thaís Armangue et al., Associations of Paediatric Demyelinating and Encephalitic Syndromes with Myelin Oligodendrocyte Glycoprotein Antibodies: A Multicentre Observational Study, 19 Lancet Neurology 234 (2020).

immunosuppressants (rituximab), which K.M. did not receive. Tr. 331-32, 359-60 (citing Pet. Ex. 26-2 at 8 tbl.2). Of the four patients with ADEM who had MRIs that showed leukodystrophy-like patterns, patient number one had progression on MRI similar to K.M. Tr. 221-22 (citing Pet. Ex. 26-2 at 10 fig.4); see Pet. Ex. 30 at 5. Genetic testing in this patient was also negative. See Pet. Ex. 26-2 at 7.

Next, Dr. Shuman discussed medications typically administered to treat ADEM. Tr. 252. Patients are usually given high dose pulse steroids followed by IVIG. Tr. 252, 305, 308. K.M. received five days of high dose steroids and then five days of IVIG. Id. The majority of ADEM patients make a complete recovery or have minimal lingering symptoms. Tr. 322; see Pet. Ex. 30-15 at 6 ("Patients usually have a good outcome with a complete recovery.").[68] However, a lack of response to treatment can occur and is not persuasive proof that ADEM is not the appropriate diagnosis. Tr. 252-53; see also Pet. Ex. 30 at 5-6. Because ADEM has a variable outcome, and additional effective therapies have been discovered since 2016, K.M.'s lack of response to high dose steroids and IVIG is not evidence used against a diagnosis of ADEM. Tr. 253. Dr. Shuman explained that the lack of response to traditional ADEM treatment does not outweigh the evidence in K.M.'s case in favor of a diagnosis of ADEM—namely, her presentation, MRIs and CSF results, and the other clinical criteria for ADEM. Tr. 263-64.

Although K.M.'s inflammatory markers on testing began to decrease once treatment began, K.M. did not improve. Tr. 253-55, 337 (citing Pet. Ex. 11 at 554). Dr. Shuman acknowledged that K.M., on May 22, 2016, was "worsening despite treatments." Tr. 309-10 (citing Pet. Ex. 11 at 41). Dr. Shuman also agreed with K.M.'s treating physician's May 22 note stating, "[b]ecause of her continued and worsening symptoms, other causes, such as metabolic disorder or neurodegenerative disorders, must be considered." Tr. 210-11 (quoting Pet. Ex. 11 at 41).

Dr. Shuman opined that the additional vaccinations K.M. received in July 2016 contributed to her lack of improvement or response to medication. Tr. 262-63; see Pet. Ex. 30-4 at 6 ("[I]t would be sensible to avoid vaccinations (or other immune stimulation) for at least six months following a diagnosis of ADEM."); see also Pet. Ex. 26 at 119-20; Pet. Ex. 31 at 25-29. However, on cross-examination, he acknowledged K.M. was worsening in May 2016, approximately two months prior to the July 2016 vaccinations, and thus, he agreed he had no way to know how the July 2016 vaccination affected K.M. Tr. 340; see also Pet. Ex. 30 at 4.

Lastly, Dr. Shuman addressed Respondent's experts' arguments that K.M.'s proper diagnosis is a leukodystrophy. Dr. Shuman was questioned on cross-examination about records from 2016 where treating physicians found the MRIs "suspicious for leukodystrophy" or "suspicious for a slowly progressive neurodegenerative disorder." Tr. 318-19 (first quoting Pet. Ex. 11 at 601; then quoting Pet. Ex. 11 at 604). He disagreed with these statements made by K.M.'s treating physicians because K.M.'s genetic testing was not positive for leukodystrophy. Id.; see also Pet. Ex. 26 at 115; Pet. Ex. 30 at 1, 3. Additionally, he opined the presence of elevated WBCs in her CSF as well as her abrupt onset were inconsistent with a leukodystrophy.

[68] Serena Massa et al., Update on Acute Disseminated Encephalomyelitis in Children and Adolescents, 8 Children 1 (2021).

Tr. 267, 355; Pet. Ex. 30 at 1. Dr. Shuman maintained the diagnosis of ADEM was made by many of K.M.'s treating providers, as recent as 2023.[69] Tr. 264-66, 353-55 (citing Pet. Ex. 42 at 137 ("[K.M.] has chronic medical conditions related to [ADEM]."); Pet. Ex. 43 at 74 (noting K.M. has "a history of hyperacute ADEM")).

Dr. Shuman agreed leukodystrophy of an unknown cause should remain a "potential diagnosis," but reiterated that extensive testing has not indicated K.M. has a leukodystrophy. Tr. 266. Throughout K.M.'s clinical course, her differential diagnosis included ADEM, leukodystrophies, and others; however, K.M.'s genetic testing has remained negative. Tr. 266-67, 312-17; Pet. Ex. 26 at 115. Although all known leukodystrophies have been ruled out, he agreed leukodystrophies of an unknown cause should continue to be tested in K.M.'s case. Tr. 343. And he agreed on cross-examination that the science behind genetics continues to progress, and there are children with undiagnosed neurogenetic disorders. Tr. 319. He also agreed that a genetic cause is not ruled out by genetic testing. Tr. 319-20. However, he concluded that K.M.'s diagnosis is more likely ADEM rather than leukodystrophy. Tr. 355.

During the hearing, Dr. Shuman pointed out the Armangue et al. article was published in 2020, four years after K.M.'s ADEM, and thus, her treating physicians who questioned whether K.M. had a leukodystrophy or ADEM did not have access to this article at the time of their opinions. Tr. 311, 352 (citing Pet. Ex. 26-2). Therefore, they may not have been aware that some cases of ADEM may show leukodystrophy-like patterns on MRI. See id.

ii. Althen Prong One

Dr. Shuman opined K.M.'s Hib and Prevnar vaccinations caused her to develop ADEM via molecular mimicry. Tr. 268. He agreed with Dr. Steinman's molecular mimicry theories, discussed above. Tr. 268-69.

In addition to Dr. Steinman's molecular mimics, Dr. Shuman proposed that CRM_{197} in Prevnar cross-reacted with a myelin component (e.g., myelin oligodendrocyte glycoprotein ("MOG")).[70] Tr. 268-69; see Pet. Ex. 26 at 118; Pet. Ex. 31 at 21-31; see also, e.g., Pet. Ex. 26-38 at 3 ("Molecular mimicry with T cell-mediated cross-activation and response against myelin proteins, such as myelin basic protein, proteolipid protein, and MOG plus B cell activation and autoantibody production, may play a role."). He explained that MOG "is found at the outermost surface of the myelin sheath." Pet. Ex. 26 at 119 (quoting Pet. Ex. 26-27 at 3 fig.1).[71] "If the CNS [blood brain barrier] is breached by inflammation, CNS microglia cross the endothelial

[69] For a list of treating physician statements regarding the evolution of diagnosis in K.M.'s case, before and after genetic testing, see Pet. Ex. 30 at 3-4.

[70] K.M. was not tested for anti-MOG antibodies, as testing for these antibodies was not routinely performed at the time of her illness in 2016. Tr. 228, 329; Pet. Ex. 26 at 119-20.

[71] Marie Cathrin Mayer & Edgar Meinl, Glycoproteins As Targets of Autoantibodies in CNS Inflammation: Mog and More, 5 Therapeutic Advances Neurological Disorders 147 (2012).

barrier, followed by T-cells." Id. at 118. And if activated by Prevnar, Hib, or the components in each (CRM_{197} in Prevnar or tetanus toxoid in Hib), an autoimmune reaction can occur. Id.

In addition to Dr. Steinman's theories, Dr. Shuman proposed that "[t]he [Prevnar] vaccine . . . is made against the common organisms of otitis media, strep pharyngitis, sinusitis, the common childhood organisms of chronic, recurrent otitis media[,] and sometimes meningitis," and the goal of the vaccine is to cross-react with those organisms. Tr. 269; see also Tr. 349-50. Because "the otitis media infection[] is the kind of infection that the [Prevnar] vaccination is designed to subdue, . . . there's congruence between the clinical infection and the vaccination antigens." Tr. 274. The homology can "supercharge" an immune system, increasing the probability of antibodies to cross-react with closely related myelin antigens. Pet. Ex. 26 at 107; see also Pet. Ex. 31 at 31, 48 ("The bacterial polysaccharide antigens are complexed to bacterial protein toxins, which increases the immunogenicity of the otherwise sluggish polysaccharides. The enhanced immunogenicity enhances molecular mimicry.")

iii. Althen Prongs Two and Three

Dr. Shuman opined the vaccines were the cause of K.M.'s ADEM, and cited to her clinical course, testing, and images, as well as literature for support. See Tr. 272. Dr. Shuman provided a very detailed and thorough summary of K.M.'s medical records and summarized her clinical course. See Pet. Ex. 26 at 2-106.

Further, Dr. Shuman opined K.M.'s history of recurrent ear infections made her more likely to develop the immune response she did. Tr. 270; see also Pet. Ex. 26 at 107. He opined K.M.'s ear infections and the Prevnar vaccine worked together in inducing her immune response. Tr. 270, 274. He further explained that this is especially true given that ear infections are the types of infection that the Prevnar vaccine is "designed to subdue, so [] there's congruence between the clinical infection and the vaccination antigens." Tr. 274. That is, the organisms that cause otitis media in children are the same as those targeted by the Prevnar vaccine. Id. K.M. was "already responding to that particular bacterium in her ears" when she was given "an immunological boost with a vaccine to build more antibody against that specific pneumococcus. And the two events coincide in a synergistic manner . . . ." Tr. 350.

Dr. Shuman agreed none of K.M.'s treating physicians proposed her vaccinations caused her injury. Tr. 349. However, K.M. underwent numerous tests to determine a cause of her symptoms, and each cause was ruled out. Tr. 272-73 (citing Pet. Ex. 30 at 16-17). Based on this extensive testing, he disagreed with Dr. MacGinnitie that an infection alone was a possible inciting event. Tr. 273.

Dr. Shuman testified that ADEM can have "a variable progression, depending on the patient[,] [] the age[,] and the nature" of the illness. Tr. 346; see Pet. Ex. 26-38 at 4 ("The clinical course of ADEM is rapidly progressive, with the development of maximum deficits within [two to five] days."). He explained that K.M.'s myelin, given her age, "ha[d] more availability," or "greater exposure" for a cross-reaction to occur. Tr. 270-71; see also Pet. Ex. 26 at 107, 112; Pet. Ex. 30 at 9 ("[Y]oung myelin is more susceptible to damage than mature

myelin."). Thus, she had more myelin "available to be attacked, open and exposed to an immune attack should an immunoreaction be precipitated." Tr. 271.

Dr. Shuman opined K.M.'s onset could have been as early as May 7 to March 30, or early to mid-April 2016, which was an appropriate timeframe. See Tr. 277-79 (March); Tr. 287 (April 11); Tr. 288-89 (April 1-April 14); Pet. Ex. 26 at 109 ("around mid-April"); Pet. Ex. 30 at 10 (April 13-April 20).

He explained that in ADEM, myelin is attacked before clinical symptoms manifest. Tr. 274. He asserted that in a one-year-old, "CNS damage occurs silently before CNS function has developed." Pet. Ex. 26 at 108. Because neurological symptoms are difficult to assess in a one-year-old, he asserted a mother is in the best position to assess early clinical symptoms. Tr. 274-75, 277; see also Pet. Ex. 26 at 108; Pet. Ex. 31 at 36, 44. Here, Petitioner, K.M.'s mother, noted K.M. "was [] not her normal self," with increased lethargy and fussiness, from March 7 to March 30. Tr. 277-79 (quoting Pet. Ex. 1 at ¶¶ 7-8). Dr. Shuman interpreted this to be "encephalopathic behavior." Tr. 279. Thus, he opined K.M.'s condition "was clinically manifesting itself as early as March 8." Id.

