In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 15-381V
Filed: February 23, 2021
PUBLISHED

MAJED EILAN and SHAMS EILAN parents and next friends of A.E., a minor,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Entitlement; Acute Disseminating Encephalomyelitis (ADEM); Measles Mumps Rubella (MMR) vaccine; Varicella vaccine

Richard Gage, Richard Gage, P.C., Cheyenne, WY, for petitioners.
Emilie Williams, U.S. Department of Justice, Washington, DC, for respondent.

RULING ON ENTITLEMENT[1]

On April 15, 2015, petitioners filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012),[2] alleging that haemophilus influenza type B ("Hib"), measles mumps and rubella ("MMR"), pneumococcal, and varicella vaccines, that their daughter, A.E., received on April 27, 2012 caused her to suffer acute disseminated encephalomyelitis (ADEM). (ECF No. 1.) For the reasons set forth below, I conclude that petitioners are entitled to compensation for A.E.'s ADEM.

[1] Because this decision contains a reasoned explanation for the special master's action in this case, it will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. *See* 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the decision 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 the special master, upon review, agrees that the identified material fits within this definition, it will be redacted from public access.

[2] Within this decision, all citations to § 300aa will be the relevant sections of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec' of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991). Because ADEM is not listed as an injury on the Vaccine Injury Table, petitioners must satisfy this burden of proof.

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition, but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based

solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine.

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. The court also indicated that, in finding causation, a Program fact-finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id*. at 1280.

II. Procedural History

On April 15, 2015, petitioners filed their petition, alleging that ten days after their daughter, A.E., received the HIB, MMR, pneumococcal, and varicella vaccinations, A.E. started experiencing intermittent high fevers and ultimately, suffered ADEM that was caused-in-fact by the vaccinations A.E. received on April 27, 2012. (ECF No. 1.)

This case was first assigned to Special Master Millman. (ECF No. 4.) During the initial status conference on June 29, 2015, petitioners' counsel stated that "this claim was filed near the expiration of the statute of limitations, and as a result, he has not yet obtained many of the medical records." (ECF No. 8.) Petitioners subsequently filed medical records in support of their claim and a Statement of Completion. (ECF Nos. 7, 9, 13.)

On January 25, 2016, respondent filed his Rule 4 report, recommending against compensation. (ECF No. 17.) Respondent stated that A.E. was not diagnosed with ADEM and the alleged 10-day onset was not reflected in the medical records filed. (*Id*. at 10-11.) Instead respondent indicated that the medical records showed that A.E. started having fevers 25 days after vaccination and started experiencing developmental regression 50 days after vaccination. (ECF No. 17, n.11.)

In response to respondent's Rule 4 report recommending against compensation, petitioners filed an expert report from neurologist Marcel Kinsbourne, M.D. (ECF No. 25; Ex. 12.) Respondent filed a responsive expert report from neurologist Michael Kruer, M.D. (ECF No. 40, Ex. A.) On September 25, 2017, petitioners filed a supplemental expert report from Dr. Kinsbourne, responding to Dr. Kruer. (ECF No. 42; Ex. 36.) Petitioners filed an amended statement of completion on July 17, 2018. (ECF No. 45.)

On July 25, 2018, Special Master Millman issued an Order, indicating that "[w]hen this case is transferred to another special master upon [her] retirement, the new special master will schedule a hearing date." (ECF No. 46.) Thereafter, the case largely remained dormant until it was reassigned to my docket on June 7, 2019. (ECF No. 48.)

On June 11, 2019, I ordered the parties to confirm how they wished to proceed and to select mutually agreeable hearing dates in February 2020, if needed. A two-day entitlement hearing was ultimately scheduled to commence February 19, 2020. (ECF Nos. 49, 65.) In the interim, respondent filed a supplemental expert report from Dr. Kruer on July 25, 2019 and petitioner filed a second supplemental expert report from Dr. Kinsbourne on November 19, 2019. (ECF Nos. 53, 64; Exs. C, 48.) A two-day entitlement hearing was held on February 19 and 20, 2020. (*See* ECF Nos. 92-93, Transcript of Proceedings ("Tr").). Drs. Kruer and Kinsbourne testified.

Following the hearing, the parties attempted to informally resolve the case; however, on December 2, 2020, respondent advised that informal resolution would not be possible. (ECF No. 103.) Petitioners subsequently confirmed on January 21, 2021, that the case is ripe for resolution. (ECF No. 105.)

III. Factual History

a. Medical Records

i. Pre-Vaccination Records

A.E. was born on April 23, 2011 and was admitted into NICU at Lehigh Valley Pediatric Associates due to jaundice. (Ex. 2, pp. 240-44, 250.) A.E. stayed at NICU for five days for phototherapy. (Ex. 2, p. 310; Ex. 43, pp. 523-27.) A.E. was discharged home with her parents in good condition on April 29, 2011. (Ex. 2, p. 240-41.) On July 1, 2011, she was seen for a routine well check and was reported to have achieved her milestones of "Palmar grasp, Regards face, Follows with eyes and social smile." Additionally, she could lift her head briefly erect when held upright and cooed and responded to loud sounds. (Ex. 2, p. 251.) On September 9, 2011, petitioners brought A.E. back for another routine well check. (Ex. 2, p. 254.) At this visit, A.E. received DTaP, HIB, IPV, pneumococcal, and rotavirus vaccinations. (Ex. 2, p. 255; Ex. 3.) At her 6-month routine well check, A.E. continued to achieve developmental milestones and received another round of vaccinations including DTaP, HIB, pneumococcal, and

rotavirus. (Ex. 2, p. 264; Ex. 3.) On February 10, 2012, A.E. had her 9-month well-child visit and was reported to have achieved her developmental milestones including crawling, sitting without support, pulling to stand, imitating speech sounds, self-feeding, and playing "Pat-A-Cake." (Ex. 2, p. 266.) At this visit, additional laboratories were ordered, including a lead screening, and A.E. received additional routine vaccinations. (Ex. 2, p. 267.)

ii. **Vaccination and Initial Treatment**

On April 27, 2012, A.E. received the HIB, MMR, pneumococcal, and varicella vaccinations during her first-year child wellness checkup. (Ex. 2, p. 274-75; Ex. 3.) Her exam was normal, and she was continuing to achieve developmental milestones such as pulling to stand, walking without support, pincer grasping, pointing, saying one to three works, looking for hidden objects, and crawling. (Ex. 2, p. 274.)

Subsequently, petitioners brought A.E. to see her pediatrician, on June 7, 2012, reporting that petitioners "were in the ER for 1-1/2 hours last night and they did nothing. [A.E. has been] sick for 17 days, high fever for 3 days, balance off, hold right ear." (Ex. 2, p. 277.) Physical examination was normal. (Ex. 2, pp. 277-78.) A.E. was assessed to have a sore throat and unspecified viral infection; however, lab results revealed A.E. tested negative for strep. (Ex. 2, p. 278.) Petitioners were advised to treat fever and pain with acetaminophen and ibuprofen as needed. (Ex. 2, p. 278.)

On June 20, 2012, A.E. returned to her PCP's office with complaint of "fever for 28 days on and off." (Ex. 2, p. 279.) It was reported that A.E. had a temperature of up to 102 and also that she had symptoms of cough, fatigue, and loss of appetite. (*Id*.) Upon physical examination, there was no abnormal findings and A.E. was assessed with fever that comes and goes. (Ex. 2, p. 280.) Two days later, A.E. returned with a complaint of fever again. (Ex. 2, p. 285.) Again, physical examinations recorded normal findings; however, A.E. was then assessed with unspecified fever, prescribed antibiotics, and had a bladder catheterization. (*Id*. at 285-86.)

On June 28, 2012, A.E. was seen by her PCP again and this time, in addition to continuing intermittent fevers up to 104, A.E. was also reported to have regressed in motor developments where "she used to pull up to stand and cruised around furniture but now she rolls over and tries to pull herself up and cannot." (Ex. 2, p. 289.) On physical examination, A.E. had "head lag when pulled up and flopped over when sat up. Muscle tone appear[ed] normal but reflexes appear[ed] decreased." (Ex. 2, p. 290.) A.E. had elevated testing results and was then admitted to Lehigh Valley Hospital for evaluation and work-up. (*Id*.) According to petitioners' health plan inpatient admissions report, A.E. was admitted to Lehigh Valley Hospital for infectious ADEM. (Ex. 2, p. 297.)

A.E. was then examined by Dr. Claudia F. Busse at Lehigh Valley Hospital. (Ex. 4, pp. 1-4.) As part of A.E.'s history of present illness, it was recorded that "6 weeks ago started to have fevers," but A.E. was seen at the emergency room and "reassured."

Also, three or four days after the onset of fevers, petitioners noted that A.E. showed loss of balance and A.E. was seen by her PCP and "reassured" regarding such symptom. (Ex. 4, p. 1.) A.E.'s admission records also indicated that petitioners noted progressive loss of truncal strength, loss of words, and ability to sit or stand, and that A.E. had drainage from both ears. (*Id.*) Dr. Busse admitted A.E. with an initial diagnoses of developmental regression with loss of truncal tone/head control and fevers. (Ex. 4, p. 4.) She also listed "tumor, encephalitis, GBS, metabolic [disorder]" as differential diagnoses. (*Id*.)

Upon admission, A.E. had a neurology consultation with Dr. Muhammed Sheikh for loss of milestone and poor trunk control. (Ex. 2, p. 291-92; Ex. 4, pp. 21-22.) Dr. Sheikh reported that A.E. started having a fever six weeks ago that only subsided when ibuprofen was used. (Ex. 2, p. 291.) He also noted that A.E. was seen by her PCP several times and A.E. was "felt to have otitis media and were prescribed an antibiotic. However the child did not improve and were seen by the pediatrician, again." (*Id*.) Petitioners told Dr. Shiekh that A.E., in the last two weeks, had significantly regressed, where she was no longer able to sit or cruise, had a spacey look, and was not babbling as much. (*Id*.) Upon examination, Dr. Shiekh noted that A.E. had a spacey look, her pupils appeared to be a little dilated, her movements appeared to be a little sluggish, and she was unable to sit independently without support. (*Id.* at 292.) Dr. Shiekh's impression was that A.E. had signs of spasticity in the lower extremities with significant poor truncal tone and balance and history of significant regression in association with a febrile illness. He recommended an MRI and spinal tap, seeking to rule out ADEM, metabolic conditions, and encephalitis. (*Id*.)

On June 29, 2012, A.E.'s condition was found unchanged and was evaluated by a speech pathologist and pediatric nutritionist, where they found that A.E. had significant swallowing difficulty and poor oral skills. (Ex. 4, pp. 102, 106-08.) A.E.'s June 28, 2012 MRI revealed evidence of brain atrophy, poor myelinization in the anterior limbs of the internal capsules, the genus of the corpus callosum, the corona radiata and the centrum semi-ovale. (Ex. 2, p. 303; Ex. 4, pp. 101, 118.) Dr. Busse stated that A.E.'s MRI findings were "concerning for underlying neurodegenerative disorder versus encephalitis." (Ex. 2, p. 303; Ex. 4, p. 101.)

A.E. was febrile overnight on June 30, 2012, but was eating better than before. (Ex. 4, p. 137.) A.E. also had a spinal tap which yielded normal cytology results, her culture remained negative, and enterovirus detection was also negative. (Ex. 2, p. 303.) A.E.'s lab study for protein CSF results on June 29, 2012 was 121. (Ex. 4, p. 111.) Additionally, Dr. Busse noted that A.E.'s CSF WBCs were 13. (Ex. 2, p. 303, Ex. 4, p. 204.) Dr. Busse's impression indicated "brain atrophy [rule out] mixed white/gray matter disease" and "fever with neurofocal exam." (Ex. 4, p. 138.) Dr. Busse wanted to wait on

lyme testing results[3] and planned to insert a PICC line[4] for possible IVIG treatment. (*Id*.) A PICC line was placed under sedation on July 1, 2012.[5] (Ex. 4, p. 157.)

By July 1, 2012, A.E. was afebrile overnight and appeared to improve in head control, but showed no improvement of muscle tone of lower extremities. (Ex. 4, p. 162.) On July 2, 2012, A.E. was able to sit in a highchair and was moving her legs, indicating a "big improvement." (Ex. 4, p. 181.) Petitioners wanted a second opinion and arrangements to transfer A.E. were made. (Ex. 2, p. 303.)

On July 3, 2012,[6] A.E. was discharged from Lehigh Valley Hospital with diagnoses of West Nile virus encephalitis and developmental regression. (Ex. 2, p. 303.) During her hospitalization, "she continued to spike fevers to a max of 101." (*Id*.) Dr. Busse noted that "[a]fter a transfer, West Nile virus antibodies results, indicating recent West Nile virus infection, with West Nile virus encephalitis being the most likely diagnosis." (*Id*.) A.E. was then transferred as an inpatient to St. Christopher's Hospital in Philadelphia. (Ex. 2, p. 303.) According to petitioners' health plan inpatient admissions report, A.E. was admitted to St. Christopher's Hospital for infectious ADEM. (Ex. 2, p. 297.)

A.E. was transferred to Dr. Douglas Thompson at St. Christopher's Hospital on July 3, 2012 with the diagnosis of "fever unknown origin." (Ex. 5, p. 21.) Upon admission and preliminary examinations from various physicians, the assessment was that A.E. was a 14-month female with weeks of intermittent fevers and rapid regression of developmental milestones. (Ex. 5, p. 52, 54.) The initial diagnoses included post-infectious etiologies, metabolic disorder or neurodegenerative disorder, and given her history of fevers and possible improving symptoms, post-infectious "seems more likely [at] this time." (Ex. 5, p. 52, 56.)

Later that day, A.E. had a consultation with infectious disease specialist, Dr. Janet Chen, for intermittent fever for six weeks and loss of milestones. (Ex. 1, p. 1.) As part of the history of present illness, Dr. Chen recorded that A.E. began having daily fevers six weeks prior to being transferred to St. Christopher's Medical Center from Lehigh Valley Hospital. (*Id*. at 1.) Additionally, initially after one day of continued fever, A.E. went to the emergency room and was discharged with a viral disease. Then, A.E. saw her PCP, who came to the same diagnosis, but after 10 days of persistent fevers, A.E. visited a different doctor who diagnosed her with left acute otitis media and treated

[3] Lyme titre results were negative. (Ex. 4, p. 182.)