Looking at the medical records, on March 7, 2016, K.M. was diagnosed with otitis media and prescribed a 10-day course of amoxicillin. Tr. 279 (citing Pet. Ex. 6 at 45). On March 30, K.M. had otalgia (earache) for one week. Id. (citing Pet. Ex. 6 at 46-47). No signs of infection were noted. Tr. 280. Dr. Shuman concluded that at this time, K.M. was recently off antibiotics, had no signs of infection, but had diffuse pain in the head. Id. Dr. Shuman testified that these complaints are evidence of encephalopathy. Id.

Next, Dr. Shuman discussed the initial April 27 MRI and based on the lesions seen, he opined the demyelination process began sometime "around mid-April," between April 13 to April 20. Pet. Ex. 26 at 109; Pet. Ex. 30 at 10. He opined the first MRI on April 27, 2016 showed "established myelin damage and myelin loss[,] push[ing] back the date of onset of [K.M.'s] ADEM by several weeks." Pet. Ex. 26 at 109. Given these MRI findings of "established damage," he placed onset five to six weeks post-vaccination, "around mid-April," which he opined was "squarely on the peak of incidence in post-vaccinal encephalomyelitis with []rabies vaccine."[72] Id. And "[t]he progression of the white matter damage" from May 2016 to September 2016, as seen on four MRIs, "is consistent with the monophasic progressive course of post-vaccinal ADEM." Id. at 116.

Dr. Shuman also testified that the fact that the lesions varied in size, shape, intensity, and age supported a finding that the demyelinating process had been going on for "at least a week." Tr. 281. "If there is a T1 hypointense lesion, it would probably be an older T2 lesion with

[72] See H. Shiraki & S. Otani, Clinical and Pathological Features of Rabies Post-Vaccinal Encephalomyelitis in Man, in "Allergic" Encephalomyelitis 58-129 (Marian W. Kies & Ellsworth C. Alvord eds., 1959) (filed as Pet. Ex. 50).

rarefaction of the tissue, and that would make it several weeks."[73] Tr. 281. Dr. Shuman agreed with Dr. Kruer that T2 MRI lesions are visible as early as six hours after a clinically apparent onset of ADEM. Pet. Ex. 30 at 9. However, he argued "[t]he clinically apparent onset of a disease occurs when function becomes disrupted, not when the disease begins," and therefore, "[t]he immunological attack on myelin begins long before the disruption of the function of myelin is clinically apparent." Id. For K.M., there was no prior baseline MRI data to use to determine the age of lesions. Id. He explained that "[d]ilation and rounding of [K.M.'s] ventricles require[d] some removal of the surrounding tissues," and it would "take[] several days to injure the myelin[] and then several days to remove the injured tissues." Id. Because K.M. was an infant, this process would take days or weeks. Id.

To support his opinion that the demyelination process had begun sometime "around mid-April," prior to K.M.'s April 27 MRI, Dr. Shuman cited studies that showed MRI findings may not correlate with symptoms. Tr. 281; Pet. Ex. 26 at 109; Pet. Ex. 30 at 10. First, he cited to a study from Khurana et al.,[74] which focused in part on the relationship between clinical course and MRI findings in ADEM cases. Pet. Ex. 47 at 1. The authors examined 13 children with ADEM, confirmed by clinical signs and symptoms, CSF, and MRI.[75] Id. Six of the children with a rapidly progressive course did not improve on IVIG and corticosteroid treatment, and were thereafter treated with plasmapheresis followed by varying degrees of recovery over several months. Id. at 1, 3. Five of the six also had a delay in onset of neuroimaging changes, ranging from one to four weeks, with lesions continuing to evolve after clinical improvement. Id. The authors hypothesized "[i]t is possible that in patients with a more rapidly progressive course, lesions are not apparent at the time of presentation or shortly thereafter, as compared with patients with a more subacute presentation." Id. at 4.

He also cited Honkaniemi et al., a study on MRIs in four patients with ADEM. Pet. Ex. 46 at 2. Three of the four patients had one-to-two-week period of fever, stomach pains, nausea, flu-like symptoms, and headache. Id. at 3. All four patients rapidly deteriorated within a few days of hospital admission. Id. at 4. MRIs were obtained on a weekly to biweekly basis during the acute phase of illness. Id. at 3. Honkaniemi et al. reported "a delay of over a month between the onset of symptoms and the appearance of lesions on conventional [MRI]." Id. at 9. And lesions appeared and/or grew in size during the recovery period. Id. at 1, 3, 7.

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[73] K.M.'s April 27, 2016 brain MRI noted "multiple asymmetric foci of parenchymal T2 signal hyperintensity, some of which are associated with T1 signal hypointensity." Pet. Ex. 7 at 197.

[74] Divya S. Khurana et al., Acute Disseminated Encephalomyelitis in Children: Discordant Neurologic and Neuroimaging Abnormalities and Response to Plasmapheresis, 116 Pediatrics 431 (2005).

[75] Of note, CSF studies showed pleocytosis and/or elevated protein at onset in seven of the 13 children and no oligoclonal bands in the 12 children who were studied. Pet. Ex. 47 at 3. Eight children received an EEG, six of which showed "slowing of background activity and focal sharp wave activity." Id.

For further support of his opinion regarding onset, Dr. Shuman also discussed K.M.'s April 25, 2016 CSF results and explained they support an inflammatory process beginning around April 11. Tr. 286-87. He noted "increased lymphocytes, monocytes, [] occasional eosinophils and basophils in the background of red blood cells," as well as "a few reactive lymphocytes and possible plasma cells." Pet. Ex. 7 at 396; see Tr. 286-87. Dr. Shuman opined it would take "probably" one week for a B cell to convert to a plasma cell, and another week for a matured plasma cell to secrete the protein seen in these results.[76] Tr. 287. Thus, he testified these plasma cells would take two weeks to appear in the CSF, which would place this process as beginning around April 11. Id.

Dr. Shuman testified that the presence of oligoclonal bands also aided in determining timing. Tr. 287-88. K.M. had 11 oligoclonal bands on May 2, which indicated a process occurring between two to four weeks prior to May 2, which would be April 1 at the earliest. Tr. 288-89 (citing Pet. Ex. 7 at 388).

Overall, given the observations consistent with encephalopathy in March 2016, the April 27 MRI lesions, the presence of plasma cells and oligoclonal bands in her CSF, Dr. Shuman concluded the timing here is appropriate to conclude the vaccinations administered on February 29, 2016 were the cause of K.M.'s condition. Tr. 288-89.

For support from the medical literature, he first discussed data regarding onset of post-rabies vaccine encephalomyelitis. Tr. 289-92 (citing Pet. Ex. 50 at 10). The information showed 209 cases with a peak onset at three weeks and six weeks following rabies vaccination. Tr. 291-92 (citing Pet. Ex. 50 at 10). Dr. Shuman acknowledged the data was from an old study (1950s) that concerned a vaccine not at issue here. Tr. 289-90. However, he maintained it "presents rational, clear data about the time course of post-vaccinal encephalomyelitis." Pet. Ex. 31 at 45.

He also cited to a table from Baxter et al.[77] See Pet. Ex. 26-6 at 11 tbl.3. Baxter et al. identified all cases of transverse myelitis and ADEM in the Vaccine Safety Datalink and calculated risk intervals for each vaccine. Pet. Ex. 26-6 at 1. Two exposure windows were used when analyzing the data: the primary exposure window of five to 28 days and a window of two to 42 days. Id. at 1, 4. They examined 47 cases of ADEM, within a window of nine months after vaccination. Id. at 5. For ADEM, Baxter et al. found "no statistically significant increased risk following any vaccine except for Tdap (adolescent and adult tetanus, reduced diphtheria, acellular pertussis) vaccine," and that statistically significant risk was only in the five- to 28-day interval. Id. at 1, 5.

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[76] In his first expert report, Dr. Shuman explained "[p]lasma cells are lymphocytes transformed into Immunoglobulin-producing and Immunoglobulin-secreting immune cells. Plasmocytes are a sign of active immunoglobulin production in the site where they are found. They are found in the CSF when there is an active immunological disease in the CNS parenchyma." Pet. Ex. 26 at 108.

[77] Roger Baxter et al., Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis, 63 Clinical Infectious Diseases 1456 (2016). Respondent also cited this article. Resp. Ex. C, Tab 8.

Dr. Shuman acknowledged Baxter et al. is silent on the increase of ADEM associated with the vaccination at issue here. Pet. Ex. 26 at 115. However, there were cases of ADEM following Prevnar within the exposure interval of five to 28 days. Pet. Ex. 26-6 at 11 tbl.3. Additionally, he asserted that the components of a Tdap vaccine are involved in the vaccinations at issue here, as described above. Pet. Ex. 30 at 13.

When examining these two studies together, Dr. Shuman opined "[t]he post-vaccinal window is really 90 days, not 28 days as specified in the Baxter [et al.] study." Pet. Ex. 30 at 14. He asserted that "[a]ll cases of ADEM occurring between 28 . . . and 90 [days post-vaccination] should have been attributed to the latent period of post-vaccinal ADEM." Id.

3. Respondent's Expert, Dr. Michael Kruer[78]

a. Background and Qualifications

Dr. Kruer is a board-certified pediatric neurologist and fellowship-trained clinical neuroimmunologist. Resp. Ex. C at 1. He received his M.D. in 2004 from the University of Arizona College of Medicine, after which he completed a neurogenomics fellowship, a pediatrics residency, and a neurodevelopmental disabilities clinical fellowship. Resp. Ex. H at 1. Since 2011, he has held various faculty and hospital positions. Id. at 1-2. He currently works at a research laboratory focused on neurogenetics of childhood neurological diseases at the University of Arizona College of Medicine. Tr. 362-63. He is also the Director of the Neuroimmunology Program and the Director of the Pediatric Movement Disorders Program at Phoenix Children's Hospital. Id.; Resp. Ex. H at 2. During his career, he has "performed research on the role of autoimmunity in neurological disease, specifically focusing on how autoantibodies directed against brain proteins may lead to disease." Resp. Ex. C at 1. He is a member of the International Pediatric MS Study Group, the American Academy of Neurology MS Study Group, and the Child Neurology Society Neuroimmunology Special Interest Group, and he has authored or co-authored over 130 publications. Id.; Resp. Ex. H at 3-21. Dr. Kruer spends 40% of his time treating patients, including those with ADEM. Tr. 365.

b. Opinion

i. Diagnosis

Dr. Kruer opined, more likely than not, K.M. does not have ADEM and instead has a neurogenetic disorder based on her clinical course, MRIs, lack of response to treatment, and treating physician statements. Tr. 367-68, 377, 401, 469, 521. He agreed "there is some diagnostic uncertainty in K.M.'s case." Tr. 438, 453. He also agreed K.M.'s presentation was initially consistent with ADEM, but Dr. Kruer opined that her distinctive progression and clinical course was incompatible with ADEM. Tr. 383, 401. He opined "K.M. most likely has an undiagnosed neurogenetic disorder that would explain her symptoms more comprehensively than a diagnosis of ADEM." Tr. 469.

[78] Dr. Kruer submitted two expert reports and testified at the hearing. Resp. Exs. C, F; Tr. 181.