[4] PICC line is a peripherally inserted central catheter that's for long term use. (*PICC Line*, STEDMANS MEDICAL DICTIONARY, at 504750.)

[5] Additionally, at St. Christopher's Hospital, a clamp and new cap was placed on PICC line on July 3, 2012. (Ex. 5, p. 17.)

[6] There were some records that indicated A.E. was discharged on July 2, 2012, but the majority of the records from Lehigh Valley Hospital listed the discharge date as July 3, 2012. Additionally, there were records from St. Christopher's Hospital that were dated July 2, 2012. (Ex. 5, pp. 1-8.) The admitting records indicate that A.E. was examined on July 3, 2012 at 3:50AM. (Ex. 5, p. 52.)

her with antibiotics. (*Id*.) Dr. Chen also noted that 15 days prior to being transferred to St. Christopher's, A.E. began having increasing weakness. (*Id*. at 2.) Notably, upon physical examination, Dr. Chen indicated A.E. was positive for head lag, had some head control when upright, low truncal tone, and was unable to sit unassisted. (*Id*. at 5.) Dr. Chen's impression was that A.E. was a 14-month female with no significant past medical history "presenting with [six] weeks of intermittent fevers [and two] weeks of neurological regression, with slight improvement in past [two] days. Doesn't appear to have acute infectious process but cannot rule out post-infectious etiology or neurologic causes." (Ex. 1, p. 5.) Dr. Chen recommended further testing including a need to review A.E.'s brain MRI and "evaluate for acute disseminated encephalomyelitis before discussing possibility of steroid or IVIG." (*Id*. at 5-6.) Included in her notes was a discussion of ADEM, in which Dr. Chen explained that:

> Acute disseminated encephalomyelitis, or ADEM, is usually a monophasic inflammatory demyelinating disease that involves the central nervous system [and] usually occurs after a nonspecific illness or more rarely, after vaccination. Diagnosis is based on clinical finding [and] abnormalities detected on MRI. ADEM is responsible for clinical encephalitis in a substantial percent of cases in the first 2 years of life. Multiple neurological signs develop over days. It often follows respiratory infections, like influenza [and] mycoplasma pneumoniae. Incidence has declined since MMR [and] varicella vaccines were implemented. Rarely, vaccines can cause postinfectious encephalitis. In the US, <1 in 1 million doses of measles vaccines is estimated to cause ADEM. History of illness 2-3 weeks within onset of ADEM is seen in 50-80% of cases … With lack of evidence of ongoing infection along with the usual timelapse of a few weeks [between] symptoms of illness - onset of ADEM makes it more likely that it is a post-infectious autoimmune process . . . The characteristic of ADEM occur over a mean of 5 days.

(*Id.* at 6-7.)[7]

On July 4, 2012, A.E. had an EEG, which showed normal sinus rhythm. (Ex. 5, p. 86.) The next day, A.E. was examined by Dr. Maria Begel who noted that A.E. had waxing and waning ability to lift her head but no new symptoms regarding her loss of developmental milestones. (*Id.* at 99.) Additionally, A.E. remained afebrile. (*Id*.) During her stay at St. Christopher's Hospital, A.E. received speech therapy and medical nutrition therapy, and consultations for occupational therapy and physical therapy. (*Id.* at 100-08, 152-53, 181.) A.E. also saw Dr. Chen again and was noted to be "clinically stable with infectious evaluation negative thus far." (*Id.* at 110.) However, on July 6, 2012, A.E. had a follow-up examination with infectious disease specialist Dr. Long, who had the impression of "unlikely acute infection of CNS or post-infectious CNS. Cannot exclude either. West Nile encephalitis possible." (Ex. 5, p. 117.)

[7] The last page of Dr. Chen's note – page 8 – was not initially filed as part of Exhibit 1. That page was later filed separately as Exhibit 59.

During her time at St. Christopher's Hospital, she remained afebrile and her truncal hypotonia improved. (Ex. 2, p. 296, 305.) Dr. Thompson stated that A.E.'s MRI at Lehigh Valley Hospital showed "diffuse white matter disease and was suggestive of a possible adrenoleukodystrophy with infection a lesser possibility," and "[s]erologies came back positive for West Nile virus IgG and negative for IgM," where the "discrepancy was felt to be non-diagnostic, but left West Nile virus a possibility." (*Id*. at 305.) Dr. Thompson stated that upon discharge, confirmatory testing, including repeat lumbar puncture with serum and CSF and metabolic studies were still pending. (*Id*.) A.E.'s physical examination at discharge did not note any abnormal findings. (*Id*.) A.E.'s CSF lab report showed "cellular CSF with lymphocytes, macrophages and few RBC. No malignant cells seen." (Ex. 5, p. 203.) On July 10, 2012, A.E. was discharged from St. Christopher's Hospital to be transferred to a rehabilitation facility, with the diagnoses of central hypotonia, acute flaccid paralysis, post-infectious encephalitis versus metabolic disorder, and West Nile IgG. (Ex. 2, p. 305; Ex. 5, p. 35.)

Upon discharge from St. Christopher's Hospital, A.E. was transferred to Good Shepherd Rehabilitation Hospital "for comprehensive rehabilitation regarding significant hypotonia and loss of developmental milestones secondary to post infectious encephalitis versus metabolic disorder." (Ex. 2, p. 308.) Although A.E.'s generalized weakness had improved, "she remains significantly regressed in her milestones" and upon admission, overall, A.E. had limited mobility and was very hypotonic. (*Id.* at 309.) A.E.'s rehabilitation diagnoses were nontraumatic brain injury, ADEM versus metabolic disorder, central hypotonia, generalized debility and weakness from acute illness, impaired mobility, regression of development milestones, impaired communication, and impaired oral motor skills. (*Id.* at 312.) A.E. spent more than three months at Good Shepherd Rehabilitation Hospital and was discharged on October 29, 2012. (*Id.* at 313.)

During her time at Good Shepherd, A.E. underwent comprehensive occupational, physical, speech, and recreational therapy. (*See generally,* Ex. 7.) Her goals of therapy included "optimize nutrition and hydration. Watch spasticity," and "[i]mprove overall strength and endurance working towards age appropriate development skills. Maintain [range of motions], prevent contractures." (Ex. 7, p. 1.) Throughout July 2012, A.E. had "good night[s]" and did not experience any fevers. (*Id.* at 145-47, 152, 156.) Additionally, A.E.'s social interactions and engagement also showed signs of improvement. (*Id.* at 168-76.) A.E. continued to have poor oral intake, but showed some continuing improvement. (*Id*. at 162, 165, 168, 176, 179.)

On a report dated July 27, 2012, Center for Disease Control and Prevention reported no evidence of infection with any of the viruses tested. This report listed onset date as May 16, 2012. (Ex. 2, p. 314-15.) On September 8, 2012, petitioners submitted a VAERS report, stating that adverse onset was June 7, 2012, where A.E. started to have fevers and by June 28, had severe neurological symptoms that petitioners believed were caused by the MMR, Varicella, HIB, and pneumococcal vaccines. (*See Id*. at 321.)

Throughout August 2012, A.E.'s oral feedings showed improvement. (Ex. 7, pp. 208-30.) Additionally, A.E. continued having good nights without new concerns, improved in tone and spasticity, and tolerated her therapies. (*Id.* at 233-59.) Although A.E.'s tone showed steady improvement, her spasticity "remain[ed] a barrier to acquisition of functional skills. Parents remain[ed] reluctant to pharmacologic intervention for tone." (*Id.* at 242.) A.E.'s August 3, 2012 progress note indicated for the first time that she tested negative for West Nile virus. (*Id.* at 208.) By August 24, 2012, A.E. had better trunk and head control and her hands were more open. (*Id.* at 59.) At the end of August 2012, A.E. had "an erupting right lower molar (an eruption cysts burst extruding yellow and bloody fluid)," and developed small "rashes on her trunk. They look like heat rashes on exam. [However,] The arthropod bites [were] disappearing." (*Id.* at 272, 275.)

In September 2012, A.E. continued to "demonstrate steady improvement in function," and did not develop any "new medical concerns." (Ex. 7, pp. 1-29, 281-286.) Of note, on September 13, 2012, A.E. "[had] runny nose, clear mucus. Some cough. No fever. No [respiratory] distress. Tone remains variable but is slight only this morning. Mother reports that she observes much improvement with [A.E.'s] fine motor skills." (*Id.* at 309.) Additionally, her viral lab results were negative. (*Id.* at 311-15.) Aside from that, A.E. continued to have good nights with no new concerns. (*Id.* at 319-25.) On September 28, 2012, A.E. was started on medication, Baclofen, for her spasticity. (*Id.* at 30, 33.) Throughout October 2012, A.E. continued to show improvement, including being alert, smiling, reaching, better overall tone, holding her head up, and eating her meals. (*Id.* at 40-69.) Baclofen dosage was changed because A.E. "was noted to be more sluggish." (Ex. 7, p. 50.) However, there were some concerns about her diet, weight, and nutrition, and in early October, A.E. had some congestion. (*Id.* at 45, 47, 54, 58-63.) By mid-October, A.E. was still having problems eating and her weight gradually decreased, but petitioner-mother was against any tube feeding at night. (*Id.* at 74, 78.) Regarding her occupational and physical therapies, A.E. was improving her gross and fine motor functions. (*Id.* at 86.)

On October 25, 2012, A.E. had another brain MRI, which showed "[a]bnormal patchy symmetric FLAIR/T2 signal hyperintensity within the periventricular and subcortical white matter, probably reflect[ing] hypomyelination or postinfectious demyelination. Suggestion of some improvement in demyelination pattern along the posterior deep white matter tracts of the centrum semiovale and corona radiata. Mild persistent intracerebral volume loss." (Ex. 7, p. 33; Ex. 8, p. 1.) On October 26, 2012, A.E. was prescribed with pediasure, enteral pump, and NG tube for her post infectious encephalitis, spastic quadriparesis, and poor oral intake. (Ex. 2, p. 328; Ex. 7, p. 118.)

A.E. was later discharged on October 29, 2012. (Ex. 2, p. 329.) Her physical therapist, Cindi Hobbes reported on A.E.'s discharge summary that A.E. "has made slow [and] steady progress towards her goal during this admission." (Ex. 7, p. 125.) PT Hobbes recommended A.E. continue physical therapy, early intervention programs, seating and equipment evaluation for customer stroller. (*Id.*) A.E.'s speech language pathologist added that A.E. had difficulty with oral motor and swallowing skills,

secondary to overall deficits in motor control and coordination. (*Id.* at 128.) A.E.'s recreational therapist reported that A.E. made "significant progress during her admission. [A.E.] now able to sit in long sit to play for at least [10 minutes]." (*Id*. at 129.)

Additionally, Dr. Rosauro Dalope described A.E.'s course while admitted at Good Shepherd in the discharge summary, stating that "upon admission, [A.E.] underwent comprehensive OT, PT, ST evaluation and treatment and pediatric psychiatry, pediatric neuropsychology, and nutrition were consulted." (Ex. 2, p. 329.) Dr. Dalope stated that

> At the time of discharge, [A.E.] continued to have global hypotonia and hypertonia with activity and persistent strong extension pattern for movement. She did demonstrate ability to weight shift in prone with the upper extremity reaching and rolling. She persisted with marked motor planning and motor control deficits. She continued to have poorly graded movement. She did have bilateral increased tone. She did demonstrate purposeful grasp and release of toys and emerging self feeding skills. Overall she had made significant improvement in fine motor and self help skills since admission.

(*Id.* at 329-30.) Upon physical examination at discharge, Dr. Dalope noted spasticity on the elbows, knees, and ankles. (*Id.* at 330.) Additionally, "[a] repeat MRI in October 2012 did not show any progression of the lesions. Some areas were showing demyelination." (*Id.* at 331; Ex. 7, p. 136.) Dr. Dalope stated that "[g]iven that there are now changes in the milestones, the patient's findings are concerning for underlying neurodegenerative disorder." (Ex. 2, p. 331.)

iii. **Post Initial Treatment Records**[8]

Petitioners continued bringing A.E. to visit her pediatrician, Dr. Oscar A. Morffi, for follow up appointments after being discharged from Good Shepherd Rehabilitation Center, throughout the rest of 2012 and throughout 2013.

On November 15, 2012, A.E. had an appointment at St. Christopher's Metabolic, Program, Neurology Section with Dr. Reena N. Jethva for "further consideration of metabolic/genetic causes." (Ex. 2, p. 9-13.) A.E.'s history of present illness reported that "[a]round 12 months, she received MMR vaccination and she initially seemed well. After about 5-10 days, she started to be more fussy and not as interactive. She developed a fever about 15 days after the MMR immunization, up to 104.7 F, fluctuating." (*Id.* at 9.) Further, A.E. "had CSF studies that were unremarkable with white blood cell count of 2, red blood cell count of 144, clear fluid, glucose 48 and protein 20." (*Id.* at 9.) On physical examination, it was noted that A.E. had generalized motor weakness, truncal ataxia, head lag but hypertonic body, abnormal fluence speech and abnormal naming ability. (*Id.* at 11.) A.E. was assessed with chronic leukodystrophy, but further testing was ordered to consider other diagnoses in the differential. (*Id.* at 12.) Also, A.E.'s developmental regression improved as she was

[8] From this point forward, specific discussion of appointments for routine childhood illnesses are omitted.

regaining some skills and her "[t]one somewhat improved but still with significant peripheral hypertonia/spasticity and central hypotonia." (*Id.* at 12.) On November 23, 2012, A.E. returned to see her PCP regarding her persistent nasal congestion. (Ex. 2, pp. 30-31.) At this visit, A.E. was diagnosed with acute sinusitis. (*Id.* at 31.)

On November 26, 2012, A.E. underwent an early intervention program evaluation[9] and A.E. was found eligible to receive early intervention services. (*Id.* at 16-27.) On January 28, 2013, A.E. had her wellness visit with Dr. Morffi. (*Id.* at 50.) A.E.'s neurological evaluation revealed normal coordination and normal tone and power in all four extremities. (*Id.* at. 51-52.) A.E. returned to her pediatrician's office on March 29, 2013 in order to have forms completed and to obtain a refill on medication. (*Id.* at 65.) Petitioner-mom stated that A.E. was apparently making slow progress. At this appointment, Dr. Deshpande "spent time reassuring mom and encouraging her to continue to work with" A.E. (Ex. 2, p. 65.)

On June 17, 2013, A.E. had a check-up visit regarding her leukodystrophy with Dr. Agustin Legido. (*Id.* at. 76.) Upon physical examination, A.E. had poor coordination, had inaccurate fine motor movements, had difficulty swallowing, was unable to bear weight on her legs, and was unable to speak. (*Id.* at 78.) A.E.'s diagnosis continued to be leukodystrophy of unknown etiology and was instructed to continue taking Baclofen and undergo a follow up MRI. (*Id.*)

During A.E.'s two-year well-child visit on June 21, 2013, it was reported that A.E. has not achieved some of her milestones including, walking unassisted, pulling to stand, saying words, and self-feeding. (*Id.* at 72.) Physical examination revealed normal findings, except for A.E.'s gait was described as waddling with assistance, and at this visit, A.E. received a DTaP vaccination. (*Id.* at 73-74.)

On July 26, 2013, A.E. had a follow up MRI. (Ex. 2, p. 88; Ex. 8, p. 3.) In comparison to her October 25, 2012 study, again the "T2 FLAIR imaging are areas of abnormal hypersensitivity within the cerebral white matter" and such "degree of hyperintensity is abnormal suggesting leukoencephalopathy and this can include leukodystrophy as suggested in the clinical history." (Ex. 2, p. 88.) Similar hyperintensity was found within the cerebral peduncles; however, there were stable findings in many regions of the cerebral hemispheres and "there may be slight progression within the frontal lobes." (*Id.*)

[9] A.E. had a subsequent evaluation in November 2013, where she was found to be eligible to received continued early intervention services. (Ex. 2, pp. 151-62.) The reports in both evaluations revealed that A.E. had at least a 25% delay below the mean in one or more areas of development and showed a need for specially designed intervention. (Ex. 2, pp. 25, 160.) A.E. continued receiving early intervention services throughout 2014 and 2015, but it was determined that she did not need preschool special education services during scheduled breaks. (Ex. 34, p. 53.) However, for 2016, she was eligible for scheduled breaks based on A.E.'s reasonable educational progress and that she "has been able to maintain and recoup skills in a reasonable amount of time following breaks." (Ex. 34, p. 84.)

On September 11, 2013, A.E. saw her PCP for a follow-up appointment regarding her encephalitis. (*Id.* at 97.) A.E. was reported as improving where her tone was better, and she was standing and being more social. (*Id.*) A review of systems indicated that A.E. experienced tremors; however, on physical examination, A.E.'s neurological findings were normal including normal coordination, normal tone and power in all four extremities. (*Id.* at 97-98.) Dr. Morffi's impression was that A.E.'s condition was improving, but also referred A.E. for further neurology consultation and physical therapy evaluation. (*Id.* at 98.)

On September 13, 2013, A.E. also saw Pediatric Nurse Practitioner, Harriot G. Silliman and Dr. Charles Brill at Nemours Dupont Pediatrics. (Ex. 8, pp. 7-12.) Dr. Brill found that A.E. "demonstrated increased tone in the extremities with extensor posturing and low truncal tone." (Ex. 2, p. 104; Ex. 8, p. 11.) Both NP Silliman and Dr. Brill suggested A.E. continue her therapeutic services and referred her to white matter specialist, Dr. Sarah Hopkins. (Ex. 2, p. 104; Ex. 8, pp. 10-12.) At their recommendation, an updated EEG was performed on September 26, 2013, and A.E.'s results were normal. (Ex. 2, p. 113.)

On October 9, 2013, A.E. had a consultation with Dr. Sarah Hopkins for a second opinion regarding white matter changes. (Ex. 2, pp. 137-44; Ex. 8 pp. 16-20.) Under history of present illness, Dr. Hopkins recorded that "2 weeks after her 12 month shots (MMR, varicella, PVC7, and HiB) … A.E. began to seem more 'lazy,' and didn't want to run around as much as usual [and] around that time she began to have fevers that were recurrent and without clear batter and began to have loss of developmental milestones." (Ex. 2, p. 137.) Additionally, Dr. Hopkins noted that when A.E. was admitted to Lehigh Valley Hospital, A.E.'s "work-up was significant for elevated protein in the CSF and white matter abnormalities on MRI." (*Id*.) Petitioners reported to Dr. Hopkins that there was no further regression since being discharged from Good Shephard Rehabilitation facility and that A.E. has been regaining skills. (*Id*.) Additionally, baclofen has significantly helped A.E. with the spasticity in her extremities. (*Id*.)

Dr. Hopkins indicated that neuroradiologist, Dr. Kandula, reviewed A.E.'s past three brain MRIs, and found, "[t]he radiological differential would include a subacute sclerosing panencephalitis (SSPE), progressive multifocal leukoencephalopathy (PML), or nonviral encephalitis." (*Id.* at 139.) On neurological and motor exams, Dr. Hopkins noted that A.E. had "decreased bulk and increased tone in the extremities, with markedly decreased truncal tone and decreased tone in face [and she had] difficulty holding her head up." (Ex. 2, p. 140.) Dr. Hopkins's impression "is that the initial event was inflammatory, most likely infectious or parainfectious, but a metabolic disorder or leukodystrophy exacerbated by infection cannot be entirely ruled out." (*Id.*) In coming to this conclusion, Dr. Hopkins consulted with a neuroradiologist and infectious disease specialist, and through her review of the medical records, she highlighted that A.E. had increased CSF protein and increased ESR, A.E.'s imaging revealed progression of myelination, and A.E. has since made developmental progress. (*Id*.) Dr. Hopkins also noted that "[w]hile ADEM can follow vaccination and present with fever and encephalopathy the pattern of white matter involvement is atypical." (*Id*.) As part of her

recommendations, Dr. Hopkins suggested petitioners file a VAERS report since they had concerns about A.E.'s vaccinations, but Dr. Hopkins also indicated that she was unable to definitively connect the event to the vaccine, only that the case bears investigating. (*Id*. at 141.) Dr. Hopkins further recommended repeated imaging on a yearly basis to assess for stability and to obtain CSF for full metabolic studies if petitioners were concerned about further progression of disease. (*Id*.)

A.E. had a follow-up appointment with Dr. Legido on October 14, 2013. (Ex. 2, p. 122.) Petitioner-mom reported that "since the last visit in April 2013, [A.E.] has improved in regards to her milestones. [A.E.] is able to walk with the help of a walker, able to speak 2 syllables, feed [herself]. Spasticity has remained stable." (*Id.*) A.E. was undergoing physical therapy three times a week, occupational therapy twice a week, speech therapy twice a week, and early intervention at home.[10] (*Id*.) Dr. Legido ordered A.E. to continue her therapy sessions and ordered mitochondria testing. (*Id.* at 124.)

On November 18, 2013, A.E. underwent spine thoracolumbar imaging which revealed mild reverse S-shaped scoliosis thoracolumbar spine with mild right inferior pelvic tilt, but no osseous lesion, fracture, or subluxation. (Ex. 2, p. 163.) A certificate of medical necessity filled out by her PCP on December 16, 2013 indicated that A.E. needed occupational therapy for her diagnoses of encephalitis, flaccid paralysis, and developmental regression. (*Id.* at 168.)

A.E. had a two-year well-child visit on January 31, 2014 with Dr. Morffi. (*Id.* at 183.) A.E. had still not met certain milestone such as walking unassisted, pulling to stand, and saying three to six words, but her physical examination revealed normal findings including normal coordination, tone, and power in all four extremities, and gait. (*Id.* at 183-84.) On May 23, 2014, A.E. visited Dr. Morffi for a three-year well-child check-up. (*Id.* at 202.) A.E. could walk unassisted, pull to stand, and say words, but was still unable to meet her milestones as to crawling upstairs, walking up steps, running, and saying short phrases. (*Id*.) A.E. had allergic rhinitis and less BMI for her age. (Ex. 2, p. 204.) About a week later, A.E. returned to her PCP's office with a complaint of an acute one-day fever. (*Id.* at 206.) Again, she was treated as having acute otitis media and upper respiratory infection. (*Id*. at 207.)

A.E. continued to have occasional office clinic visits from Good Shepherd Rehabilitative Hospital and received frequent outpatient speech, occupational, and physical therapy from OP Pediatric Rehabilitation Program Health and Technology Center after she was formally discharged in October 2012. (*See* Exs. 11, 51.) A.E.'s first return to Good Shepherd was on November 9, 2012, where her listed diagnoses now stated Acute demyelinating encephalomyelitis first. (Ex. 11, p. 1.) It was noted that

[10] According to A.E.'s therapy plan after an initial assessment at OP Pediatric Rehabilitation Program Health and Technology Center, A.E. was recommended to receive intensive speech, occupational, and physical therapy 2-3x/week. (Ex. 11, p. 39.) According to A.E.'s physical and occupational therapy notes, it appears that A.E.'s insurance approved physical therapy twice a week and occupational therapy three times a week. (*See e.g.*, Ex. 11, pp. 202, 599, 924.)

since her discharge, A.E. was doing "fairly well." (*Id.*) After physical examination, Dr. Dalope assessed that, "[A.E. was now] 18 months old with a diagnosis of postinfectious acute demyelinating encephalomyelitis. She is still showing some slow but steady progress. She has maintained most of her functions that she had when she left here." (*Id.* at 2.) A.E. was to continue physical, occupational, and speech therapy as well as continue Baclofen for her spasticity. (*Id.* at 2-3.) However, during A.E.'s next visit on February 25, 2013, she was assessed by Dr. Dalope to be a "22-month-old female with a history of acute onset of encephalopathy with diffuse brain damage of unknown etiology, which has left her with spastic quadriparesis and global developmental delay." (*Id.* at 5.) Dr. Dalope, however, was "extremely impressed today in the 4 months since [A.E.'s] discharge [with] how interactive and alert she is and the gains that she has made including independent sitting, standing with assistance, using more signs." (*Id*.) A.E.'s subsequent visit records presented A.E. with spastic quadriplegia secondary to unknown etiology affecting the white matter. (Ex. 11, pp. 14-24.) During her August 7, 2014 visit, A.E. received Botox injections to her legs bilaterally. (*Id.* at 22.) A.E. continued receiving Botox injections subsequently. (*Id.* at 28, 34.)

Since November 2012, A.E. has been receiving physical, occupational, and speech therapy, varying from twice to three times a week for each respective session. (Exs. 11, 51.) The medical diagnosis remained "NTBI, post infectious encephalitis" or "NTBI, encephalopathy" for the majority of her treatment and A.E. was making progress towards her short-term and long-term goals. In August 2014, A.E.'s physical therapist noted that, "[s]ince her Botox she demonstrates improved tolerance to bracing and therefore improved assisted gait." (Ex. 11, p. 1401.) A.E. started wearing braces around her legs and continued with aquatic therapy and balance exercises. (*Id.* at 1107, 1119-26.) In October 2014, A.E. was crawling on hands and knees, meeting her new goals; however, A.E. was reported sick for several weeks and due to that "she has demonstrated significant deconditioning as a result of being sick." (*Id.* at 1478.) During A.E.'s physical session on November 7, 2014, petitioner-mom reported that A.E.'s MRI showed improvement, however her medical diagnosis was never changed or updated. (*Id.* at 1536.) A.E. continued showing steady progress and was benefitting from Botox injections in 2015. (*Id.* at 1847.)

On October 31, 2014, a brain MRI was performed and as compared to A.E.'s July 26, 2013 results, "the degree of signal abnormality in central white matter is less. However, there appears to be a greater degree of signal abnormality and subcortical white matter especially in the temporal lobes." (Ex. 6, p. 1.) The MRI report further stated that the "improving appearance raises the question of ADEM rather than leukodystrophy. Clinical correlation is recommended." (*Id*. at 2.)

Following her October 31, 2014 MRI, A.E. visited Dr. Legido for a "[f]ollow up of ADEM." (Ex. 43, p. 274; Ex. 44, p. 174). In giving a full history of present illness, Dr. Legido wrote that, after five to ten days of receiving the MMR vaccination when she was 12 months, A.E. started to become more fussy and not as interactive. Then about 15 days after MMR vaccination, A.E. developed a fever and about when she was 14-15 months, she started experiencing developmental regression. (Ex. 44, p. 174.)

Additionally, he wrote that when she was hospitalized, she had unremarkable CSF studies, and it "was felt that an infectious etiology could not be found and that other etiologies had to be investigated. She was [diagnosed] with ADEM." (*Id.*) Dr. Legido assessed A.E. with infectious ADEM and wrote that she was making slow progress with language, fine, and gross motor skills. He recommended that she continue supportive therapies. (*Id.* at 177.)

Throughout 2015, 2016, and 2017, A.E. went to her PCP's office for various complaints including persistent fevers, sore throat, earache, cough, nasal congestion, and wellness check-up. (*See Id.* at 1-51.) Dr. Vilas Deshpande wrote a note on September 16, 2016, indicating that A.E. is not receiving the second MMR, DTaP, and IPV vaccines because of a bad reaction and that A.E. has been diagnosed with encephalitis. (Ex. 43, p. 225; Ex. 44, p. 125.)

In September 2016, A.E. began kindergarten and had an IEP in place. (Ex. 35, p. 2.) A.E. was categorized with orthopedic impairment and speech and language impairment. (*Id.* at 7.) A.E. was eligible for specially designed instruction in order to make gains in the general education curriculum. (*Id.* at 32.) A.E.'s IEP recommended "supplemental physical support, physical therapy as a related service, speech and language support as related services, OT as a related service, transportation as a related service (life van), and PCA [personal care assistant] as a related service." (*Id.* at 32.) A.E. had an eye exam on November 30, 2016 with Dr. Mark S. Trachtman. (Ex. 45; Ex. 44, p. 107.) Dr. Trachtman described A.E. as a "five-year-old who has a history of cerebral palsy." (Ex. 45, p. 4.) A.E. was "found to definitely be myopic and could benefit from corrective glasses." (*Id*.)