At the outset, Dr. Kruer explained that ADEM is a neuroinflammatory disorder characterized by new onset neurological symptoms including encephalopathy and it is diagnosed using the criteria delineated by the International Pediatric MS Study Group.[79] Tr. 376-77 (citing Resp. Ex. F, Tab 3 at 2). Using this criteria, he opined K.M. does not have ADEM. Resp. Ex. F at 2. Dr. Kruer opined K.M. met three of the four criteria. Tr. 370-382. He agreed K.M. met the first criterion, "[a] first polyfocal clinical CNS event with presumed inflammatory demyelinating cause," the second criterion, "[e]ncephalopathy that cannot be explained by fever," and the fourth criterion, "[b]rain MRI is abnormal during the acute (three-month) phase." Tr. 379-80, 382 (quoting Resp. Ex. F, Tab 3 at 2).

He also opined K.M. satisfied the third criterion, that "[n]o new clinical and MRI findings emerge[d] three months or more after the onset;" however, this is based on the lack of MRI done at or around the three-month mark. Tr. 381-82 (quoting Resp. Ex. F, Tab 3 at 2). He testified that "there's agreement that there was not obvious new clinical findings in terms of a second or additional attack," but "there was a definite evolution of the MRI findings." Tr. 382. "[T]he MRI findings definitely evolved over time and certainly seemed to evolve when comparing the initial findings in April and later findings in early September 2016." Id. However, he agreed that K.M. met the third criterion because there was no MRI done between May and September 2016, and thus, it is not known what her MRI would have shown at or around the three-month mark.[80] Tr. 499.

Dr. Kruer examined the MRIs and detailed his reasoning why they are inconsistent with ADEM. He agreed the first two MRIs were consistent with ADEM. Tr. 384-88. The first MRI, obtained April 27, 2016, showed "ill-defined, poorly demarcated areas of white matter hyperintensity;" "some relative symmetry;" and "relatively normal" brain volume. Tr. 384-87. The second MRI, dated May 2, 2016, revealed a "brain [that] appear[ed] whiter than it should be" and was consistent with ADEM. Tr. 387-88.

He opined the third MRI, dated May 23, 2016, however, did not "rule out or refute a diagnosis of ADEM," but demonstrated "relatively symmetric" lesions, which is unusual for ADEM.[81] Tr. 393-94, 463. Dr. Kruer opined these abnormalities could suggest a genetic

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[79] See supra Section II.B.1.

[80] Dr. Kruer's testimony on this point may have been misinterpreted by the undersigned. Assuming that Dr. Kruer disagreed that the third criteria was met, however, does not change the undersigned's finding that K.M. had ADEM.

[81] Dr. Kruer and Dr. Shuman discussed their opinions about whether K.M. had an abnormality of the corpus callosum that suggested she had a developmental abnormality. See Tr. 393, 692-93. The undersigned does not discuss this testimony because any such abnormality is not material to the question of whether K.M. had ADEM. To the extent that there is any issue about whether the abnormality in the corpus callosum is somehow determinative of the diagnosis of ADEM, or any other issue here, the undersigned finds Dr. Shuman's opinions more persuasive, especially given that he is board certified in neuroimaging.

condition. Tr. 395. Regardless, he agreed the May 23 MRI was "still potentially consistent with ADEM." Tr. 395, 466.

Moving forward to the fourth and fifth MRIs, he opined the September 2016 and August 2017 MRIs were "remarkably similar" and not consistent "with the usual presentation of ADEM." Tr. 391, 440. According to Dr. Kruer, K.M.'s August 30, 2017 MRI showed a "tremendous amount of change;" there was "global atrophy" of the brain, affecting the cerebellum, brainstem, and cortex, inconsistent with ADEM, although it could be "remotely possible." Tr. 390.

On cross-examination, Dr. Kruer opined the three-month period for the third criterion ("[n]o new clinical and MRI findings emerge three months or more after the onset") would conclude in late July 2016. Tr. 498; see Resp. Ex. F, Tab 3 at 2. He acknowledged that K.M. did not have an MRI from May 23, 2016 until September 1, 2016, during and after the three-month window. Tr. 498-99. Dr. Kruer also agreed that while K.M.'s MRIs showed significant progression from May 23 to September 1, 2016, the MRIs were relatively stable from September 1, 2016 to August 30, 2017. Tr. 525. Therefore, he agreed there was no way to discern whether the MRI progression seen in September 2016 was present in June, July, or August of 2016. Tr. 498-99.

Overall, Dr. Kruer concluded there was "an evolution of K.M.'s MRI findings from [] more punctate, hyperintense white matter lesions . . . largely within the white matter of the brain that over time became more symmetric, and . . . more confluent, to the point that it involved much of K.M.'s white matter." Tr. 392. On cross-examination, however, he agreed that demyelination was "one possible explanation" for the increased symmetry on MRI. Tr. 466.

Dr. Kruer cited to Honkaniemi et al. to illustrate the typical evolution of brain MRIs in ADEM. Tr. 413-14 (citing Pet. Ex. 46 at 7 fig.4); see Resp. Ex. I at 1-3. These MRI images showed that over time, "with the evolution of ADEM, the brain volume is largely preserved," which is typical for ADEM. Tr. 414 (citing Pet. Ex. 46 at 7 fig.4). When he compared the MRIs in Honkaniemi et al. to K.M.'s MRIs, Dr. Kruer stated the initial images were similar, but the later MRIs differed, as K.M.'s showed "severe atrophy of the brain." Tr. 414-15; see Resp. Ex. I at 1-3. He opined that the degree of brain atrophy in K.M. is not typical for ADEM, particularly when appropriate treatment was administered; instead, he opined it suggested an alternative diagnosis. Tr. 415-16.

Dr. Kruer addressed Armangue et al. and the leukodystrophy-like presentation of ADEM cases on MRI. Tr. 441 (citing Pet. Ex. 26-2). He agreed with Dr. Shuman and Armangue et al. that these rare presentations of ADEM are possible. Tr. 441-42. But he testified that even if K.M. did have leukodystrophy-like ADEM, it would not explain her lack of response to treatment. Tr. 442-43. Additionally, he thought the MRI findings here showed an evolution distinct from the leukodystrophy-like ADEM cases in Armangue et al. Tr. 463 (citing Pet. Ex. 26-2); see also Resp. Ex. F at 10-11. However, Dr. Kruer agreed with Dr. Shuman that there are rare cases of ADEM that have similar imaging as the leukodystrophy-like cases shown in Armangue et al. Tr. 401.

Further, Dr. Kruer opined the MRIs alone are not diagnostic of ADEM. Tr. 461-62; see also Tr. 469 ("K.M.'s MRI[s] [are] not pathognomonic for any condition."); Resp. Ex. C at 3 ("[T]he MRI findings were not pathognomonic for any single specific condition and thus not diagnostic in and of themselves (as [K.M.'s] treating physicians also concluded)."). But because the imaging is not typical of ADEM, he asserted she more likely has a different diagnosis. Resp. Ex. F at 2. He opined K.M.'s MRIs are compatible with a leukodystrophy. Tr. 434.

Moving forward, Dr. Kruer provided additional reasons he did not believe K.M. had ADEM. He asserted improvement should be seen when ADEM is treated within a reasonable timeframe; however, K.M. did not respond to treatment or improve.[82] Tr. 396-400. He agreed more aggressive treatment may be necessary in some cases. Tr. 399. And on cross-examination, he agreed it was "possible" that K.M. could be a case of ADEM that did not have a good outcome despite treatment. Tr. 484-85. He also agreed that the clinical course of ADEM can be variable. Tr. 396.

Contrary to Dr. Shuman, Dr. Kruer opined that a chronic vegetative state with no evidence of recovery is not typical of ADEM "and should provoke a reconsideration of that presumptive diagnosis." Resp. Ex. C at 4. At the hearing, he testified that "if we diagnose a patient with a neuroimmunologic condition and we treat a patient with gold standard treatments for a neuroimmunologic condition, we should expect that there would be a response if there's a neuroimmunologic condition, even if it's partial," and this was not seen here. Tr. 532; see also Resp. Ex. C at 4. However, he agreed that K.M. did not receive the immunotherapies (rituximab or cyclophosphamide) given to the four patients with leukodystrophy-like ADEM in Armangue et al. Tr. 503.

Next, Dr. Kruer discussed K.M.'s clinical course and gave his opinions about why it does not support a diagnosis of ADEM. See Tr. 416-37. Dr. Kruer did not dispute that K.M. met her developmental milestones and was documented as being a well child with normal growth and development prior to the vaccinations at issue. Tr. 451.

Dr. Kruer agreed the presence of 11 oligoclonal bands on May 2, 2016 indicated inflammation, although their presence was unusual for ADEM. Tr. 420-21, 491. But he agreed that the oligoclonal bands "[do not] clinch any particular diagnosis." Tr. 423. He also agreed her lab results at this time signified significant inflammation. Tr. 422. Based on those test results (high WBCs and 11 oligoclonal bands) and MRIs in May 2016, Dr. Kruer agreed with K.M.'s treating physicians that her testing and imaging "could represent ADEM" and such diagnosis was "absolutely appropriate." Id. He maintained that these symptoms and findings were not specific to ADEM but that ADEM "was a very reasonable working diagnosis." Tr. 425-26.

By May 10, 2016, after K.M. received five days of IVMP and IVIG, she was noted to have an "[i]nsufficient overall improvement of symptoms," which was "a red flag" to Dr. Kruer, as some degree of improvement should have been seen. Tr. 425-26 (quoting Pet. Ex. 7 at 197);

[82] He opined that the onset of K.M.'s neurological symptoms was April 22, 2016, when she had "slumping behavior." Tr. 397. The start of her treatment was May 3, 2016. Tr. 398.

see also Tr. 431; Resp. Ex. F at 8. He reiterated K.M.'s lack of improvement with treatment in late May 2016 was evidence against a diagnosis of ADEM, necessitating consideration of other possible explanations for K.M.'s symptoms. Tr. 429-32.

By September 2016, K.M.'s working diagnosis changed from ADEM to a leukodystrophy. Tr. 436. K.M. now had hypsarrhythmia, which he noted was "a sign of severe developmental brain dysfunction" and is "associated with infantile spasms and epileptic encephalopathies." Tr. 437. He opined that the development of hypsarrhythmia with ADEM does not routinely occur and this argues "more strongly" in favor of a neurodegenerative disease of leukodystrophy. Id.; see also Resp. Ex. F at 5.

He acknowledged elevated WBCs in the CSF, which K.M. had, are atypical for many forms of leukodystrophy and would weigh against a diagnosis of many forms of leukodystrophy. Tr. 512; Resp. Ex. F at 4. He agreed that ADEM is a condition that he would assess a patient with when they present with an abrupt onset of neurological symptoms and unexplained decline. Tr. 373. He also agreed that an abrupt change or regression in a patient with a genetic condition can be explained sometimes by an antecedent event. Tr. 446-47. Other times, an abrupt regression cannot always be explained. Tr. 447.

In support of his opinions regarding alternative diagnoses, he described leukodystrophy and neurodegenerative diseases. He explained a neurodegenerative disease is an "umbrella term" that includes leukodystrophy and refers to "a condition that affects a previously healthy child and leads to a progressive regression and loss of both cognitive and motor function, oftentimes with seizures." Tr. 434. A leukodystrophy is a disorder of the white matter that is typically genetic in etiology, "although in some cases, patients will be diagnosed with leukodystrophy based upon their clinical findings, their radiologic picture, but [without] any obvious or apparent cause identified." Tr. 377, 434. Both terms are connected to genetics. Tr. 434-35, 518. However, Dr. Kruer maintained leukodystrophy "is not a diagnosis made on purely genetic grounds," and "[a]s such, genetic testing does not 'rule out' leuko[dystrophy]."[83] Resp. Ex. F at 2; see also Resp. Ex. F, Tab 4 at 4.

At the hearing, he testified that K.M. more likely than not has an undiagnosed neurogenetic disorder. Tr. 439, 469. He acknowledged that genetic testing did not reveal a specific cause in this case. Tr. 445-46, 508. But he disagreed that genetic causes have been ruled out here and opined that the fact that a specific genetic cause has not been identified is not dispositive. Tr. 402-03, 446; Resp. Ex. C at 5. He testified that the field of pediatric

[83] Dr. Kruer indicated leukoencephalopathy is the more inclusive term. Resp. Ex. F at 2; see also Resp. Ex. F, Tab 4 at 3 ("[L]eukodystrophies are genetic leukoencephalopathies, but not all genetic leukoencephalopathies qualify as leukodystrophies."). For clarity, the undersigned will use only leukodystrophy throughout this Ruling.

neurogenetics continues to change and improve since 2016. Tr. 339-71, 406 (citing Resp. Ex. C, Tab 4);[84] see also Resp. Ex. F at 1; Resp. Ex. C, Tab 5.[85]

In summary, Dr. Kruer agreed it is not "entirely clear that [K.M.] conclusively has a genetic leukodystrophy." Tr. 518. He agreed her genetic testing did not reveal a specific cause of her disease. Tr. 508. And he acknowledged that the abnormal WBCs in K.M.'s CSF were atypical for many forms of leukodystrophy and weigh against those diagnoses. Tr. 512. Notably, Dr. Kruer stated, "I'll fully acknowledge the point that [] there were select cases within [the] Armangue [et al.] paper that did talk about a leukodystrophy-like pattern, and I think that that's an important consideration in this case as well." Tr. 463. He agreed "there is a rare leukodystrophy-like presentation of ADEM." Tr. 441. But he maintained "a genetic condition is far more likely, even though we don't have any culprit gene identified." Tr. 518-20.

ii. Causation

Dr. Kruer opined "there is not a preponderance of evidence that [K.M.'s] immunization(s) led to her symptoms." Resp. Ex. C at 12; see also Tr. 448-49.

Dr. Kruer did not dispute that ADEM can be caused by vaccination. Tr. 455; see Resp. Ex. C, Tab 1 at 1 (noting ADEM typically follows a viral infection or immunization); Resp. Ex. F, Tab 8 at 1 ("In children, ADEM is preceded by 71 to 77% of patients by an infection or a vaccination.").[86] However, he opined there is "no relationship between [Prevnar], DTaP, or Hib and ADEM." Resp. Ex. C at 9 (citing Pet. Ex. 26-6 at 10 tbl.2). Additionally, he noted none of K.M.'s treating physicians attributed causation to her vaccinations. Tr. 449.

He did not find an infectious cause "more likely than not" the cause of her symptoms given the numerous infectious negative tests. Tr. 459-60. He testified that "K.M. did have instances of infectious symptoms on multiple occasions," although "there was not a specific infectious agent that was identified on testing." Tr. 456-57.

Dr. Kruer agreed that encephalopathy can present as irritability, and the records indicated K.M. had irritability in March 2016. Tr. 453. However, he testified that irritability is not a symptom specific to encephalopathy. Tr. 522. He agreed that in a one-year-old child, it may be difficult to ascertain a precise date of symptom onset. Tr. 453. He opined, however, that K.M.'s neurological symptoms began on April 22, 2016. Tr. 397, 523. This is 53 days after vaccination, and "that is not suggestive of vaccine involvement." Tr. 449.

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[84] Kotaro Narita et al., Whole-Exome Analysis of 177 Pediatric Patients with Undiagnosed Diseases, 12 Sci. Reps. 14589 (2022).

[85] Alyssa Blesson & Julie S. Cohen, Genetic Counseling in Neurodevelopmental Disorders, 10 Cold Spring Harbor Persp. Med. 1 (2020).

[86] Soufiane Arktout, Prognosis Factors in Children with ADEM: Clinical, Biological, and Radiological Features, 6 Int'l J. Radiology & Imaging Tech. 1 (2020).

4. Respondent's Expert, Dr. Andrew MacGinnitie[87]

a. Background and Qualifications

Dr. MacGinnitie is board certified in allergy/immunology and pediatrics. Resp. Ex. A at 2; Resp. Ex. G at 11. He received his M.D. from University of Chicago in 1998, after which he completed a pediatric residency at Boston Children's Hospital and Boston Medical Center, an allergy/immunology fellowship at Boston Children's Hospital, and a pediatric clinical fellowship at Harvard Medical School from 1998 to 2004. Resp. Ex. G at 1. Since 2004, Dr. MacGinnitie has held academic appointments as well as hospital appointments in Massachusetts and Wisconsin. Id. at 1-2. He currently works as a Professor of Pediatrics at the Medical College of Wisconsin and is the Division Chief of the Division of Asthma, Allergy, and Immunology at Children's Wisconsin. Id.; Tr. 538-39. He "maintain[s] an active clinical practice seeing more than 1600 patients annually and ha[s] extensive experience in caring for children and adults with a variety of immunologic diseases including reactions to vaccines." Resp. Ex. A at 2. Around 10%-15% of these patients would be under the age of 18 months. Tr. 607. He "also perform[s] research and [has] published articles in a number of areas related to Allergy/Immunology including food allergy, vaccine reactions, and primary immunodeficiency." Resp. Ex. A at 2. He is a member of professional societies, holds editorial positions on journals, and has published in the field of immunology. Tr. 538; Resp. Ex. G at 4, 13-18. Dr. MacGinnitie does not treat patients with ADEM. Tr. 644, 684.

b. Opinion

Dr. MacGinnitie opined, more likely than not, K.M.'s condition was not related to her February 29, 2016 Hib and Prevnar vaccinations. Tr. 542-43.

i. Diagnosis

In his expert reports, Dr. MacGinnitie expressly deferred to Dr. Kruer on diagnosis, although he agreed that K.M. "suffered an acute demyelinating disorder." Resp. Ex. A at 7; Resp. Ex. E at 1. Dr. MacGinnitie has no experience treating patients with ADEM. Tr. 644, 684. However, during the hearing, Dr. MacGinnitie opined there is "some diagnostic uncertainty." Tr. 543. He was compelled by Dr. Kruer's testimony that K.M. did not meet the ADEM criteria and he opined K.M. more likely than not has a neurogenetic disorder. Tr. 543, 601.

Throughout his expert reports, Dr. MacGinnitie referred to K.M.'s diagnosis as ADEM, but at the hearing, he testified that his expert reports should have stated K.M. has an "acute neurologic disorder." Tr. 604. He maintained K.M. "more likely" suffered from a genetic issue that is not currently identified. Tr. 606. For the purposes of his testimony, however, he assumed K.M. had ADEM. Tr. 543.

[87] Dr. MacGinnitie submitted two expert reports and testified at the hearing. Resp. Exs. A, E; Tr. 411.

ii. Althen Prong One

Dr. MacGinnitie disagreed that Dr. Shuman or Dr. Steinman presented a reliable medical theory to explain how Hib and Prevnar can cause ADEM. Tr. 548. He testified that "for certain diseases, there is evidence that molecular mimicry occurs and causes autoimmunity." Tr. 549; see also Tr. 572-73, 660-61. "[W]hile it's been easy to show in mice, it's been hard to [] demonstrate in human[s] or . . . experiments that replicate real world conditions." Tr. 549; see also Tr. 637 ("I think animal studies are typically not as reliable as human studies . . . . I would not say that all mouse studies are useless or shouldn't be done."). He cited Root-Bernstein, an article cited by Dr. Steinman, and noted the authors summarized the issues with the idea that molecular mimicry is a general theory of autoimmunity. Tr. 550-52 (citing Pet. Ex. 29-33).

Dr. MacGinnitie raised issues with each of Petitioner's theories. First, with regard to Dr. Steinman's first theory (molecular mimicry between phosphoglycerol moieties), Dr. MacGinnitie offered several reasons why he believed this theory is unreliable. Resp. Ex. E at 2-5. Because phosphate is in various components of all cells, "autoimmunity directed at phosphate would not explain the limited degree of autoimmunity seen in ADEM and other demyelinating diseases." Id. at 2. And phospholipids, which are more limited, are ubiquitous across eukaryotes, and given this, Dr. MacGinnitie would expect antibodies against phospholipids to attack or bind to every cell in the body, leading to autoimmunity against the entire body, and not leading to only ADEM. Resp. Ex. E at 2-4; Tr. 555-56.

In response, Dr. Steinman stated that in some autoimmune disorders, for example, antiphospholipid syndrome, only certain systems or parts of the body are affected. Tr. 122-23, 556, 699-700. Dr. MacGinnitie agreed analogies can be useful but stressed that Dr. Steinman provided no evidence that this theory can lead to ADEM in particular. Tr. 556-57. He testified that phospholipids in antiphospholipid syndrome are different than the phospholipids here because they activate rather than destroy cells. Tr. 557. And with neuromyelitis optica spectrum disorder ("NMOSD"), another example used by Dr. Steinman, the antibodies were injected directly in the CNS of mice to generate disease, or another mechanism to disrupt the blood-brain barrier was used, indicating the presence of antibodies alone was insufficient to cause disease.[88] Tr. 557-59.

Ho et al., cited by Dr. Steinman, examined antibodies against phospholipids, which Dr. MacGinnitie noted are not present in the Prevnar vaccine. Tr. 559 (citing Pet. Ex. 29-13). Rather, phosphate groups linked within the sugars are present in Prevnar, which Dr. MacGinnitie argued are a different class of macromolecules. Id.; Resp. Ex. E at 3. Dr. MacGinnitie maintained it is unlikely these antibodies cross-react. Tr. 559. While Dr. MacGinnitie agreed Ho et al. showed antibodies can recognize and react with phospholipids, he opined they do not react with all phospholipids. Tr. 563-64; Resp. Ex. E at 4.

[88] It is unclear what study Dr. MacGinnitie referred to during the hearing as he failed to identify the study during his testimony.

Dr. MacGinnitie next addressed Dr. Steinman's second and third molecular mimicry theories (CRM_{197} in Prevnar[89] and tetanus toxoid in Hib cross-reacting with neurofascin) and argued they are not reliable theories. Tr. 566; Resp. Ex. E at 5-9. Dr. MacGinnitie thought Dr. Steinman's degree of homology on BLAST searches was not notably significant. Resp. Ex. E at 9; see also Tr. 566-68. Relying on Wheeler and Bhagwat,[90] Dr. MacGinnitie asserted an E-value should be 0.001 or lower to support a finding of significant homology, and here, Dr. Steinman's E-values[91] "are far above those that would be considered significant." Resp. Ex. E at 7 (citing Resp. Ex. E, Tab 12 at 2 (noting E-values "in the range of 0.001 to 0.0000001 are commonly used to restrict the alignments shown to those of high quality.")). However, Wheeler and Bhagwat stated the threshold for an E value should be set at 10 "to ensure that no biologically significant alignment is missed." Resp. Ex. E, Tab 12 at 2. In response, Dr. MacGinnitie testified that the authors "[did] not state that anything less than 10 is biologically significant," they just used a conservative threshold. Tr. 641.