A.E. saw her PCP for several office visits throughout 2018 and 2019, where her assessments listed ADEM. (Ex. 47, pp. 1-11.) On September 10, 2018, A.E. visited Dr. Legido for ADEM follow-up for the first time since November 2014. Although A.E. was still taking Baclofen, it "doesn't seem to help," but the Botox was working better and managing the stiffness. (*Id.* at 35.) Dr. Legido found that A.E. has "presumptive ADEM (based on improving white matter changes on repeat MRI brain and improving clinical status)." (*Id.* at 38.) Dr. Legido discussed with petitioners that "there is no current treatment to reverse the damage to the brain," and that he was "unsure of specific cause of ADEM." Additionally, Dr. Legido noted that in A.E.'s case it was "viral versus post vaccine." (*Id.* at 38.) Additionally, A.E. continued with physical and occupational therapy. (Ex. 51.) Her 2018 occupational therapy records indicated the medical diagnosis as "Encephalitis, Developmental Regression, Leukodystrophy," while her 2018 physical therapy records maintained the same medical diagnosis, "NTBI, post infectious encephalitis." (*See e.g.*, *Id.* at 1-4, 49-53.) A.E. also had speech therapy sessions between May 2019 and August 2019, where her medical diagnosis was now spastic quadriparesis cerebral palsy. (*Id.* at 120-37.) She was discharged from skilled speech therapy services after having met her short term goals. (*Id.* at 121.)

IV. Expert Opinions

a. Petitioners' Expert, Dr. Marcel Kinsbourne

In support of their claim, petitioners presented an expert opinion by neurologist Marcel Kinsbourne, M.D. Dr. Kinsbourne has served as a senior fellow at the Center for the Study of Aging and Human Development at Duke University, an adjunct professor of neurology at Boston University School of Medicine, a research professor at the Center for Cognitive Studies at Tufts University, and a professor of psychology at New School University. (Ex. 13, p. 2.) Dr. Kinsbourne obtained his B.M.B. Ch. from Oxford University Medical School in 1955 and his medical degree from State of North Carolina in 1967. (*Id.* at 1.) According to his curriculum vitae, Dr. Kinbourne sits on various editorial boards relating to neurology and psychology. He has numerous publications relating to various neurological disorders. (*Id.* at 3-33.) He has largely been retired from clinical practice since the early 1990's. (Tr. 95-96.)

In his first report, Dr. Kinsbourne opined that it is biologically plausible that both the MMR vaccine and the varicella vaccine can cause ADEM, and here, a temporal relationship existed between A.E.'s vaccinations and the onset of A.E.'s ADEM. Specifically, Dr. Kinsbourne stated that:

> ADEM is an immune-mediated demyelinating disorder of the central nervous system, which commonly presents with fever and sometimes headache. These prodromal events are followed by the emergence of neurological findings, including motor deficits, and lowered level of consciousness, coupled with evidence of multifocal lesions of demyelination on neuroimaging, "that usually occurs a few days or weeks following vaccine administration or virus-like disease."

(Ex. 12, p. 4 (citing Inst. of Med. (US) Vaccine Safety Comm., *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (Kathleen R. Stratton, Cynthia J. Howe & Richard B. Johnston Jr. eds., 1994)).) Moreover, Dr. Kinsbourne stated that a wide range of bacterial and viral antigens are capable of causing ADEM and, citing to various medical literature, MMR vaccination has been well documented as a cause of ADEM and other neurological disorders. Dr. Kinsbourne relied on articles by Garg, Weibel, and Landrigan. (Ex. 12, p. 5.) Additionally, Dr. Kinsbourne indicated that the varicella vaccine, as a member of the herpes family, has been reported to cause encephalitis. (*Id.* at 6.) Although "[a] variety of mechanisms have been suggested as the means by which infections can initiate autoimmune diseases," Dr. Kinsbourne focused on molecular mimicry. But ultimately, he indicated that it is challenging to identify the exact mechanism and therefore, it is medically reasonable to assume that one or more mechanism was responsible for A.E.'s ADEM. (*Id.* at 6-7.)

Dr. Kinsbourne also opined that the interval between A.E.'s MMR and varicella vaccination and the onset of her fevers and ataxia "is consistent with medical literature

as to temporal intervals between provocative events, notably infections, and the onset of ADEM." (*Id.* at 7.) Addressing A.E.'s diagnosis, Dr. Kinsbourne explained that:

> ADEM is an inflammatory disorder and in some three-quarters of cases, the onset of ADEM occurs in the wake of an identifiable febrile prodromal illness or immunization and with prominent constitutional signs and encephalopathy of varied degrees. The febrile prodrome may last three weeks or more. It abates as the neurological deficits take hold.

(*Id.* at 4.) Thus, Dr. Kinsbourne opined that the "conspicuously febrile onset" of A.E.'s disorder and the "initially elevated sedimentation rate and liver function test levels" were consistent with A.E.'s ADEM diagnosis. Dr. Kinsbourne, using the Brighton Collaboration Encephalitis Working Group diagnostic definitions, opined that A.E. satisfied four of the nine categories of neurological deficits, further supporting her ADEM diagnosis. Dr. Kinsbourne stated that:

> [A.E.'s] case abundantly satisfies these criteria as regards (1) to encephalopathy, (6) motor weakness, (7) altered deep tendon reflexes and (9) cerebellar dysfunction; ataxia. MRI findings displaying multifocal white matter lesions on T2 weighted sequences, and these features, as well as the monophasic course of her illness confirm the ADEM diagnosis. These criteria were intended to inform the diagnosis of ADEM in cases of alleged vaccine injury.

(Ex. 36, p. 2.)

Additionally, Dr. Kinsbourne stated that "[e]vidence is absent for alternative causation." (Ex. 12, p. 8.) Dr. Kinsbourne reported that "the clinical diagnosis of leukodystrophy was never supported by neuroradiological, clinical laboratory or genetic finding," and that ADEM is A.E.'s current diagnosis as established by her treating physicians, Dr. Sarah Hopkins and Dr. Kimberly Kuchinski,[11] and A.E.'s most recent neuroimaging study on October 31, 2014. (*Id.* at 3, 7.)

In his supplemental expert reports, in response to Dr. Kruer's challenging A.E.'s ADEM diagnosis, Dr. Kinsbourne addressed A.E.'s elevated liver enzymes, the possibility of blood contamination causing elevated CSF proteins, and A.E.'s neuroimaging study results. Dr. Kinsbourne concluded that "elevated liver enzyme levels neither favor nor disfavor the diagnosis of ADEM," since "elevated liver enzymes are frequently found without any known cause." (Ex. 48, p. 1.) Dr. Kinsbourne also maintained that A.E.'s CSF protein was elevated even when accounting for blood contamination and further stated that "[c]orrection of CSF levels for blood found in CSF to be widely practiced." (Ex. 36, p. 1; Ex. 48, pp.1-2.) Regarding A.E.'s neuroimaging, Dr. Kinsbourne agreed that A.E.'s diffuse symmetric brain lesions, pre-existing cerebral atrophy, and delayed myelination are not typical or features of ADEM, but Dr.

[11] From the rehabilitation records, it appears that Dr. Kuchinski replaced Dr. Dalope as A.E.'s primary doctor at Good Shepherd.

Kinsbourne asserted that these aspects do not rule out ADEM. (Ex. 36, p. 2; Ex. 48, pp. 2-3.) Dr. Kinsbourne thought that the neuroimaging studies were more important in ruling out leukodystrophy and showing lessened white matter abnormalities in supporting a diagnosis of ADEM. (Ex. 48, p. 2.)

Additionally, Dr. Kinsbourne stated that "remission is consistent with the monophasic trajectory observed in ADEM," and emphasized that A.E.'s most updated medical records show that A.E.'s "development has slowly but steadily continued to improve." (Ex. 36, p. 2; Ex. 48, p. 3.) Dr. Kinsbourne maintained that A.E.'s "relentless stable, slow progress" indicates that her condition is monophasic, which ADEM typically is, and therefore, "ADEM is the only medically reasonable diagnosis in evidence." (Ex. 48, p. 3.)

With regard to the temporal relationship, Dr. Kinsbourne maintained that a three week onset and the duration of A.E.'s fevers are not inconsistent with ADEM. Specifically, Dr. Kinsbourne stated that although the timing of A.E.'s fever was not typical of a post immunization fever, "the fever may have been a marker of a subacute onset of the ADEM," and that "[t]here is no established time limit for the duration of fever in ADEM," but "[r]elevant publication note that it can be prolonged." (Ex 36, p. 1; Ex. 48, p. 1.)

b. Respondent's Expert, Dr. Michael Kruer

Respondent presented an expert opinion from pediatric neurologist, Michael Kruer, M.D. Dr. Kruer is board certified in pediatric neurology and trained in clinical neuroimmunology. Dr. Kruer established the Sanford Pediatric Neuroimmunology Clinic in Sioux Falls and currently serve as a specialist consultant in pediatric neuroimmunology at Phoenix Children's hospital, where he is also co-director of the hospital's Neurogenetics Program. Dr. Kruer has treated both adult and pediatric patients with ADEM, multiple sclerosis, autoimmune encephalitis, and related disorders. (Ex. A, p. 1.)

Dr. Kruer opined that "the constellation of fever starting so long after vaccine administration, elevation of liver enzymes, and prolonged fever all argue against vaccine-mediated injury." (*Id.* at 3.) First, Dr. Kruer stated that "fever onset 3 weeks later attributable to immunization is unheard of and is clinically and immunologically implausible." (*Id.* at. 2.) Additionally, Dr. Kruer stated that vaccines are not known to cause elevations of liver enzymes[12] or prolonged fevers as the facts in A.E.'s case provide. (*Id.* at 2.)

Further, Dr. Kruer contested A.E.'s ADEM diagnosis, emphasizing that there was no laboratory evidence to support an ADEM diagnosis and A.E.'s neuroimaging was not consistent with ADEM. (*Id.* at 3.) Specifically, Dr. Kruer found that Dr. Kinsbourne's characterization of A.E.'s levels of white blood cells in her cerebrospinal fluid (CSF) as

[12] During the hearing, Dr. Kruer later clarified that the elevated liver enzymes are "of unknown significance" and do not "clearly point us away" from an ADEM diagnosis. (Tr. 200-01.)

abnormal to be misleading, when, according to Dr. Kruer, A.E.'s protein levels were within normal value and therefore, not showing any CNS inflammation. (*Id.* at. 3.) Additionally, with regard to neuroimaging, A.E.'s symmetric pattern of involvement is not suggestive of ADEM and her diminished cerebral volume and delayed demyelination suggest that "another process (distinct from ADEM) is at work." (Ex. A, pp. 3-4.) Additionally, Dr. Kruer opined that A.E.'s prolonged fever was "inconsistent with ADEM-associated fever, which typically abates once the neurological symptoms begin." (*Id.* at. 4.) Dr. Kruer also found the fact that A.E.'s primary treating physicians did not treat her with ADEM therapeutics as supportive against a diagnosis of ADEM. (*Id.* at 3.) Ultimately, Dr. Kruer contested the diagnosis based on timing of A.E.'s fevers, the duration of her prolonged fevers, the elevated liver enzymes, the unreliable presence of elevated CSF protein, and lesions revealed in A.E.'s neuroimaging. (*See* Exs. A, C.) Dr. Kruer agreed that A.E. did not have leukodystrophy, but "[t]here are scores of other disorders which might present with the symptoms that AE did in the context that they occurred without invoking either ADEM or leukodystrophy." (Ex. A, p. 4-5.)

In his supplemental expert report, Dr. Kruer continued to challenge A.E.'s diagnosis, stating that "there are more factors arguing against ADEM than arguing for the diagnosis." (Ex. C, p. 3.) Dr. Kruer maintained that A.E.'s pattern of demyelination is crucial in diagnosing ADEM and that there exists a unifying diagnosis that explains A.E.'s baseline cortical atrophy and delayed myelination as well as her other symptoms. (*Id.* at 3-4.) In his opinion, it is "[m]ore likely, AE does NOT have ADEM and does NOT have a classic leukodystrophy (as captured in the medical records) but she does instead have a (likely neurogenic) disorder that features developmental delay, cortical atrophy, delayed myelination, and a waxing and waning of symptoms." (*Id.* at 3) (emphasis original).)

V. Discussion

Acute disseminated encephalomyelitis or "ADEM" is an immune-mediated demyelinating disorder of the central nervous system, often seen in childhood and generally considered to be monophasic. (Daniela Pohl et al., *Acute Disseminated Encephalomyelitis*, 87 NEUROLOGY S38 (2016) (Ex. A, Tab 4, p. 1).) It shares some characteristics with multiple sclerosis and often occurs post-infectiously. (*Id*.) It is generally understood as a syndrome of brain inflammation and demyelination occurring in temporal association to an antecedent event. (James J. Sejvar et al., *Encephalitis, myelitis, and acute disseminated encephalomyelitis (ADEM): Case definitions and guidelines for collection, analysis, and presentation of immunization safety data*, 25 VACCINE 5771, 5775 (2007) (Ex. 30, p. 5).) It shares many features with encephalitis, but is distinguished from acute encephalitis based on the predominance of demyelinating rather than cytotoxic injury. (*Id*.) Clinically, however, ADEM can be difficult to distinguish from encephalitis. (*Id*.) The "hallmark" of ADEM is the demonstration of scattered, focal or multifocal (disseminated) areas of inflammation and demyelination within the cerebral subcortical and deep cortical white matter. (*Id*.)