Regarding the Gautam et al. papers, Dr. MacGinnitie acknowledged the authors showed "amino acid similarity under very specific animal models could lead to an immune reaction," but argued these studies are unreliable comparisons for humans. Tr. 568-69. He explained mouse studies are used as guides for what might happen in humans. Tr. 569. But Gautam et al. used complete Freund's adjuvant, an adjuvant not used in humans, and thus, the inflammation generated by complete Freund's adjuvant is not comparable to inflammation in human vaccination. Id. And Root-Bernstein showed "this is the only adjuvant that's ever been shown to allow development of molecular mimicry in mouse models." Tr. 569-70. Therefore, Dr. MacGinnitie argued this literature is not reliable for showing effects of human vaccination. Tr. 570.

Dr. MacGinnitie acknowledged that although Prevnar does contain an adjuvant (alum), it is "widely used in human vaccines[,] [is] not associated with significant side effects," and it "decreases systemic inflammatory responses to vaccination." Tr. 570. "[U]nlike [complete Freund's adjuvant], which is a powerful trigger of diffuse inflammation, alum seems to lead to a protective immune response without significant systemic side effects." Id.

Additionally, with regard to Dr. Steinman's reliance on data from the IEDB, Dr. MacGinnitie explained that because the purpose of a vaccination is to induce an immune response, "it is not surprising or notable that vaccine proteins are identified in the IEDB." Resp. Ex. E at 7; see also Tr. 571. He added that "the fact that a region of the diphtheria toxin can generate a human T-cell response after vaccinations is not surprising and does not provide evidence that vaccination can trigger autoimmunity." Resp. Ex. E at 7.

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[89] Dr. MacGinnitie agreed the homology between CRM_{197} and diphtheria toxin is significant. Resp. Ex. E at 7; Tr. 567-68.

[90] David Wheeler & Medha Bhagwat, BLAST QuickStart: Example-Driven Web-Based BLAST Tutorial, in Comparative Genomics (Nicolas H. Bergman ed., 2007).

[91] Dr. Steinman's E-values were as low as 0.21 (Prevnar) and 1.2 (Hib). Pet. Ex. 29 at 32-40.

Dr. MacGinnitie took issue with some of Dr. Steinman's literature given the age of the studies when "[m]ore contemporary articles indicate . . . significant overlap between viral and bacterial DNA and that of humans." Resp. Ex. E at 7. For example, he noted two recent papers found sequence similarity between viruses and bacteria to be very common up to nine consecutive amino acids. Tr. 550 (citing Resp. Ex. E, Tab 13;[92] Resp. Ex. E, Tab 14).[93] The authors found that "this calls into question the idea that sequence similarity alone would be enough to cause molecular mimicry and development of autoimmune disease." Id.; see also Resp. Ex. E at 8. Dr. MacGinnitie noted that "one of the papers . . . says that if sequence similarity were enough, we'd expect the prevalence of autoimmune disease to be effectively 100 percent, and that's not what is seen." Id. (citing Resp. Ex. E, Tab 13); see also Resp. Ex. E at 8.

Overall, Dr. MacGinnitie maintained "[s]equence similarity alone is not enough to demonstrate molecular mimicry as a trigger of disease." Resp. Ex. E at 9. For further support, he cited to the Institute of Medicine ("IOM") 2012 Report,[94] which stated "[l]inear amino acid sequence homology or even similar conformational structure between an exogenous agent and a self-antigen alone are not sufficient to prove molecular mimicry is the pathogenic mechanism for a disease" because "[m]any such homologies exist, and the vast majority of these are not associated with biologically relevant autoimmune phenomena or actual human disease." Resp. Ex. A at 10 (quoting Resp. Ex. A, Tab 4 at 10). He concluded Dr. Steinman has not identified significant homology between CRM_{197} in Prevnar or tetanus toxoid in Hib, and his theories are not reliable when three parts of evidence are put together. Tr. 571.

Dr. MacGinnitie also addressed Dr. Shuman's theory regarding molecular mimicry between CRM_{197} and MOG[95] and opined it was also unreliable. Tr. 574. Unlike Dr. Steinman, Dr. Shuman did not indicate areas of homology. Id.; Resp. Ex. A at 9. But even if homologies exist, Dr. MacGinnitie maintained "sequence similarity is not enough." Tr. 574-75; see also Resp. Ex. A at 10.

Next, he noted there is no data showing an increased incidence of ADEM following vaccination or infection with Hib or pneumococcus. Tr. 543; Resp. Ex. E at 10. He asserted the lack of association with infections is significant because if molecular mimicry were to occur, "wild type infection would be an even stronger inducer." Tr. 543-44. He explained that "[t]ypically[,] infection causes a stronger immune response, more inflammation, and the fact that there's no evidence of . . . these wild type infections . . . argue[s] against vaccines causing

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[92] Darja Kanduc et al., Massive Peptide Sharing Between Viral and Human Proteomes, 29 Peptides 1755 (2008).

[93] Brett Trost et al., Bacterial Peptides Are Intensively Present Throughout the Human Proteome, 1 Self/Nonself 71 (2010).

[94] Inst. of Med., Evaluating Biological Mechanisms of Adverse Events, in Adverse Effects of Vaccines: Evidence and Causality 57, 70-73 (Kathleen Stratton et al. eds., 2012).

[95] Dr. MacGinnitie agreed MOG antibodies were not available for testing at the time of K.M.'s onset in 2016. Tr. 575; Resp. Ex. E at 12.

demyelinating disorder via molecular mimicry." Tr. 544. However, he acknowledged that molecular mimicry was a leading theory to explain how infections or vaccination can cause ADEM, although he maintained it is "unlikely" to occur. Tr. 689-91.

Baxter et al. examined the risk of ADEM in the five- to 28-day interval following vaccination. Tr. 545 (citing Pet. Ex. 26-6 at 11 tbl.3). Dr. MacGinnitie indicated an increased risk of ADEM following Prevnar cannot be determined because there were only three Prevnar cases. Tr. 545-46 (citing Pet. Ex. 26-6 at 11 tbl.3). And for Hib, there were no cases. Tr. 546 (citing Pet. Ex. 26-6 at 11 tbl.3). Thus, he concluded Baxter et al. "did not show any increase or decrease in risk with any of the vaccines that are at issue in this case." Id. On cross-examination, he acknowledged the authors found an increased risk of ADEM post-Tdap vaccine, and components of Tdap are contained in Hib (tetanus) and Prevnar (CRM_{197} homology). Tr. 671-73.

Sharma and Dale indicated "ADEM is preceded by infection or vaccination in 50%-85% of cases," with "[c]ommon antecedent infections includ[ing] flu-like illnesses (56%-61%), followed by nonspecific upper respiratory tract infections (12%-17%) and gastroenteritis (7%)." Tr. 547 (quoting Pet. Ex. 26-38 at 3). Dr. MacGinnitie also noted the authors indicated "[p]ostimmunization ADEM accounts for only 5% of cases of ADEM" and Hib and Prevnar were "absent from [their] list" of vaccines associated with ADEM. Id. (quoting Pet. Ex. 26-38 at 3).

iii. Althen Prong Two

Dr. MacGinnitie opined there is not sufficient evidence to conclude K.M.'s Hib and/or Prevnar vaccines more likely than not caused her to develop ADEM (assuming she has ADEM). Tr. 575. He agreed K.M. "definitely had an inflammatory process." Tr. 685. He thought the vaccines at issue were unrelated to her illness, although he testified that he could not entirely exclude vaccination as a cause of K.M.'s condition. Tr. 600, 687-88.

First, he noted infections are a more likely cause of ADEM than vaccines. Tr. 575; see also Resp. Ex. A at 11. Here, he opined K.M. had several infections prior to onset of her illness. Tr. 576. K.M. was diagnosed with an ear infection on March 7, 2016. Tr. 670. On March 30, 2016, she did not have an ear infection. Tr. 579-80 (citing Pet. Ex. 6 at 46). She had classic symptoms of an upper respiratory infection, which is an antecedent infection in ADEM, although he agreed physical examination findings did not show objective evidence to support his assertion. Tr. 579, 625.

Dr. MacGinnitie did not believe K.M. had evidence of a pneumococcal infection at the time of vaccination. Compare Resp. Ex. A at 14 ("There is no direct evidence that [K.M.] ever had a pneumococcal infection."), and Tr. 581 ("[T]here doesn't seem to be any evidence of that."), with Tr. 586 ("[T]here's [] not direct evidence that she had pneumococcal infection, although it's certainly possible. . . . So while I certainly can't exclude and it's certainly possible and perhaps even likely that she had pneumococcal infection, it's not definite."), and Tr. 587 ("[I]f I had to guess, I'd say it's two-thirds chance that at some point she did have pneumococcal infection."). Nor was K.M. diagnosed with otitis media. Tr. 581.

However, he disagreed with Dr. Shuman that an infection is an unlikely trigger here. Tr. 584. He argued symptoms of an infection can be present even when testing is negative. Tr. 585. He also argued K.M. was not tested for common causes of otitis media, pneumococcus, some flu infections, or other infections. Id. Therefore, "while there was no evidence of active infection at the time she presented or within a few days, . . . that [does not] rule[] out or even provide[] strong evidence against vaccination[96] as a trigger." Id.

He did not agree that the combination of an infection and vaccination could lead to a stronger immune response. Tr. 580. However, colonization "[was] certainly possible." Tr. 582. He explained that colonization refers to when a person carries a bacteria but does not have an illness. Tr. 581. Although "[m]any children are colonized with bacteria, . . . people are almost never colonized with the serotypes or the specific kinds of pneumococcus that are present in the Prevnar vaccine." Tr. 582. He discussed a study that showed 23% of patients carried pneumococcus in their nasopharynx, but 93% of the time it was not one of the vaccine serotypes. Id. (citing Resp. Ex. K at 9).[97] Thus, he concluded "it seems unlikely that [K.M.] was colonized with the same serotype that she was vaccinated against." Id. And "if anything, colonization with pneumococcus decreases your response to vaccination, . . . go[ing] against . . . this theory that the combination was stronger." Id.; see also Tr. 584 (citing Resp. Ex. J;[98] Resp. Ex. L).[99] On cross-examination, Dr. MacGinnitie noted colonization is typically not tested for in patients. Tr. 624.

Dr. MacGinnitie opined there is no evidence that K.M. developed an exaggerated response to Prevnar; instead, her response was "completely appropriate." Tr. 587-90 (citing Resp. Ex. A at 15-16); see also Resp. Ex. A at 14. He also indicated he is not aware of any data to support a finding that an excessive or high response would be harmful. Tr. 590; Resp. Ex. A at 16. Nor did K.M. have a condition that would have been a contraindication for vaccination. Tr. 592-93; see also Resp. Ex. E at 15-16.

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[96] Although Dr. MacGinnitie used the word "vaccination," he may have meant to say "infection."

[97] Michael Pichichero et al., Acute Otitis Media Pneumococcal Disease Burden and Nasopharyngeal Colonization in Children Due to Serotypes Included and Not Included in Current and New Pneumococcal Conjugate Vaccines, 22 Expert Rev. Vaccines 118 (2023). The specific study that Dr. MacGinnitie discussed, which was discussed in Pichichero et al., was not filed.

[98] Elena Mitsi et al., *Streptococcus pneumoniae* Colonization Associates with Impaired Adaptive Immune Responses Against SARS-CoV-2, 132 J. Clinical Investigation 1 (2022).

[99] Beatriz F. Carniel et al., Pneumococcal Colonization Impairs Mucosal Immune Responses to Live Attenuated Influenza Vaccine, 6 JCI Insight 1 (2021).

He cited to Borrow et al.,[100] which "showed that patients who had significant infections with pneumococcus . . . had a decreased immune response to subsequent vaccination." Tr. 591 (citing Resp. Ex. A, Tab 16). Given this study, he maintained that "if K.M. did have preceding pneumococcal infection, if anything, [it] would have decreased her response to the Prevnar." Tr. 592. Thus, Dr. MacGinnitie opined "Dr. Shuman is incorrect when he state[d] that previous exposure to pneumococcal infection would predispose [her] to a vigorous response to vaccination." Resp. Ex. A at 16. He concluded that "previous pneumococcal infections, if present, would be expected to weaken rather than strengthen [K.M.'s] response to the Prevnar she received." Id. at 17.

Although he is not a pediatric neurologist or neuroimmunologist, and does not treat patients with ADEM, Dr. MacGinnitie opined that he would have expected a response to IVIG in a significant inflammatory or autoimmune process. Tr. 594. And the fact that IVIG was not beneficial would argue against Petitioner's theories. Id.

Overall, Dr. MacGinnitie agreed that the cause of K.M.'s illness is "not fully clear." Tr. 679. He agreed that Baxter et al. identified an increased risk of ADEM after Tdap vaccination. Tr. 681-82. And he agreed that diphtheria and tetanus are included in CRM_{197}. Tr. 683. Lastly, Dr. MacGinnitie agreed K.M.'s inflammatory illness had no direct link to an infection. Tr. 685. And he does not entirely exclude vaccination as the cause of K.M.'s ADEM. Tr. 688.

iv. Althen Prong Three

Dr. MacGinnitie opined the onset of neurologic symptoms occurred April 22, 2016, 53 days after vaccination. Tr. 581, 594-95. Based on his review of the case, he opined this timeframe was not medically appropriate in which to infer vaccine causation. Tr. 595.

Dr. MacGinnitie also noted the Hib and Prevnar vaccines at issue here were not K.M.'s first Hib and Prevnar vaccinations. Tr. 576. He explained that with secondary responses, an immune response is faster and more effective than the initial response. Tr. 577, 595. Because of this, he would have expected a shorter onset of four to six weeks as the outer limit. Tr. 578, 595.

Next, he addressed some of Petitioner's literature about onset. In response to Dr. Steinman's reliance on Schonberger et al., Dr. MacGinnitie cited Safranek et al.,[101] a study that reexamined cases of GBS post-swine flu vaccination in two states (Michigan and Minnesota), specifically examining the medical records, which Schonberger et al. did not do. Tr. 595-96 (citing Resp. Ex. E, Tab 15); see also Resp. Ex. E at 10. "[Their] findings suggest[ed] that there was an increased risk of developing [GBS] during the six weeks following vaccination in adults." Tr. 596 (quoting Resp. Ex. E, Tab 15 at 1). They also found no increased risk for GBS

[100] Ray Borrow et al., Serotype-Specific Immune Unresponsiveness to Pneumococcal Conjugate Vaccine Following Invasive Pneumococcal Disease, 76 Infection & Immunity 5305 (2008).

[101] Thomas J. Safranek et al., Reassessment of the Association Between Guillain-Barré Syndrome and Receipt of Swine Influenza Vaccine in 1976-1977: Results of a Two-State Study, 133 Am. J. Epidemiology 940 (1991).

beyond six weeks. Id. (citing Resp. Ex. E, Tab 15 at 1). Dr. MacGinnitie opined this article was more reliable than Schonberger et al., and he concluded the outer limit for vaccine causation would be six weeks. Tr. 596, 600.

He also noted the timing in the Gautam et al. articles showed neurologic signs in mice within 30 days or up to 45 days. Tr. 597. And in response to Dr. Shuman's reliance on onset data following a live rabies vaccine, Dr. MacGinnitie opined the vaccines are "very different" and in no way analogous to K.M.'s case. Tr. 597-98. He opined these patients were vaccinated against rabies and developed rabies from the live virus. Tr. 598. Here, K.M. did not receive a live vaccine and "[there is] no evidence she was infected with the thing she was immunized with." Id.

With regard to Dr. Shuman's assertions that onset was earlier (than April 22) due to the results of K.M.'s CSF, Dr. MacGinnitie agreed that "the immune response responsible for autoimmune disease starts earlier" than clinical symptoms appear. Tr. 599. He agreed "[t]here was an immune response that must have been present for some time prior to onset of symptoms." Id. However, he opined there was no reliable evidence of such timing here and testified it "would all be speculation." Tr. 599-600. He specifically agreed that the oligoclonal bands in K.M.'s May 2 CSF testing show an immune response had been occurring for approximately four weeks, and up to six weeks. Tr. 688-89.

III. LEGAL FRAMEWORK

A. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 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 & Hum. 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).

Petitioner's burden of proof is by a preponderance of the evidence. § 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 & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

In particular, a petitioner must prove 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 & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999));

see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. 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." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63 (2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

B. Factual Issues

Petitioner must prove, by a preponderance of the evidence, the factual circumstances surrounding her claim. § 13(a)(1)(A). To resolve factual issues, the special master must weigh the evidence presented, which may include contemporaneous medical records and testimony. See Burns v. Sec'y of Health & Hum. Servs., 3 F.3d 415, 417 (Fed. Cir. 1993) (explaining that a special master must decide what weight to give evidence including oral testimony and contemporaneous medical records).

Medical records, specifically contemporaneous medical records, are presumed to be accurate and generally "warrant consideration as trustworthy evidence." Cucuras v. Sec'y of Health & Hum. Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). But see Kirby v. Sec'y of Health & Hum. Servs., 997 F.3d 1378, 1382 (Fed. Cir. 2021) (rejecting the presumption that "medical records are accurate and complete as to all the patient's physical conditions"); Shapiro v. Sec'y of Health & Hum. Servs., 101 Fed. Cl. 532, 538 (2011) ("[T]he absence of a reference to a condition or circumstance is much less significant than a reference which negates the existence of the condition or circumstance." (quoting Murphy v. Sec'y of Health & Hum. Servs., 23 Cl. Ct. 726, 733 (1991), aff'd per curiam, 968 F.2d 1226 (Fed. Cir. 1992))), recons. den'd after remand, 105 Fed. Cl. 353 (2012), aff'd mem., 503 F. App'x 952 (Fed. Cir. 2013). The weight afforded to contemporaneous records is due to the fact that they "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions. With proper treatment hanging in the balance, accuracy has an extra premium." Id. To overcome the presumptive accuracy of medical records, a petitioner may present testimony which is "consistent, clear, cogent, and compelling." Sanchez v. Sec'y of Health & Hum. Servs., No. 11-

685V, 2013 WL 1880825, at *3 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) (citing Blutstein v. Sec'y of Health & Hum. Servs., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)), mot. for rev. den'd, 142 Fed. Cl. 247 (2019), vacated on other grounds & remanded, 809 F. App'x 843 (Fed Cir. 2020).

There are situations in which compelling testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. Campbell v. Sec'y of Health & Hum. Servs., 69 Fed. Cl. 775, 779 (2006) ("[L]ike any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking."); Lowrie v. Sec'y of Health & Hum. Servs., No. 03-1585V, 2005 WL 6117475, at *19 (Fed. Cl. Spec. Mstr. Dec. 12, 2005) ("[W]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent." (quoting Murphy, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009); Bradley, 991 F.2d at 1575.

Despite the weight afforded medical records, special masters are not bound rigidly by those records in determining onset of a petitioner's symptoms. Valenzuela v. Sec'y of Health & Hum. Servs., No. 90-1002V, 1991 WL 182241, at *3 (Fed. Cl. Spec. Mstr. Aug. 30, 1991); see also Eng v. Sec'y of Health & Hum. Servs., No. 90-1754V, 1994 WL 67704, at *3 (Fed. Cl. Spec. Mstr. Feb. 18, 1994) (Section 13(b)(2) "must be construed so as to give effect also to § 13(b)(1) which directs the special master or court to consider the medical records (reports, diagnosis, conclusions, medical judgment, test reports, etc.), but does not require the special master or court to be bound by them").

C. Causation

To receive compensation through the Program, Petitioner must prove either (1) that K.M. suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that K.M. suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Petitioner must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because Petitioner does not allege K.M. suffered a Table Injury, she must prove a vaccine K.M. received actually caused her injury. To do so, Petitioner must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. Petitioner must provide a sound and reliable 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 & Hum. Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioner cannot

establish entitlement to compensation based solely on her assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether Petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The special master must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioner's favor when the evidence weighs in her 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 (noting that "close calls" are resolved in Petitioner's favor).

Testimony that merely expresses the possibility—not the probability—is insufficient, by itself, to substantiate a claim that such an injury occurred. See Waterman v. Sec'y of Health & Hum. Servs., 123 Fed. Cl. 564, 573-74 (2015) (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard). The Federal Circuit has made clear that the mere possibility of a link between a vaccination and a petitioner's injury is not sufficient to satisfy the preponderance standard. Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

IV. ANALYSIS

A. Diagnosis

As Federal Circuit precedent establishes, in certain cases it is appropriate to determine the nature of an injury before engaging in the Althen analysis. Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1346 (Fed. Cir. 2010). Since "each prong of the Althen test is decided relative to the injury[,]" determining facts relating to the claimed injury can be significant in a case where diagnosis is not clear. Id. Here, the parties dispute diagnosis, and so it is appropriate to first resolve that issue.

Petitioner's experts opine that K.M.'s appropriate diagnosis is ADEM. Respondent's experts disagree and assert that K.M. did not have ADEM, and that a neurodegenerative genetic condition is more likely. The undersigned finds that the preponderant evidence weighs in favor of finding that K.M.'s diagnosis is ADEM based on her clinical course, her MRI and CSF results, and the opinions of her treating physicians and experts.

The International Pediatric MS Study Group's proposed criteria for an ADEM diagnosis provides a useful framework for analysis. First, prior to her illness, K.M. did not have any prior neurological condition or event suggesting that she had any CNS abnormality.[102] K.M.

[102] See supra note 81.

experienced her "first polyfocal clinical CNS event with a presumed inflammatory demyelinating cause" in April 2016, manifested by irritability, and clearly present on April 22, 2016, when she was noted to be slumping over to one side. Resp. Ex. F, Tab 3 at 2. There is no evidence that K.M. had any prior CNS demyelinating event. The experts also agree this criterion was met.

Second, K.M.'s CNS event was characterized by "[e]ncephalopathy that cannot be explained by fever." Resp. Ex. F, Tab 3 at 2. Dr. Shuman established that medical records show that K.M. was afebrile on March 30, 2016, April 23, 2016, she had only a low grade fever on April 25, 2016 (38.5°C rectally), and she was afebrile on April 27. See Tr. 240 (Dr. Shuman testifying that for a fever to be significant, it would need to be greater than 40°C). K.M.'s altered level of consciousness, or encephalopathy, worsened although she was afebrile. Tr. 238-41. Dr. Kruer agreed that K.M.'s encephalopathy could not be explained by fever.

The third criterion is "[n]o new clinical and MRI findings emerge three months or more after onset." Resp. Ex. F, Tab 3 at 2. The undersigned finds this criterion was met. The experts agreed there were no new clinical findings three months after onset. With regard to the MRI findings, Dr. Kruer argues that MRI findings evolved from April to September 2016, but acknowledged it is not known what her MRI would have shown at or around the three-month mark. Because there was no MRI done between May and September 2016, and therefore, there was no MRI at or around the three-month mark, there is no evidence to show what K.M.'s MRI would have shown at or around this period. Even though there are changes seen in September 2016, five months later, there is no way for the undersigned to discern when these changes occurred, since there was no MRI done around the three-month mark. Thus, the undersigned finds this criterion met.[103] See Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioner's favor).

And for the fourth criterion, "[b]rain MRI is abnormal during the acute (three-month) phase," the experts agreed the criterion was met. Resp. Ex. F, Tab 3 at 2.