In this case, there is actually no dispute as to whether A.E.'s MMR and varicella vaccines can cause ADEM. Respondent's expert, Dr. Kruer, has agreed that they can. Rather, the primary focus of this case has been the question of whether A.E. actually suffered ADEM at all. Absent a diagnosis of ADEM, petitioners have not otherwise articulated any basis for concluding that A.E.'s injury was vaccine-caused. In resolving this question, I turn first to the disputed point of whether A.E.'s treating physicians diagnosed ADEM. Concluding that they did, I then separately consider whether that diagnosis was sound based on Drs. Kinsbourne's and Kruer's discussions of the relevant diagnostic criteria. Concluding that there is preponderant evidence favoring the diagnosis of ADEM, I then apply the three *Althen* prongs to the facts of A.E.'s case. Last, I examine whether respondent has established any causal factor unrelated to vaccination.

a. A.E.'s Treating Physicians Did Diagnose ADEM

As a threshold matter, a key aspect of respondent's defense in this case is his assertion that A.E.'s treating physicians never moved beyond a differential diagnosis to "definitely" or "conclusively" diagnose A.E. with ADEM. (ECF No. 74, pp. 13-14.) Although A.E.'s presentation clearly presented her physicians with a difficult diagnosis, respondent's line of reasoning is unpersuasive for two reasons. First, respondent downplays the seriousness with which A.E.'s treating physicians initially considered ADEM and post-infectious etiologies. Second, respondent does not give sufficient weight to the fact that the treaters ultimately concluded with the fullness of time that ADEM was her likely diagnosis.

Both respondent and Dr. Kruer assert that none of A.E.'s treating physicians actually diagnosed her with ADEM. (*Id.*; Tr. 161-62.) However, this is not accurate. As Dr. Kinsbourne addressed in his recitation of the medical records, A.E.'s later medical records include the explicit diagnosis of ADEM by Drs. Totlani (Ex. 47, p. 2), a pediatrician, and Legido, a neurologist. (Ex. 66, pp. 5-9; Tr. 73-76.) Dr. Legido's neurology record in particular included a complete recitation of A.E.'s prior history, including her presenting symptoms, hospital transfer, and reference to the difficulty in reaching a diagnosis.[13] (Ex. 66, pp. 5-6.) He diagnosed ADEM of either viral or post-

[13] In his prehearing brief, respondent notes that there is a reference in A.E.'s Good Shepherd Rehabilitation records to a discharge diagnosis of ADEM made at St. Christopher's Hospital. (ECF No. 74, p. 14, n.11 (citing Ex. 2, p. 329.) Respondent indicates that this is a mischaracterization, because A.E. was discharged from St. Christopher with only a differential diagnosis. (*Id*. (citing Ex. 2, p. 305.).) Respondent's observation is correct with regard to that specific notation, however, other assessments in the Good Shepherd records refer to the complete list of differential diagnoses. (Ex. 2, pp. 308-13.) In any event, this isolated reference is not a factor in this analysis. Nor is there evidence that this notation unduly influenced subsequent records. Dr. Legido's record also includes an abbreviated notation that characterizes A.E. as having been diagnosed with ADEM at St. Christopher's. (Ex. 66, p. 6 ("she was dx with ADEM.").) However, there are several reasons for understanding this notation as interpretive rather than mistaken. First, Dr. Legido is himself affiliated with St. Chistopher's and therefore a part of A.E.'s overall team of care providers that reached this differential diagnosis. Second, even though he was first consulted after A.E.'s hospitalization, he includes a substantive description of A.E.'s hospital course at St. Christopher's, clearly evidencing he is aware of her complete history and is not basing his opinion merely on the fact of a discharge diagnosis. (*Id*.) Third, the competing aspect of the differential diagnosis at St.

vaccine etiology. (*Id*. at 8.) Dr. Legido first became a part of A.E.'s care when she was seventeen months old. (*Id.* at 1.)

Dr. Legido's ultimate assessment was the culmination of a long history in which ADEM or post-infectious etiology more generally remained a durable aspect of a difficult differential diagnosis in contrast to other types of disorders, such as metabolic disorders, leukodystrophies, or other neurodegenerative conditions, all of which were eventually ruled out. (*See, e.g.*, Ex. 2, p. 297 (pediatrician recording hospital transfer to Lehigh Valley Hospital for "infectious ADEM"); Ex. 4, p. 4 (initial differential diagnosis including encephalitis); Ex. 2, p. 292 (initial neurology consultation indicates ADEM will need to be ruled out); Ex. 4, p. 101 (following first MRI, differential diagnosis including postinfectious encephalitis versus neurodegenerative disorder); Ex. 2, p. 303 (Lehigh Valley Hospital discharge diagnosis of West Nile virus encephalitis); Ex. 2, p. 297 (pediatrician recording hospital transfer to St. Christopher's Hospital for "infectious ADEM"); Ex. 5, p. 52 (upon initial evaluation at St. Christopher's Hospital noting of differential diagnosis that "post-infectious [etiology] seems more likely"); Ex. 1, p. 6-7 (discussing ADEM at length and noting of A.E. that she "doesn't appear to have acute infectious process but cannot rule out post-infectious process or neurologic causes."); Ex. 5, p. 117 ("unlikely acute infection of CNS or post-infectious CNS. Cannot exclude either."); Ex. 5, p. 35 (discharged from St. Chrisopher's with differential diagnosis of post-infectious encephalitis versus metabolic disorder); Ex. 7, p. 33 (second MRI interpreted as possibly including postinfectious demyelination); Ex. 2, pp. 138-40 (second opinion from neurologist Dr. Hopkins indicating after three MRIs that "the initial event was inflammatory, most likely infectious or parainfectious, but a metabolic disorder or leukodystrophy exacerbated by infection cannot be entirely ruled out."); Ex. 6, p. 1-2 (final MRI report indicating that "improving appearance raises the question of ADEM rather than leukodystrophy.").) Dr. Kruer explained during the hearing that, while ADEM, post-infectious encephalitis, and encephalitis, are different concepts, usage of the terminology is "a little bit inconsistent" and "the terms are used a little bit loosely by different practitioners." (Tr. 163.) He agreed that "ADEM is often thought to be post-infectious." (Tr. 164.)

Dr. Kruer did acknowledge that later records include the diagnosis of ADEM, but suggested that he "can't say with certainty" why that diagnosis was made and that his impression is that it was merely "carried forward" due to the lack of a clear alternative diagnosis. (Tr. 164-65.) In light of his own opinion that A.E.'s diagnostic possibilities should have been broadened to include evaluation for neurogenetic conditions, Dr. Kruer sought to explain this narrowing of A.E.'s differential diagnosis as merely "chart lore." (Tr. 162-65.) That is, Dr. Kruer suggests that once a set of potential diagnoses are charted by a group of physicians, those diagnoses take undue precedence in the minds of the physicians moving forward as acute care gives way to chronic

---

Christopher's was a metabolic disorder and Dr. Legido's reference to the prior ADEM diagnosis was immediately followed by his confirmation that a subsequent metabolic workup by Dr. Jethva was normal. (*Id*.) Fourth, the implicit crux of Dr. Legido's record as a whole is that he is closing out the differential diagnosis in favor of ADEM. He specifically indicates in his impression that A.E. now carries a "presumptive" diagnosis of ADEM in consideration of her repeat MRIs and improving clinical picture. (*Id*. at 8.)

management of symptoms. (*Id*.) Importantly, however, while this may be a relevant concern in the medical community, it is not axiomatic. It is not inherently bad for a physician treating residual effects or sequela to give weight to the direct observations or conclusions of another physician involved contemporaneously in earlier diagnosis and treatment. Especially in light of the St. Christopher records as a whole, including both Dr. Chen's initial "extensive" consideration of ADEM during hospitalization (Exs. 1, pp. 1-7, 59) and Dr. Legido's later explicit culminating diagnosis (Ex. 66, pp. 5-9), both of which are supported by records which reveal their thinking, Dr. Kruer's blanket skepticism is not persuasive. Effectively, Dr. Kruer's citation to chart lore in this case is a restatement of his disagreement with the treating physicians under a different guise and does not cast doubt on the *fact of* A.E.'s ADEM diagnosis as contained in the medical records

Dr. Kruer is correct, however, that during her hospitalizations and initial evaluations none of A.E.'s treating physicians *conclusively* diagnosed her with ADEM in light of ongoing evaluation. Dr. Kruer does acknowledge that ADEM was referenced throughout this medical history, and also that infectious disease specialist Dr. Chen considered the diagnosis "extensively." (Tr. 161-62.) Nonetheless, he opines that these assessments must be given less weight because treatment for ADEM was not initiated, opining that this constitutes "strong evidence" against the diagnosis having been made. (Tr. 138-40, 165, 183-84.) Dr. Kinsbourne in contrast opined that the hesitance in administering IVIG and steroids was due to the fact that these treatments are not free of risk or side effect and in the case of IVIG also expensive. (Tr. 103-04.) He also proposed that these treatments were not pursued later because A.E. was already improving. (Tr. 106.) Dr. Kruer disagreed, however, and stressed that IVIG and steroids are so low risk that the lack of treatment must signal the lack of a diagnosis. (Tr. 138-40, 183-84.) Neither expert's view finds strong support in the medical records.

In her consultation, Dr. Chen explained the basis for steroids and IVIG as treatments for ADEM and included discussion of such treatment among her recommendations. (Ex. 59; Ex. 1, p. 6.) She noted, however, that further review of A.E.'s MRIs should first be completed to confirm ADEM. (Ex. 1, p. 6.) Nonetheless, Dr. Kinsbourne persuasively noted, based on Dr. Chen's full discussion of the condition, that she must have intended ADEM to be part of her diagnostic impression, stating "I don't see how else you can interpret her train of thought and her complete emphasis on ADEM." (Tr. 104-06.) The recommended steroid and IVIG treatments were not subsequently administered at St. Christopher's, yet A.E.'s discharge indicated a differential diagnosis of "postinfectious encephalitis vs metabolic disorder," meaning that following Dr. Chen's consultation ADEM was explicitly not ruled out during A.E.'s subsequent hospitalization at St. Christopher's.[14] (Ex. 5, p. 35.) Dr. Chen did specifically stress in her discussion of steroids and IVIG treatments for ADEM that

[14] Dr. Chen herself appears to have used ADEM and "postinfectious encephalitis" interchangeably, writing in her discussion of ADEM that "[r]arely, vaccines can cause postinfectious encephalitis." (Ex. 1, pp. 6-7.) As noted above, Dr. Kruer confirmed that these terms are used loosely by different practitioners. (Tr. 163-64.)

"[t]here are no controlled clinical trials on treatments," perhaps providing some basis for suspecting Dr. Chen was doubtful of the efficacy of these treatments. (Ex. 59.) In any event, the medical records do not reveal any specific reason IVIG or steroids were not administered. Notably, both experts focused exclusively on the value of steroids and IVIG in treating ADEM and neither expert addressed what effect, if any, these treatments would have on a metabolic disorder, which was the other side of the differential diagnosis at St. Christopher's.

One additional clue exists in the truncation of A.E.'s hospitalization at Lehigh Valley Hospital when she was transferred to St. Christopher's Hospital. While still at Lehigh Valley Hospital, A.E. had a PICC line installed for the purpose of administering IVIG. (Ex. 4, pp.138, 157.) Shortly thereafter, the physicians at Lehigh Valley consulted Dr. Shulman at Children's Hospital of Philadelphia. (*Id.* at 181-82.) It was Dr. Shulman who recommended that Lehigh Valley not proceed with the IVIG in anticipation of the fact that A.E. would be transferred and additional infectious disease work up, likely including serum and antibody testing, would be explored. (*Id*.) During the hearing, Dr. Kruer confirmed his understanding that this was the reason that IVIG treatment was halted before being administered. (Tr. 186-88.) He explained that, because IVIG treatment introduced donor antibodies into the patient, it would confound any subsequent serum or antibody testing. (*Id*.) Once A.E. was transferred to St. Christopher's Hospital, she was seen for consultation by infectious disease specialist Dr. Chen. (Ex. 1; Ex. 59). As noted above, Dr. Kruer acknowledges that Dr. Chen "extensively considered" ADEM. (Tr. 162.) However, A.E. was still undergoing work up for a possible infectious etiology for her condition. (Ex. 1, 59.) Though Dr. Chen linked IVIG treatment to review of A.E.'s MRI, consistent with Dr. Kruer's explanation of Dr. Shulman's recommendation, Dr. Chen also felt that serum testing for Epstein Barr virus and cytomegalovirus was warranted, suggesting another reason Dr. Chen may have withheld IVIG treatment, at least initially. (Ex. 1, pp. 5-6.)

In sum, the record as a whole does not provide any meaningful discussion of why these treatments were not administered and both experts' explanations as to the motives of A.E.'s treating physicians are speculative. In contrast to Dr. Kruer's interpretation, the medical records reflect that A.E.'s IVIG treatment plan may be better understood as delayed or inchoate due to facility transfer and subsequent testing rather than never having been contemplated and the fact that A.E. did not receive IVIG or steroid treatment therefore does not appear to illuminate her physicians' thinking as to her correct diagnosis. "Since medical records typically record only a fraction of all that occurs, the fact that reference to an event is omitted from the medical records may not be very significant." *Murphy v. Sec'y of Health & Human Servs.,* 23 Cl. Ct. 726, 733 (Fed. Cl.1991), *aff'd,* 968 F.2d 1226 (Fed. Cir. 1992) (citing *Clark v. Sec'y of Dep't of Health & Human Servs.*, No. 90-45V, 1991 WL 57051 (Cl. Ct. Mar. 28, 1991)). Because A.E. was treated by multiple physicians at multiple facilities, all of whom were struggling with a challenging differential diagnosis, the medical records are inscrutable for any precise reason IVIG or steroids were not administered.

On the whole, petitioners persuasively contend that "[t]he medical records support the diagnosis of ADEM. The process by which the diagnosis was derived was lengthy, but that is simply the nature of this neurologic injury . . . [the treating physicians] simply followed a conservative path to the correct diagnosis." (ECF No. 84, p. 3.) In that regard, Dr. Kinsbourne repeatedly stressed that A.E.'s presentation in the longer course confirmed the monophasic course of A.E.'s condition. (Tr. 34-35, 38-39, 40-43, 68, 77, 89, 99-102, 107-08.) While Dr. Kruer stressed that ADEM is not the only monophasic condition that could potentially explain a course such as A.E.'s (Tr. 142-44, 194), Dr. Kinsbourne noted that the other specific conditions previously identified in A.E.'s differential diagnosis tended to be progressive (Tr. 61, 68, 89). In that regard it is significant that Dr. Legido likewise confirmed that his diagnostic opinion was specifically informed in part by "improving white matter changes on repeat MRI and improving clinical signs." (Ex. 66, p. 8.)

Accordingly, while this remains a difficult case and A.E.'s treating physicians did struggle to move beyond a differential diagnosis for a considerable period, the medical records, when viewed as a whole, include preponderant evidence that her treating physicians did ultimately, albeit remotely, arrive at a diagnosis of ADEM. This is significant because medical records are generally viewed as particularly trustworthy evidence created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993). Though neither binding nor sacrosanct, treating physician opinions are probative and are often afforded considerable weight in themselves. *Andreu ex rel. Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1376 (Fed. Cir. 2009); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1326 (2006) ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show [s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280).

b. Expert Analysis of A.E.'s Correct Diagnosis Further Supports Petitioners' Claim

i. Diagnostic Criteria at Issue

Turning to the expert presentations regarding diagnosis, the basic tenets of ADEM diagnosis are not meaningfully disputed. While Drs. Kinsbourne and Kruer cite to different diagnostic rubrics (by the Brighton Working Group Collaboration for Dr. Kinsbourne and by the International Pediatric Multiple Sclerosis Study Group for Dr. Kruer) the ultimate diagnostic requirements are essentially the same. The Brighton Working Group Collaboration includes multiple degrees of diagnostic certainty, but the International Pediatric Multiple Sclerosis Study Group sets forth a single list of findings, all of which must be present to render a diagnosis. However, under either approach, the basic elements of diagnosis are as follows:

- A polyfocal clinical CNS event with presumed inflammatory demyelinating cause; and

- Encephalopathy; and
- Brain MRI abnormalities consisting of diffuse or multifocal white matter lesions; and
- A monophasic pattern to illness; and
- No clear alternative diagnosis.

(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) (Ex. A, Tab 1); Pohl et al., *supra*, at Ex. A, Tab 4; Sejvar et al., *supra*, at Ex. 30.)

Applying this diagnostic framework, the experts both agree that A.E. demonstrated a monophasic pattern of illness. (Tr. 38-39, 197-98.) They also agree that A.E.'s initial presentation constituted a polyfocal clinical CNS event. Specifically, Dr. Kinsbourne highlighted a loss of milestones and especially a regression in motor skills and truncal hypotonia. (Tr. 19-23.) Dr. Kruer agreed more broadly that it is reasonable to consider A.E.'s presentation as a polyfocal clinical CNS event. (Tr.129.) The experts also agree that A.E.'s MRI showed abnormalities affecting white matter, specifically in the corona radiata and central semiovale, areas commonly affected by ADEM. (Tr. 58-59, 208.) Dr. Kruer also agreed that none of the specific alternative diagnoses proposed by the diagnostic literature fit A.E.'s case. (Tr. 144, 206.) Additionally, Dr. Kruer in particular stressed that there is no "gold standard test" for ADEM and that it is a clinical diagnosis. (Tr. 137-38.)

Where the experts disagree is on several finer points. Specifically, Dr. Kruer disagrees that there is evidence that A.E.'s polyfocal clinical CNS event had an inflammatory demyelinating cause and further disagrees that there is evidence of encephalopathy. Dr. Kruer also disagrees that A.E.'s specific MRI abnormalities are consistent with the accepted characteristics of ADEM lesions. And, finally, he opines that an unspecified neurogenetic disorder is more likely. Each of these points is discussed separately below. The evidence preponderates, albeit closely, in favor of the ADEM diagnosis on each point. Accordingly, despite being a close case and a somewhat atypical presentation, A.E.'s condition can be said to fit both the requirements of the International Pediatric Multiple Sclerosis Study Group framework favored by Dr. Kruer and the highest level of diagnostic certainty under the Brighton Working Group Collaboration's standard as favored by Dr. Kinsbourne.

ii. Polyfocal Clinical CNS Event with Presumed Inflammatory Demyelinating Cause

As noted above, Dr. Kruer agreed that it is reasonable to characterize A.E.'s presentation as a polyfocal CNS event. (Tr. 129, 157.) However, he does not agree that A.E.'s presentation is consistent with an inflammatory demyelinating event. (Tr. 129, 194-95.) The MRI evidence of demyelination is discussed separately below.

Turning to the question of clinical signs of inflammation, there are two possible indicators of CNS inflammation in this case, fever, and elevated protein in CSF.[15]

1. Fever

Dr. Kinsbourne opined that A.E.'s fever was in itself a neurological indicator and constituted the first manifestation of A.E.'s ADEM. (Tr. 121-22.) This is consistent with the literature filed in this case that recognizes fever as a prodromal symptom of ADEM. (Pohl et al., *supra*, at Ex. A, Tab 4, p. 3.) He also opined that the fever represents the inflammatory aspect of the condition. (Tr. 48-49.) This is likewise supported by the Brighton Working Group Collaboration, which explained in discussing CNS inflammation broadly that "[f]ever, while non-specific, is an easily measurable and reliable indicator of an inflammatory process; in the presence of the various additional criteria provided for nervous system dysfunction, it could allow for identification of likely cases of encephalitis without being overly specific."[16] (Sejvar et al., *supra*, at Ex. 30, p. 4.)

Dr. Kruer agreed that fever can be a prodrome symptom of ADEM preceding other symptoms (Tr. 140) and did not dispute that as a general matter fever is evidence consistent with the type of inflammation diagnostic of a relevant polyfocal clinical CNS event in ADEM. He did, however, opine that the timing and duration of A.E.'s own fever was inconsistent with the typical presentation of ADEM.[17] (Ex. A, p. 3; Ex. C, p.1; Tr. 140-41.) Dr. Kinsbourne agreed that the fever presentation would be atypical but stressed that it would still be within the ADEM diagnostic framework. (Ex. 36, p. 1; Tr. 102, 117-18.) A.E.'s neurologist, Dr. Hopkins, likewise explicitly provided a second opinion concluding that A.E.'s initial presentation was inflammatory as evidenced by her fever. (Ex. 2, pp. 139-40.)

Dr. Kinsbourne is correct in his assertion that the relevant diagnostic literature relied upon by the experts do not establish specific limiting factors for the duration of a prodromal fever in ADEM. (Ex. 36, p. 1; Sejvar et al., *supra*, at Ex. 30; Krupp et al., *supra*, at Ex. A, Tab 1; Pohl et al., *supra*, at Ex. A, Tab 4.) Moreover, both experts

[15] Dr. Hopkins also identified A.E.'s elevated erythrocyte sedimentation rate ("ESR") as an indicator that A.E. experienced an inflammatory process at onset. (Ex. 2, p. 140.) Dr. Kruer acknowledged the fact of the elevated ESR finding (Ex. A, p. 2), but the experts did not otherwise discuss the clinical value of the finding.

[16] Under the diagnostic criteria established by the Brighton Working Group, inflammation is not *required* as a diagnostic criterion demonstrating CNS inflammation in ADEM because it is often absent. (Sejvar et al., *supra*, at Ex. 30, p. 5.)

[17] In his supplemental report at Exhibit C, Dr. Kruer noted that Dr. Kinsbourne had responded only to his discussion of the atypicality of the duration of A.E.'s fever and left unaddressed his comment that the fever was too remote from vaccination to have been a vaccine reaction. (Ex. C, p. 1.) In response, Dr. Kinsbourne clarified that he is not of the opinion that A.E.'s fever was a post-immunization fever, but rather a marker of subacute onset of her ADEM. (Ex. 48, p. 1.) During the hearing, Dr. Kinsbourne further confirmed that his opinion is not that the fever itself was vaccine-related, but rather that the fever was caused by A.E.'s ADEM which was caused by her vaccination. (Tr. 96.)

stressed that ADEM is clinically heterogenous. (Tr. 84-85 (Kinsbourne), 136-37 (Kruer).) Additionally, Dr. Kinsbourne supported his view by citation to three separate case reports wherein the authors arrived at an ADEM diagnosis following prolonged fever. (Tr.45-51; Nahid Khosroshahi et al., *Acute Disseminated Encephalomyelitis in a 5-Month Old Infant*, 2 IRANIAN J. OF CHILD NEUROLOGY 53 (2008) (EX. 63); George Imataka & Osamu Arisaka, *An infant with steroid-refractory cytomegalovirus-associated ADEM who responded to immunoglobulin therapy*, 18 EUR. REV. FOR MED. PHARMACOLOGICAL SCIENCES 2148 (2014) (EX. 64); Margherita Di Costanzo et al., *Acute Disseminated Enephalomyelitis Presenting as Fever of Unknown Origin: Case Report*, 11 BMC PEDIATRICS 103 (2011) (EX. 65.) Dr. Kruer disputed the ADEM diagnosis in two of the three, but suggested he could not entirely dismiss the third.[18] (Tr. 191-93 (discussing Khosroshahi et al., *supra*, at Ex. 63; Imataka & Arisaka, *supra*, at Ex. 64; Di Costanzo et al., *supra*, at Ex. 65.) Ultimately, nothing in the record, apart from Dr. Kruer's own clinical judgment, rules out the possibility of a prolonged fever being associated with ADEM. Moreover, although he called the prolonged fever a clinical "red flag," Dr. Kruer was careful to couch his opinion in terms of what is typical of ADEM rather than what is more rarely seen in ADEM. (Tr. 140.) In that regard Dr. Kruer also acknowledged that "[i[t's hard to argue on the basis of symptoms alone that a child does not have ADEM, because ADEM can do quite a bit in term of what symptoms it can cause." (Tr. 137.)

An additional consideration is the relationship between onset of the fever and onset of the other symptoms of neurological damage. Dr. Kruer initially suggested that the fact that A.E.'s fever continued after onset of her neurological symptoms means her presentation is not explainable as ADEM. (Ex. A, p. 3.) Dr. Kinsbourne disagreed, citing a small retrospective study of 42 children diagnosed with ADEM. That study found that 67% of subject patients had a fever and 24% were febrile during hospitalization. (John A.D. Leak et al., *Acute Disseminated Encephalomyelitis in Childhood: Epidemiologic, Clinical and Laboratory Features*, 23 THE PEDIATRIC INFECTIOUS DISEASE J. 756, 759 (2004) (Ex. 52, p. 4).) Ultimately, Dr. Kruer testified regarding fever in ADEM that "[w]hen it is encountered, it can precede the onset of neurological symptoms, but not always." (Tr. 140.)

Finally, Dr. Kruer suggests that fever is in itself a nonspecific and common symptom and that in A.E.'s case it may be explained by an infectious illness. (Tr. 141, 195.) In A.E.'s specific case, however, her fever was recorded as being of unknown origin and an infectious etiology was never confirmed despite significant investigation.

[18] It is often noted that "[C]ase reports 'do not purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value'…. [but] 'the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" *See Paluck v. Sec'y of Health & Human Servs.,* 104 Fed. Cl. 457, 475 (2012) (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011). Here, I note that these case reports are not offered to prove causation, but only to reflect that the clinical presentation of certain symptoms at issue can be associated with the diagnosis of ADEM. In this context, case reports have a greater potential to be illuminating. Even if fully crediting Dr. Kruer's challenge as to the correctness of the ADEM diagnosis contained in each case report, they would still constitute some evidence suggesting that members of the relevant medical community agree that prolonged fever can potentially be viewed as consistent with ADEM.

Moreover, even if an infectious illness was present, that does not in itself call the diagnosis of ADEM into question as ADEM often follows infection. (*E.g*., Tr. 164.) In any event, even if fevers are generally nonspecific and common, A.E.'s own fever presentation occurred in a specific context, namely as prelude to a developmental regression. From the time of her initial hospitalization, A.E.'s fevers were considered a part of her overall clinical presentation rather than as a separate, coincidental illness. For example, upon admission to Lehigh Valley Hospital, Dr. Busse recorded:

> Diagnoses:
> - Neurodevelopmental
>
> Regression w/ loss of
> Truncal tone/head control
> - Fevers
>
> D[ifferential] D[iagnosis] tumor, encephalitis, GBS, metabolic [disorder]

(Ex. 4, p. 4.) In the same record she indicated "amoxicillin to be stopped/no evidence of active infection." (*Id*.)

Accordingly, there is preponderant evidence that A.E.'s fever, though prolonged, was a symptom of her ADEM. Additionally, there is preponderant evidence that A.E.'s fever constitutes evidence of a presumed inflammatory cause of her polyfocal clinical CNS event as required by the diagnostic criteria.

2. CSF test results

A more specific method of detecting CNS inflammation in ADEM is demonstration of leukocytes in the cerebral spinal fluid. (Sejvar et al., *supra*, at Ex. 30, pp. 3-4.) Dr. Kinsbourne did initially cite elevated white blood cells upon A.E.'s lumbar puncture. (Ex. 12, p. 2.) Specifically, while still at Lehigh Valley Hospital, a CSF test of June 29, 2012 showed 13 WBCs/cmm, 25, 111 RBCs/cmm and protein of 121 mg/dl. (Ex. 4, p. 79.) However, Dr. Kruer explained that A.E.'s CSF sample was contaminated by blood and her test result, though it "appears to be abnormal," actually lacks clinical value. (Ex. A, p. 3.) Dr. Kinsbourne concurred as to the white blood cell count, but contended that A.E. also had elevated protein in her CSF, which could be adjusted to account for the blood contamination and remained "substantially" elevated after adjustment. (Ex. 36, pp. 1-2 (citing Dean A. Seehusen et al., *Cerebrospinal Fluid Analysis*, 68 AM. FAM. PHYSICIAN 1103 (2003) (Ex. 40).) Dr. Hopkins recorded the same observation when she offered her second opinion indicating that A.E.'s initial presentation was inflammatory. (Ex. 2, p. 140.)

Dr. Kruer indicated in response that "[c]orrections can be helpful, but they are notoriously unreliable." (Ex. C, p. 1.) In support of that contention, however, Dr. Kruer cited a 1986 missive by Dr. Ryan Anbar primarily cautioning against *ruling out* a condition based on a traumatic tap with adjusted white blood cell count. (Ryan D. Anbar, *Pitfalls in Interpretation of Traumatic Lumbar Puncture Formula*, 140 AM. J. OF DISEASES OF CHILDREN 737 (1986) (Ex. C, Tab 1).) In any event, during the hearing, Dr. Kruer

characterized A.E.'s lab results as being less helpful in reaching his opinion. (Tr. 138.) He acknowledged that CSF lab results are helpful in confirming CNS inflammation, but "not absolutely required for a diagnosis of ADEM." (*Id*.)