Dr. Shuman and Dr. Kruer disagreed about whether K.M.'s later MRIs, especially the September 1, 2016 and August 30, 2017 MRIs, showed typical findings characteristic of ADEM. Dr. Kruer opined that they showed global atrophy, severe atrophy of the white space all through the brain, not consistent with ADEM. Instead, he opined these findings were consistent with leukodystrophy, and that K.M. had a neurodegenerative disorder of genetic origin. Dr. Shuman disagreed, explaining that the demyelinating process had consumed the white matter of the brain, evidencing a severe outcome, which is the "most dreaded outcome of ADEM." Tr. 217. He cited Armangue et al., which showed four children who had leukodystrophy-like ADEM. He explained that leukodystrophy-like ADEM is rare and can cause a severe outcome. Notably, Dr. Kruer agreed that "there is a rare leukodystrophy-like presentation of ADEM." Tr. 441. He testified, "I'll fully acknowledge the point that, yes, there were select cases within that

[103] If the undersigned misunderstood Dr. Kruer's testimony on this point, the third criteria may not have been met. However, the undersigned's opinion as to diagnosis would remain ADEM for all of the other reasons discussed herein.

Armangue [et al.] paper that did talk about a leukodystrophy-like pattern, and I think that that's an important consideration in this case as well." Tr. 463.

The undersigned credits Dr. Kruer's veracity and acknowledgement that there are rare ADEM cases where MRIs show a leukodystrophy-like pattern as an important consideration here. Although rare, Armangue et al. provides evidence of such cases. Thus, the undersigned finds there is agreement between both Dr. Shuman and Dr. Kruer that infants with ADEM can and do have leukodystrophy-like findings on MRI. The undersigned further finds that K.M.'s later MRI results are consistent with a leukodystrophy-like pattern that can be seen in ADEM.

Additionally, the undersigned finds no evidence of a genetic abnormality to account for the MRI findings or K.M.'s condition. The fact that there is no genetic testing evidence to support a diagnosis of a neurodegenerative disease casts considerable doubt on such a diagnosis and renders it less persuasive.

Moreover, K.M.'s clinical course was consistent with ADEM. Dr. Shuman effectively testified that K.M. presented with encephalopathy, that she was irritable, and that she was hard to console, all consistent with a decreased level of consciousness. As her condition progressed, she could not fix and follow, she had an impaired ability to swallow requiring the need for a gastrostomy tube, motor impairments, and speech regression. She developed hypsarrhythmia, indicating a poorly myelinated brain that is inflamed. These symptoms and abnormalities are consistent with ADEM. While Dr. Kruer opined that K.M.'s chronic vegetative state is unusual for ADEM, he also agreed that in rare cases there can be bad outcomes.

Regarding K.M.'s CSF abnormalities, including pleocytosis and oligoclonal bands, the parties' experts are in agreement. Pleocytosis is associated with inflammation in the spinal fluid. K.M. had numerous inflammatory cells in her CSF indicating that she was experiencing an immune system response in her brain. Dr. Shuman and Dr. Kruer also agree that while oligoclonal bands are not seen in majority of ADEM patients, they can be present. And Dr. Kruer agreed that K.M.'s pleocytosis in her CSF weighed against a diagnosis of leukodystrophy and was more consistent with ADEM. K.M.'s treating physicians also noted that her CSF pleocytosis was atypical for leukodystrophy. Therefore, the undersigned finds that K.M.'s CSF results are consistent with ADEM and not with a neurodegenerative genetic condition.

Further, the undersigned finds that K.M.'s treating physicians' initial diagnosis was ADEM and her most current diagnosis is ADEM. After her MRI appearance changed and showed a leukodystrophy-like pattern, her treating physicians undertook an extensive diagnostic workup for a neurodegenerative/leukodystrophy diagnosis but failed to find evidence of any metabolic or genetic cause to support such a diagnosis. During the period K.M. was undergoing this workup, some of her medical records referred to leukodystrophy and/or neurodegenerative disorder as her diagnosis. After the workup was completed, and no metabolic or genetic cause was found, her diagnosis ultimately returned to ADEM.

Finally, Petitioner's current diagnosis is ADEM. Medical records from K.M.'s treating pediatrician and neurologist from visits in 2023 state that her diagnosis is ADEM. See Pet. Ex. 42 at 137 (pediatrician noting "[K.M.] has chronic medical conditions related to [ADEM]"); Pet.

Ex. 43 at 90 (neurologist assessing K.M. on May 5, 2023 with numerous neurodevelopmental abnormalities "secondary to an early life inflammatory event suggestive of hyperacute ADEM").

In conclusion, the undersigned finds Petitioner has shown by preponderant evidence that K.M.'s diagnosis is ADEM.

B. Causation

1. Althen Prong One

Under Althen prong one, Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu, 569 F.3d at 1375; Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound and reliable" medical or scientific explanation. Boatmon, 941 F.3d at 1359; see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 257 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support her 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 ("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 & Hum. 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))).

For the following reasons, the undersigned finds Petitioner has provided preponderant evidence of a sound and reliable theory by which the Hib and/or Prevnar vaccines can cause ADEM, and therefore, Petitioner has satisfied the first Althen prong.

First, ADEM is known to be an illness that can be caused by vaccinations. The medical literature cited in this case provides support for finding that vaccinations can cause ADEM. See, e.g., Pet. Ex. 26-38 at 3; Pet. Ex. 29-2 at 1; Pet. Ex. 30-17 at 1-2, 6; Pet. Ex. 46 at 2; Resp. Ex. C, Tab 1 at 1; Resp. Ex. F, Tab 8 at 1.

Vaccine Program case law also supports a finding that vaccinations can cause ADEM. Special masters have found in favor of petitioners in reasoned decisions where ADEM is the alleged injury. See, e.g., Camerlin ex rel. Camerlin v. Sec'y of Health & Hum. Servs., No. 99-615V, 2003 WL 22853070 (Fed. Cl. Spec. Mstr. Oct. 29, 2003) (ADEM/transverse myelitis post-Hib vaccination); Eilan ex rel. A.E. v. Sec'y of Health & Hum. Servs., No. 15-381V, 2021 WL 1085925 (Fed. Cl. Spec. Mstr. Feb. 23, 2021) (ADEM following measles, mumps, and rubella ("MMR") and/or varicella vaccinations);[104] Pasco ex rel. M.P. v. Sec'y of Health & Hum. Servs., No. 16-500V, 2022 WL 6616736 (Fed. Cl. Spec. Mstr. Sept. 23, 2022) (transverse myelitis and

[104] But see, e.g., Sparrow ex rel. L.S. v. Sec'y of Health & Hum. Servs., No. 18-295V, 2024 WL 1599165, at *30 (Fed. Cl. Spec. Mstr. Mar. 19, 2024) (dismissing MMR/ADEM petition where special master found preponderant evidence L.S. had viral encephalomyelitis).

ADEM following MMR and varicella vaccinations); Kennedy v. Sec'y of Health & Hum. Servs., No. 09-474V, 2012 WL 1929801 (Fed. Cl. Spec. Mstr. May 8, 2012) (ADEM post-Tdap and/or meningococcal vaccinations); Lozano v. Sec'y of Health & Hum. Servs., No. 15-369V, 2017 WL 3811124 (Fed. Cl. Spec. Mstr. Aug. 4, 2017) (ADEM post-Tdap vaccination); Lerwick ex rel. Lerwick v. Sec'y of Health & Hum. Servs., No. 06-847V, 2011 WL 4537874 (Fed. Cl. Spec. Mstr. Sept. 8, 2011) (ADEM post-DTaP vaccination); Althen, 418 F.3d at 1282 (affirming lower court's finding of preponderant evidence that tetanus toxoid caused ADEM and optic neuritis); Brown v. Sec'y of Health & Hum. Servs., No. 09-426V, 2011 WL 5029865 (Fed. Cl. Spec. Mstr. Sept. 30, 2011) (ADEM post-influenza vaccine);[105] Hawkins v. Sec'y of Health & Hum. Servs., No. 99-450V, 2009 WL 711931 (Fed. Cl. Spec. Mstr. Feb. 27, 2009) (ADEM following hepatitis B vaccination).

Lastly, the experts here agree that vaccinations can cause ADEM. See, e.g., Tr. 110 (Dr. Steinman testifying that vaccines can cause ADEM); Tr. 455 (Dr. Kruer testifying ADEM "could be caused by immunization"); Tr. 575, 659 (Dr. MacGinnitie acknowledging ADEM occurs post-vaccination); Pet. Ex. 26 at 115 (Dr. Shuman opining certain vaccines are "immunologically capable of creating ADEM").

Next, the leading theory for how vaccines can cause ADEM is molecular mimicry. See Tr. 689-91 (Dr. MacGinnitie agreeing that molecular mimicry was a leading theory to explain how vaccines can cause ADEM); see also Pet. Ex. 26-38 at 3 ("Molecular mimicry . . . may play a role."); Resp. Ex. E, Tab 25 at 10 (noting "molecular mimicry may contribute to the symptoms of ADEM").[106] Therefore, the theory of molecular mimicry is an accepted theory for how vaccines can cause CNS demyelinating illnesses including ADEM. See, e.g., Palattao v. Sec'y of Health & Hum. Servs., No. 13-591V, 2019 WL 989380, at *35-37 (Fed. Cl. Spec. Mstr. Feb. 4, 2019) ("[M]any of the existing Program decisions in which [transverse myelitis] has been found to be caused by a vaccine rely on a mechanism [of] []molecular mimicry . . . ."); Caruso v. Sec'y of Health & Hum. Servs., No. 15-200V, 2017 WL 5381134, at *14, *14 n.19 (Fed. Cl. Spec. Mstr. Oct. 18, 2017) (finding a petitioner satisfied Althen prong one under a theory of molecular mimicry in an influenza/ADEM case); Reinhardt v. Sec'y of Health & Hum. Servs., No. 17-1257V, 2021 WL 1851491, at *16-18 (Fed. Cl. Spec. Mstr. Apr. 2, 2021) (determining a petitioner established Althen prong one in an influenza/bilateral optic neuritis case under the theory of molecular mimicry); Kennedy, 2012 WL 1929801, at *14 (finding Tdap and/or meningococcal vaccinations caused the petitioner's ADEM through molecular mimicry).

Specific to Hib and Prevnar vaccines, Dr. Steinman opines that the causal mechanism of molecular mimicry explains how these vaccines can cause ADEM. He offers three ways

[105] But see, e.g., Caruso v. Sec'y of Health & Hum. Servs., No. 15-200V, 2017 WL 5381154, at *1 (Fed. Cl. Spec. Mstr. Oct. 18, 2017) (dismissing an influenza/ADEM petition where onset was "too attenuated temporally to establish a medically acceptable timeframe for vaccine-induced ADEM").

[106] Inst. of Med., Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines, in Adverse Effects of Vaccines: Evidence and Causality, supra note 94, at 525, 546-47.

molecular mimicry could occur using examples of homology between the vaccines and self proteins that could illicit a pathological immune inflammatory response causing the demyelinating condition known as ADEM. The first theory involves homology between phosphoglycerol in the Prevnar vaccine (in serotypes 23F and 18C) and phospholipid components of the myelin. The second theory is based on the protein carrier CRM_{197} in Prevnar. CRM_{197} is a nontoxic form of diphtheria toxin used to make the vaccine more effective (immunogenic). Dr. Steinman identified homologous sequences between the diphtheria toxin and myelin basic protein/neurofascin which can illicit neuroinflammation. The third theory is based on tetanus toxoid in the Hib vaccine. Dr. Steinman identified homologous sequences between tetanus toxoid and neurofascin. This sequence was reported in the IEDB, noting an association with neuroinflammation. To support these three examples, Dr. Steinman produced patents, medical literature, and BLAST and IEDB searches, all reliable and reputable sources.

Respondent's expert, Dr. MacGinnitie does not reject the mechanism of molecular mimicry as a sound and reliable theory, but instead explains that while the theory has been easy to prove in animal studies, it has been difficult to prove in humans. Dr. MacGinnitie also expressed specific concerns about the three examples of homology posited by Dr. Steinman. However, neither the Vaccine Act nor case law require evidence of animal or human studies to prove the pathogenic mechanism. Given the state of current scientific knowledge, it would not be possible for a petitioner to provide that level of proof. Further, proof of causation would require scientific certainty, which is a bar too high. See Knudsen, 35 F.3d at 549 (explaining that "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program").

The undersigned finds that while the models of molecular mimicry offered here have not been studied or verified in a laboratory, or written about in scientific papers, they are based on sound and reliable sources, and they explain how molecular mimicry occurs or could occur here. Even assuming Petitioner had not offered these three examples of homology, the undersigned would have found molecular mimicry to be a sound a reliable theory to explain how vaccinations, including Hib and Prevnar, can cause ADEM.

For these reasons, the undersigned finds that Petitioner has proven by preponderant evidence a sound and reliable causal theory establishing that Hib and/or Prevnar vaccines can cause ADEM, satisfying Althen prong one.

2. Althen Prong Two

Under Althen prong two, Petitioner 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 injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner 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 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as

treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence since they are created contemporaneously with the treatment of the vaccinee. Cucuras, 993 F.2d at 1528. While the medical records and opinions of treating physicians must be considered, they are not binding on the special master. § 13(b)(1)(B) (specifically stating that the "diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court").

A petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano, 440 F.3d at 1325. Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

There are three reasons why the undersigned finds preponderant evidence of a logical sequence of cause and effect establishing that the Hib and/or Prevnar vaccinations administered to K.M. on February 29, 2016 caused her to develop ADEM. First, K.M. was appropriately diagnosed with ADEM, and Petitioner has proffered a sound and reliable mechanism of vaccine causation.

Second, the evidence shows that some children with ADEM have a clinical course characterized by leukodystrophy-like pattern on MRI, as discussed in detail above, in the section on diagnosis. For all the reasons discussed in the analysis of diagnosis section above, the undersigned finds that K.M.'s clinical course is consistent with a leukodystrophy-like type of ADEM.

Third, no alternative cause was found for K.M.'s ADEM. Extensive testing was done for infectious, metabolic, and genetic causes. The medical records detail the testing for an infectious cause and the results were negative. Although K.M. had CSF pleocytosis, indicating infection or autoimmune inflammation, cultures were done which did not reveal any infection. During her initial hospital admission, K.M. was seen by numerous consultants, including an infectious disease physician. No infectious process was ever identified. At a family meeting on May 9, 2016, K.M.'s parents were informed that there was no identified infectious cause for her symptoms.[107]

In late May and early June 2016, K.M. received metabolic/genetic testing at Johns Hopkins and KKI. In August 2016, K.M.'s parents met with the genetic counselor at Johns Hopkins who informed them that the mitochondrial genetic testing was negative and normal. At this point, all the tests were negative and no underlying genetic cause for K.M.'s illness was identified. In September 2016, K.M. had an evaluation at the Leukodystrophy Clinic at CHOP. She underwent a workup for leukodystrophy but again, all testing was negative.

[107] In addition to the factual summary in this Ruling, for a summary of the testing done for infections, see Pet. Ex. 30 at 16-17; Pet. Br. at 57.

In summary, no metabolic or genetic cause was found to explain K.M.'s ADEM. K.M. underwent extensive testing at Johns Hopkins, KKI, and the Leukodystrophy Clinic at CHOP for all known genetic abnormalities that cause white matter demyelination, including WES testing. All the tests were negative for a genetic cause. During the testing, the physicians acknowledged that K.M.'s CSF pleocytosis was atypical for a leukodystrophy. Therefore, there are two reasons weighing against finding that K.M. has a genetic cause for her ADEM—negative genetic testing and CSF pleocytosis.

Lastly, even if K.M. did have an infection, Petitioner's experts opined that the combination of infection and vaccination could have caused her ADEM. Dr. Steinman opined that if K.M. had a strep infection, she would have had a more intense immune response to vaccination. Dr. Shuman opined that K.M.'s history of recurrent ear infections made her more likely to develop the immune response she did. The organisms that cause otitis media in children are the same as those targeted by the Prevnar vaccine. K.M.'s immune system was already responding to that bacterium in her ears when she received "an immunological boost with a vaccine to build more antibody against that specific pneumococcus." Tr. 350. Therefore, the infection and vaccination could have worked in a synergistic manner to cause ADEM. Dr. MacGinnitie opined that there was no evidence that K.M. had an infection of the type that would be protected against by the Prevnar vaccine. He also was not aware of any data to suggest that having an infection affects the immune response. However, the undersigned finds Petitioner's position that receiving a vaccination while having an infection (even where the infection is not one protected against by the vaccination) causes a more intense immune response is persuasive. It is also consistent with case law in the context of ADEM.

Petitioner points out those cases where the combined or synergistic effect of infections and vaccinations were found to cause ADEM. In Camerlin, the special master granted entitlement to compensation in a case of ADEM/transverse myelitis following administration of a Hib vaccination. Camerlin, 2003 WL 22853070, at *1. The child in Camerlin was diagnosed with otitis media 11 days prior to Hib vaccination, similar to K.M., and had a fever after vaccination, like K.M. Id. The special master found that the child's immune system was "primed by this prior infectious process" and the Hib vaccine was a "substantial factor" in triggering his ADEM/transverse myelitis. Id. at *10. Thus, "[b]ut for the Hib vaccine," the Camerlin child would not have suffered from ADEM/transverse myelitis. Id. Similarly, in Brown, the petitioner received an influenza vaccine before he developed sinusitis one month later and an upper respiratory infection three weeks later. Brown, 2011 WL 5029865, at *1. The special master found the petitioner entitled to compensation, finding "the antigenic insult began with the influenza vaccination" and "[t]he addition of petitioner's one or two infectious episodes one month or more after vaccination added a greater imposition upon petitioner's immune system, resulting in ADEM." Id. at *45.

In conclusion, the undersigned finds that Petitioner has proven by preponderant evidence a logical sequence of cause and effect establishing that the Hib and/or Prevnar vaccinations K.M. received caused her to develop ADEM. Thus, Petitioner has satisfied the second Althen prong.

3. Althen Prong Three

Althen prong three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That phrase has been defined as a "medically acceptable temporal relationship." Id. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." De Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen prong one). Id.; Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1579, 1243 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542.

K.M. received the vaccinations on February 29, 2016. Generally, the experts agree that she had clear objective evidence of encephalopathy characterized by slumping or leaning on April 22, 2016. Dr. Steinman, however, placed onset prior to April 22, and as early as the first few days in April based on the fact that K.M. had plasmacytoid/plasma cells in her CSF on April 25. He testified that these cells take days to weeks to appear, "likely a few weeks." Tr. 106. Dr. Steinman testified that Schonberger et al. noted an increased risk of neuroinflammation concentrated in the five-week period after vaccination. In Pellegrino et al., the majority of cases reported had onset between two and 30 days, with 19% developing ADEM one month following vaccination. Onset in the case reported by Kira et al. occurred 17 days post-vaccination. Based on Dr. Steinman's opinion assuming onset was in "the first few days of April," and using the dates of April 1 to April 4 to represent "the first few days of April," onset occurred around 32 to 35 days after vaccination. Tr. 146.

Dr. Shuman testified that onset was April 1 at the earliest, based on the presence of oligoclonal bands in the CSF on May 2. The presence of 11 oligoclonal bands in the CSF on May 2 indicated that the immune process began two to four weeks prior to May 2, which was April 1 at the earliest and mid-April at the latest. Given Dr. Shuman's testimony, onset occurred around 32 to 46 days post-vaccination.

Dr. Kruer placed onset on April 22, 2016, based on K.M.'s objective neurological behavior of slumping to one side. This places onset at 53 days. He did not offer an opinion as to when onset would have been based on the CSF findings of plasma cells or oligoclonal bands. And lastly, Dr. MacGinnitie initially opined that the onset of K.M.'s neurological symptoms was April 22, although he agreed that the presence of oligoclonal bands in the CSF on May 2 was consistent with an immune response occurring for approximately four to six weeks. Using the CSF results, this would place onset between March 21 and April 4, or 21 days to 35 days after vaccination.

The undersigned finds the fact that plasma cells were present on April 25 and oligoclonal bands were present May 2 to be reliable indicators of the immune response in the CNS, based on the testimony of Drs. Steinman, Shuman, and MacGinnitie. Using these indicators, dates in early April, April 1 to April 4, were referenced by the experts. These dates put onset of the immune response at 32 to 35 days after vaccination. This time frame is within the risk window described in the literature cited by the experts.

The first clinical symptoms of K.M.'s ADEM are difficult to discern. Dr. Steinman opined that K.M.'s behavior was not normal in early April, as evidenced by the testimony of her parents. Respondents' experts place onset of clinical symptoms on April 22, when K.M. leaned to one side and could not sit up or hold her head up, which is 53 days post-vaccination. The experts agreed, however, that K.M.'s immune response began prior to the onset of clinical symptoms.

The experts gave differing opinions about the range of an appropriate temporal association between vaccination and onset of symptoms given the mechanism of molecular mimicry. Dr. Steinman, citing to Schonberger et al., testified that the risk ADEM was highest at five weeks but still appropriate at nine to 10 weeks after vaccination. Dr. MacGinnitie opined that a temporal association would be appropriate up to six weeks post-vaccination.

Using the time frame of 32 to 35 days after vaccination (based on the presence of plasma cells and oligoclonal bands in the CSF), onset is well within the six-week time frame referenced by both Dr. Steinman and Dr. MacGinnitie. Using the 53-day time frame based on K.M.'s clearly abnormal behavior on April 22, onset would be at almost eight weeks, within the time frame asserted by Dr. Steinman but beyond that asserted by Dr. MacGinnitie. The undersigned notes, however, that an onset of eight weeks has been accepted as appropriate in other cases where molecular mimicry is the causal mechanism at play. See, e.g., Spayde v. Sec'y of Health & Hum. Servs., No. 16-1499V, 2021 WL 686682, at *18-19 (Fed. Cl. Spec. Mstr. Jan. 27, 2021) (finding an onset of 60 days "exceedingly close" to the generally accepted timeframe of 56 days and appropriate given the mechanism of molecular mimicry) (citing Paluck v. Sec'y of Health & Hum. Servs., 786 F.3d 1373, 1383-84 (Fed. Cir. 2015) (finding the "special master [] erred in setting a hard and fast deadline . . . between vaccination and [] onset")).

Moreover, here the experts agree that K.M.'s immune response began before April 22, which weighs in favor of finding an appropriate temporal association.

Therefore, undersigned finds that Petitioner has met her burden of proof as to Althen prong three.

V. CONCLUSION

Based on the record, and for the reasons discussed above, the undersigned finds there is preponderant evidence that K.M.'s diagnosis is ADEM. Further, there is preponderant evidence to satisfy all three Althen prongs and to establish that K.M.'s Hib and/or Prevnar vaccinations caused her to develop ADEM. Thus, the undersigned finds that Petitioner is entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master