While Dr. Kruer notes a need for caution that may temper the weight that can be placed on this finding, Dr. Kinsbourne is correct that A.E.'s CSF showed elevated protein even after adjusting for the traumatic tap. Balancing the competing opinions, it appears that A.E.'s CSF result does provide some additional and "helpful," albeit non-specific, evidence supporting the conclusion that her initial polyfocal CNS event had an inflammatory cause.

iii. Encephalopathy

For purposes of diagnostic criteria, "[t]he term 'encephalopathy' was defined by consensus and refers to an alteration in consciousness (e.g. stupor, lethargy) or behavioral change unexplained by fever, systemic illness or postictal symptoms." (Krupp et al., *supra*, at Ex. A, Tab 1, p. 3.) In that regard, Dr. Kinsbourne explained that A.E.'s records, including her initial hospital intake, reflect multiple explicit notations that A.E. was experiencing lethargy. (Tr. 17-19 (discussing Ex. 2, p. 285), 20-21 (discussing Ex. 4).) A later history also described A.E.'s initial presentation as being "less interactive." (Tr. 30-31 (discussing Ex. 2, pp. 9-13).) Additionally, Dr. Kinsbourne explained that these findings of lethargy did not track with the course of A.E.'s fever and therefore the fever could not explain the lethargy. (Tr. 118-20.)

Dr. Kruer did not agree that A.E.'s medical records contained evidence of encephalopathy. (Tr. 129-30.) He agreed that the lethargy recorded by the treating physicians is consistent with encephalopathy, but opined that it is nonspecific and inadequate to constitute a diagnosis of encephalopathy. (Tr. 131.) Instead, Dr. Kruer felt that because encephalopathy was directly relevant to the diagnostic assessment of ADEM, had the treating physicians felt encephalopathy was present, they would have explicitly recorded encephalopathy instead of only noting lethargy. (Tr. 131, 154-55.) Dr. Kruer agreed, however, that for a 13-month old like A.E., determining the presence of an encephalopathy would be a "series of observations" looking for appropriate responses. (Tr. 154.)

It is difficult to separate this aspect of Dr. Kruer's diagnostic impression from his overall interpretation of the medical records as not containing any ADEM diagnosis, which is a conclusion against the weight of preponderant evidence. This does warrant some consideration in weighing the competing expert opinions. *See, e.g.*, *Milik v. Sec'y of Health & Human Servs.*, 822 F.3d 1367, 1381 (Fed. Cir. 2016) (finding that the special master did not abuse his discretion in weighing expert testimony based in part on one expert's "flawed assumption" regarding onset). Contrary to Dr. Kruer's assessment, though much doubt remained at the time of A.E.'s initial presentation, the treating physicians on the whole seriously considered the possibility of ADEM during A.E.'s hospitalization and also ultimately, and much later, diagnosed ADEM. In light of the clear and well-established diagnostic standards, this necessarily includes a

judgement that an encephalopathy was likely present. Accordingly, the description of symptoms contained in the contemporaneous records should be viewed in that context.

Specific reference to lethargy first appears in the record by parental report to the pediatrician. (Ex. 2, p. 289.) That exam does not appear to confirm the finding, but did result in a consultation with Dr. Shaikh. (*Id*. at 290.) Looking closely at Dr. Sheikh's subsequent record of his initial neurology consultation with A.E., he initially elicited a parental report of A.E. "becoming more lethargic." (Ex. 4, p. 21.) He then indicates that he "interrogat[ed]" the parents to further reveal that she had stopped cruising, regressed in babbling and speaking, had balance issues, and "has a spacey look." (*Id*.) These observations are *potentially* consistent with altered consciousness, lethargy, confusion, or general malaise, which is how Dr. Kruer characterized encephalopathy.[19] (Tr. 154-55.) Dr. Sheikh then performed a neurological exam in which he noted A.E. to be "alert and awake," but also specifically recorded that he had confirmed that "she had a very spacey look," directly paralleling the parental observation, and also "appeared to be a little sluggish" in her movements.[20] (Ex. 4, p. 22.) A.E. was afebrile at the time of this exam. (*Id*. at 21.) Following this examination and history, Dr. Sheikh specifically indicated as part of this same record that the condition of ADEM, which, as discussed above, diagnostically includes encephalopathy, would need to be ruled out. (*Id*. at 22.) In sum, Dr. Sheikh elicited and recorded a parental history consistent with encephalopathy, confirmed that history with parallel language in his examination notes, and ultimately included the encephalopathic condition at issue in his differential diagnosis. Although Dr. Kruer is correct that a specific notation of encephalopathy would have been helpful, considering this neurology consultation as a whole and in the context of the complete medical records, the history, exam, and resulting impression, all point, albeit circumstantially, to the conclusion that Dr. Sheikh found or suspected the presence of an encephalopathy.

Accordingly, considering the medical records as a whole, there is preponderant evidence that A.E. suffered an encephalopathy consistent with the relevant diagnostic criteria.

---

[19] A.E.'s simultaneous, but separate, motor skill regression makes it more difficult to assess the reason(s) why A.E.'s activity level declined. For example, the fact that she stopped cruising and was having balance issues was likely related to her muscle tone issues. (Ex. 4, pp. 21-22.) However, the specific reports of lethargy, loss of babbling, and spacey look cannot reasonably be explained in relation to her motor skills. Dr. Kinsbourne did, however, separately suggest that A.E.'s loss of words may have been related to motor function issues, though this would be less easily applied to mere babbling. (Tr. 52-53.)

[20] Dr. Shaikh also noted on his physical exam that "[p]upils appear to be a little dilated, however, they were briskly reactive to light." (Ex. 4, p. 22.) During the hearing, I asked both experts about this finding. Neither expert opined that the finding was significant in A.E.'s own case, but both agreed that it is generally a nonspecific finding potentially consistent with encephalopathy. (Tr. 120-21 (Kinsbourne), 156-57 (Kruer).)

iv. MRI studies

Interpretation of A.E.'s MRIs represents the closest and most difficult question in her diagnostic picture. From June of 2012 to October of 2014, A.E. underwent MR imaging on five separate occasions. (Ex. 4, p. 118; Ex. 8, p. 18; Ex. 8, p. 3; Ex. 60, p. 1; Ex. 6, p. 1.) Each of the five MRI studies was reviewed and interpreted by a different radiologist or neuroradiologist. Additionally, Dr. Kruer reviewed all of the MRI studies and offered testimony regarding the first and last.[21] (Tr. 168.) A.E.'s diagnosing neurologist, Dr. Legido, also based his diagnostic impression on A.E.'s repeat MRIs. (Ex. 66, p. 8.) Additionally, A.E. received an additional neurology opinion from Dr. Hopkins, who reviewed four of the MRIs in consultation with a sixth neuroradiologist, Dr. Chowdury. (Ex. 2, pp. 139-41.)

The first MRI study of June 28, 2012 was conducted at Lehigh Valley Hospital and was interpreted by Dr. Joshua Bemporad. (Ex. 4, pp. 117-19.) Dr. Bemporad is a neuroradiologist.[22] As interpreted by Dr. Bemporad, this study was "concerning for volume loss" and also showed "decrease in the expected amount of myelination." (*Id*. at 118.) Dr. Bemporad's impression was that the study was "concerning for underlying neurodegenerative disorder." (*Id*.) Dr. Kinsbourne stressed, however, that Dr. Bemporad's impression as recorded is premised on a mistaken understanding that A.E. had not lost milestones. (Tr. 54-56.) Indeed, Dr. Sheikh's neurological consultation of the same date, which prompted the first MRI study, confirmed "significant regression." (Ex. 4, p. 22.) Dr. Kinsbourne also stressed more generally that the areas of decreased myelination implicated by A.E.'s MRIs, the corona radiata and centrum semiovale, are areas commonly affected by ADEM. (Tr. 58-59.) As noted above, Dr. Kruer likewise agreed these areas are commonly affected by ADEM. (Tr. 208.)

Comparing selected T2 weighted axial cuts of A.E.'s first MRI to an example of an ADEM-affected brain from Pohl, et al, Dr. Kruer opined that A.E.'s imaging showed hypomyelination, as developmental feature, rather than an inflammatory demyelinated lesion as expected in ADEM. (Tr. 173-76; Ex. D, p. 6.) Dr. Kruer highlighted two facets of comparison. First, the ADEM exemplar showed a developmentally "normal" brain as evidenced by the dark appearance of the white matter. (Tr. 174; Ex. D, p. 6 (right image).) In contrast, Dr. Kruer opined that A.E.'s image is not as dark as would be developmentally expected, meaning that there is hypomyelination. (Tr. 175-76; Ex. D, p. 6 (left images).) Interestingly, whereas Dr. Bemporad based his interpretation in part on the suggestion that A.E. had not lost milestones and further recommended additional

[21] Dr. Kruer testified that he reviewed all of the MRI studies that were conducted; however, he misidentified the number of studies as four rather than five. (Tr. 168.) The specific images he presented testimony regarding were from the studies dated June 28, 2012 and October 31, 2014. (Ex. 4, p. 118; Ex.6.)

[22] The medical record does not specify whether Dr. Bemporad is a neuroradiologist; however, his qualifications are listed on the Lehigh Valley Health Network website. *See* https://www.lvhn.org/doctors/joshua-bemporad, last accessed February 5, 2021.

clinical correlation, Dr. Kruer indicated that delayed myelination should not require clinical correlation. (Tr. 176.)

Second, in comparing A.E.'s T2 weighted imaging to the exemplar, Dr. Kruer opined that A.E.'s imaging lacks comparable "fluffy kind of confluent cloud-like white matter lesions." (Tr. 174.) On later questioning, however, he acknowledged that additional images in his presentation that have undergone post-processing by FLAIR (fluid attenuated inversion recovery) do provide evidence of white matter lesions. (Tr. 178-79.) However, he opined that these remain inconsistent with ADEM due to having a symmetrical presentation. (*Id*.)

The second MRI study of October 25, 2012 was conducted on behalf of Nemours Dupont Hospital at Lehigh Magnetic Imaging Center and was interpreted by Dr. Jason Zicherman, a neuroradiologist.[23] (Ex. 8, p. 1.) In this second MRI, volume loss was still noted, but characterized as mild. (*Id*.) Dr. Zicherman observed patchy, but "fairly symmetric," hypomyelination. In contrast to Dr. Bemporad, Dr. Zicherman felt the clinical history suggested that the finding could represent postinfectious demyelination rather than hypomyelination. (*Id*.) There is no specific indication this second MRI study was compared to the first, though Dr. Zicherman did reference a "suggestion of some improvement in demyelinating pattern." (*Id*.) Dr. Kruer did not discuss the specific finding of this study in either his reports or his testimony.

The third MRI study was conducted on July 26, 2013, again at Lehigh Valley Magnetic Imaging Center on behalf of Neumours Dupont Hospital. (Ex. 8, p. 3.) However, this study was interpreted by Dr. Elliot Shoemaker, who is listed as a radiologist.[24] In this instance, comparison was made to the prior October 25, 2012 study. (*Id*.) Dr. Shoemaker indicated that the white matter hyperintensity is "nonspecific" in appearance, but felt it could be consistent with leukodystrophy, which was noted to be consistent with A.E.'s history. (*Id*.) Dr. Shoemaker mostly focused on the degree of hyperintensity and did not address whether the abnormality was symmetrical. (*Id*.) The report includes no discussion of volume loss. Dr. Kruer did not discuss the specific finding of this study in either his reports or his testimony.

The fourth MRI study was conducted on behalf of Neumours Dupont Hospital by an unspecified outside facility on September 18, 2013 and was interpreted by neuroradiologist Dr. Kandula. (Ex. 60, pp. 1-4; Ex. 2, pp. 137-141.) Comparison was made to the first and second MRI studies of June 28, 2012 and October 25, 2012 respectively, but not to the third study. (Ex. 60, p. 1.) Here, the hyperintensities are specifically noted to be both asymmetrical and patchy. (*Id*.) Mild volume loss is noted. (*Id*. at 2.) The findings were considered "nonspecific," but the differential diagnosis

[23] As with Dr. Bemporad, there is no indication of the face of A.E.'s medical record that Dr. Zicherman is a neuroradiologist; however, his qualifications are listed on the Lehigh Valley Health Network website. *See* https://www.lvhn.org/doctors/jason-zicherman, last accessed on February 5, 2021.

[24] Qualification in neuroradiology cannot be confirmed for Dr. Shoemaker based on the record of this case or on the relevant facility's website.

included nonviral encephalitis with clinical correlation recommended. (*Id*.) Dr. Kinsbourne testified that nonviral encephalitis would include ADEM and that the other conditions listed in the differential diagnosis (SSPE and PML) are inflammatory demyelinating disorders, but could not explain A.E.'s condition because they are progressive and that has not been her course. (Tr. 60-61.) Dr. Kruer did not discuss the specific findings of this MRI study, but did agree that A.E.'s course was monophasic rather than progressive. (Tr. 197-98.)

The fifth and final study was performed on October 31, 2014 by the Lehigh Valley Health Network and was interpreted by Dr. Mark A. Osborne, a radiologist.[25] (Ex. 6, pp. 1-2.) Comparison was made to the third MRI study of July 26, 2013. (*Id*. at 1.) According to Dr. Osborne, A.E.'s brain was of "normal size, configuration." (*Id*.) He indicated "[a]s previously on FLAIR scan there are too numerous to count ill-defined, patchy high signal intensity in cerebral white matter." (*Id*.) Dr. Osborne also observed that the white matter abnormalities were improving and therefore opined that "[t]his improving appearance raises the question of ADEM rather than leukodystrophy. Clinical correlation is recommended." (*Id*. at 2.) Dr. Kinsbourne stressed during his testimony the fact that Dr. Osborne was provided a history of leukodystrophy, which was the impression provided on the prior MRI study to which Dr. Osborne compared his study. (Tr.61-63; Ex. 8, p. 17.) According to Dr. Kinsbourne, the fact that Dr. Osborne suggested ADEM in contrast to the provided history should carry extra weight. (Tr. 61-63.)

Dr. Kruer opined that this final MRI demonstrated some interval improvement in myelination, but that delayed myelination persists in the posterior area. (Tr. 177; Ex. D, p. 7.) However, he opined that "this shows that there has been interval improvement, there has been positive development, radiologically, but again, I think it stands in sharp contrast to what's typical for ADEM, which is where one has a developmentally appropriate brain upon which are superimposed these fluffy cloud-like lesions. So to me, again, this is fundamentally not consistent with ADEM from a radiological standpoint." (Tr. 177.)

Among those interpreting A.E.'s MRI studies, a majority suggested that her imaging is potentially consistent with ADEM. Dr. Osborne explicitly referenced ADEM, while Dr. Kandula's prior September 18, 2013 radiology report included nonviral encephalitis in the differential diagnosis and noted the findings to be patchy and asymmetrical. (Ex. 8, p. 17; Ex. 60, pp. 1-4.) Dr. Zicherman felt that postinfectious demyelination was possible in preference to hypomyelination. (Ex. 8, p. 1.) Upon review of A.E.'s repeat MRIs, Dr. Legido likewise concluded that A.E.'s diagnosis was ADEM. (Ex. 66, p. 8.) Dr. Hopkins and Dr. Chowdury reviewed four of the five MRIs and stressed the lack of progression. (Ex. 2, p. 140.) Dr. Hopkins opined that the pattern of white matter involvement is "atypical" of ADEM, but stressed that ADEM fit

[25] Dr. Osborne's qualifications as listed on the facility's website do not indicate any additional qualification in neuroradiology. *See* https://www.lvhn.org/doctors/mark-osborne, last accessed on February 5, 2021.

the clinical history of a post-vaccination inflammatory event with encephalopathy and further noted the likelihood of an infectious or parainfectious etiology. (*Id*.)

Only Dr. Bemporad offered any kind of confidence that A.E.'s MRIs reflected hypomyelination and not demyelination. However, Dr. Kinsbourne reasonably calls Dr. Bemporad's impression into question based on his misapprehension of the clinical history. (Ex. 4, pp. 117-19; Tr. 54-56.) In any event, Dr. Kruer did ultimately acknowledge that A.E.'s first MRI evidenced white matter lesions in addition to what he interpreted as hypomyelination. (Tr. 178-79.) To the extent Dr. Shoemaker alternatively favored leukodystrophy, Dr. Kruer disagreed that A.E. suffered leukodystrophy. (Tr. 144.)

Dr. Kruer's basis for rejecting the white matter lesions seen in A.E.'s MRI as evidence of ADEM was that they were symmetrical in appearance. (Tr. 178-79.) However, this interpretation was not shared by the treating radiologists on the whole. The September 18, 2013 report specifically noted the lesions to be asymmetrical. (Ex. 60, pp. 1-4.) Dr. Osborne additionally characterized the lesions as "too numerous to count" and "ill-defined," characteristics that call into question any clear delineation of symmetry, and also specifically raised the question of ADEM in his report. (Ex. 6, p. 1.) Even Dr. Zicherman, the one radiologist that specifically cited symmetrical lesions was equivocal in describing them as "fairly" symmetrical. (Ex. 8, p. 1.) Importantly, the confirmed monophasic course of A.E.'s condition indicates that the radiologists were all interpreting the same lesions, albeit with interval improvement.

The other notable finding discussed by Dr. Kruer is the presence of volume loss; however, this finding neither supports nor contradicts petitioners' claim. To the extent Dr. Bemporad described atrophy, Dr. Kruer would disagree. (Tr. 180.) However, as with the hypomyelination he observed, Dr. Kruer did opine that this finding is more in keeping with a developmental abnormality than ADEM. (*Id*.) Dr. Kruer indicated that the improvement in A.E.'s volume loss from the time of her first MRI to her last is consistent both with a developmental process and potentially with the type of neurogenetic condition he posits. (Tr. 180-81.) Dr. Kruer also agreed as a general matter that ADEM can result in atrophy, but opined that the severity necessary for that finding to be present is not comparable to A.E.'s case. (Tr. 180.) Importantly, however, there was not agreement among the reviewing radiologists as to the significance of these findings. Some opined that A.E.'s imaging reflected demyelination rather than hypomyelination. Moreover, the finding of volume loss did not prevent Drs. Zicherman and Osborne from specifically invoking ADEM. In any event, even if A.E. did have features of developmental abnormality inclusive of hypomyelination and volume loss, Dr. Kruer acknowledged that A.E. additionally had white matter lesions. (Tr. 178-79.) Accordingly, while the interpretation of the MRIs as showing developmental abnormality may partially inform Dr. Kruer's overall assessment, it does not invariably lead to the conclusion that ADEM was not also present based on the presence of additional lesions consistent with ADEM.[26]

[26] On this specific point, Dr. Kruer cited to Occam's razor as a central tenet of clinical diagnosis. (Ex. C, p. 2.) Specifically, he notes that "[a]pplied to diagnosis, Occam's razor indicates that A.E. is more likely to

It is important to note Dr. Kruer is not a radiologist, but does review MRI imaging in his clinical practice.[27] (Tr. 166-67.) In that regard, petitioners objected during the hearing to the presentation of Dr. Kruer's testimony regarding the MR imaging as expert testimony. (Tr. 166.) Petitioners stressed that Dr. Kruer is not a radiologist and not specifically trained in radiology. (*Id*.) Petitioners distinguished between the ability of a physician to review MRIs in clinical practice and the qualification necessary to offer expert testimony criticizing the opinions of board-certified radiologists. (*Id*.) Petitioners raise an important point; however, a treating neuroradiologist's opinion is not *per se* controlling as to the correct interpretation of an MRI study. *Nuttall v. Sec'y of Health & Human Servs*., 122 Fed. Cl. 821 (2015) (finding the special master did not abuse his discretion by weighing expert opinion more heavily than the report of a treating neuroradiologist), *aff'd* 640 Fed. Appx. 996 (Fed. Cir. 2016). Accordingly, I advised petitioners during the hearing that I would permit Dr. Kruer's testimony, but consider their argument with regard to the weight of that testimony. (Tr. 166.)

Here, Dr. Kruer's testimony provides important additional explanation regarding the diagnostic considerations that are attendant to interpretation of MR imaging relative to ADEM. His testimony is persuasive on those points and this is information not easily discernable from the face of the radiology reports. However, in terms of exercising interpretive, clinical judgment with respect to the specific images themselves, Dr. Kruer has acknowledged that this is a very difficult case radiologically speaking and that the many different radiologists and neuroradiologists consulted in A.E.'s care differed in their interpretations of the same findings. (Tr. 209.) Also significant is that Dr. Kruer offered opinions only as to two out of five MRI studies conducted in this case.[28] In that regard, A.E.'s diagnosing neurologist, Dr. Legido, arrived at his ultimate and competing

---

have a single unifying diagnosis that explains her baseline cortical atrophy and delayed myelination as well as the symptoms she developed in June 2012 than she is to have both random cortical atrophy/delayed myelination AND ADEM. (*Id*. at 2-3 (emphasis original).) While this represents a reasonable guiding principle, at some point the principle of parsimony envisioned by Occam's razor must give way to a difficult or unusual diagnostic picture where simple or usual explanations are exhausted, especially where no other unifying diagnosis has been identified. Occam's razor holds in effect that the simplest explanation is *usually* the best. In that regard, in addition to testifying that A.E.'s imaging was not consistent with ADEM in his opinion, Dr. Kruer did also testify that A.E.'s imaging was "unusual" and "not a classic, common presentation" more generally and without reference to any specific diagnosis. (Tr. 209.) In effect, this aspect of Dr. Kruer's opinion is premised on the idea that it is too unlikely that a developmentally delayed child would experience ADEM from a post-infectious process. While this may find support in a general statistical sense, Dr. Kruer has offered no opinion that it is impossible or improbable in a pathophysiological sense. In fact, Dr. Kruer did separately opine that a reasonable alternative explanation would be that A.E. had underlying neurological dysfunction brought to attention or "unmasked" by her acute illness, raising the very question of whether that acute event could nonetheless be ADEM. (Tr. 143.)

[27] He also suggested that his interpretation of MRI images has been subjected to peer review insofar as he has included MRI imaging in prior papers he has published. (Tr. 167.)

[28] I also asked Dr. Kruer to confirm whether the specific images of axial cuts he presented during the hearing were the best views to capture the findings at issue. He indicated that they were "very reasonable" but not beyond argument. (Tr. 208.)

impression of ADEM based on the clinical significance of the repeat MRI findings. (Ex. 66, p. 8.) Given the closeness of this case and the number of qualified individuals who have interpreted the same images with inconsistent results, there is no basis for giving outsized weight to Dr. Kruer's interpretation as compared to the other interpretations present in this record.[29]

Based on all of the above, and in consideration of Dr. Kruer's testimony as well as the opinions of all of the neurologist, radiologists, and neuroradiologists to have reviewed A.E.'s MRI studies, there is preponderant evidence that A.E.'s imaging demonstrates diffuse or multifocal demyelinating white matter lesions consistent with a diagnosis of ADEM.

v. Alternative diagnoses

In addition to the above, respondent may also present evidence relating to an alternative cause to demonstrate the inadequacy of petitioner's evidence supporting her case in chief. *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1353 (Fed. Cir. 2008). Moreover, the diagnostic criteria for ADEM suggest that ADEM is itself a "diagnosis of exclusion." (Pohl et al., *supra*, at Ex. A, Tab 4, p. 2.) In that regard, Dr. Kruer has opined that he believes that A.E. has a neurogenetic condition and that whole exome sequencing would be appropriate. (Tr. 135-36.) Critically, however, "the Vaccine Act does not require the petitioner to bear the burden of eliminating alternative causes where the other evidence on causation is sufficient to establish a prima facie case." *Walther v. Sec'y of Health & Human Servs.*, 485 F.3d 1146, 1150 (Fed. Cir. 2007). The Court of Federal Claims has also similarly observed that petitioners do not bear a burden to "discount *every* potential cause that exists within the entire realm of possibility." *Pafford ex rel. Pafford v. Sec'y of Dep't of Health & Human Servs.*, 64 Fed. Cl. 19, 35 (2005) (emphasis original), *aff'd* 451 F.3d 1352 (Fed. Cir. 2006).

In this case, Dr. Kruer does not suspect any specific neurogenetic condition that may be present. Nor has A.E. undergone any genetic testing that would reveal such a condition. Instead, Dr. Kruer opines in effect that advances in genetic testing make exploration of such conditions medically reasonable. (Tr. 135-36, 204-05.) The diagnostic criteria Dr. Kruer prefers as authoritative, Pohl et al., provides further guidance relevant to the exploration of differential diagnoses. (Pohl et al., *supra*, at Ex. A, Tab 4.) Pohl et al. includes a table of "red flags for a diagnosis of ADEM and possible differential diagnoses." (Pohl et al., *supra*, at Ex. A, Tab 4, p. 4 (Table 3).) Consistent with Dr. Kruer's opinion in this case, that table lists "genetic/metabolic disorders" as possible causes of diffuse, symmetrical brain lesions upon imaging. (Tr. 204-05; Pohl et al., *supra*, at Ex. A, Tab 4, p. 4 (Table3).) However, Pohl et al., also includes a further table that more specifically provides for "Differential diagnosis of

[29] Notably, this case presents a far different scenario than what was examined in the prior *Nuttall* case. In *Nuttall*, the special master had to distinguish between two detailed competing expert presentations that focused on distinctions of clinical judgment well beyond what was discernable from the radiology reports. *Nuttal v. Sec'y of Health & Human Servs.*, No. 070810V, 2015 WL 691272 (Fed. Cl. Spec. Mstr. Jan. 20, 2015), *aff'd* 640 Fed. Appx. 996 (Fed. Cir. 2016). Moreover, there were far fewer radiology and neuroradiology records in that case. *Id*.

ADEM guided by MRI." (Pohl et al., *supra*, at Ex. A, Tab 4, p. 4 (Table 4).) This table provides a further list of specific conditions that may be implicated by atypical MRI findings. (*Id*.) During the hearing I confirmed with Dr. Kruer that he agrees that none of the listed conditions are implicated by A.E.'s own medical history as reflected in her medical records. (Tr. 206.) This also includes leukodystrophies, which was referenced as part of A.E.'s own differential diagnosis. (Tr. 144.)

I also asked Dr. Kruer to explain more generally the interplay between his opinion as to the need to explore neurogenetic conditions and the idea of ADEM as a diagnosis of exclusion. He testified:

> ADEM is a diagnosis of exclusion in the sense that ADEM is not an appropriate diagnosis if there's a different distinct specific diagnosis that seems to fit better. So it's a diagnosis of exclusion in that context, but I think it's also a diagnosis of inclusion. That's why they have these criteria, because it's not simply that anything that has new onset neurological symptoms as ADEM until proven otherwise. ADEM is a specific entity that's been shown over time to be diagnostically specific, and it has to pass the common sense test. It has to look like ADEM, it has to present like ADEM, it has to act like ADEM, it has to have the imaging consistent with ADEM. And so if you don't have these things, then I think it fundamentally questions whether ADEM is present. I believe your question is if I think ADEM is there, do I look for neurogenetic conditions. No, I don't. If I believe that ADEM is the fundamental diagnosis, I'll treat it as ADEM. I'll reasonably go through some of these alternative diagnoses with some testing, but if it looks and acts like ADEM, I'll treat it like ADEM.

(Tr. 207-08.)

Dr. Kruer has confirmed that none of the specific alternative diagnoses suggested by the relevant diagnostic criteria are implicated. Moreover, in light of the preceding analysis, there is preponderant evidence that A.E.'s condition is consistent with the diagnostic criteria for ADEM. Although he would disagree with the latter conclusion, Dr. Kruer's above testimony confirms that in that context he would not necessarily search for a neurogenetic condition. Accordingly, petitioner has no burden to exclude the possibility of any neurogenetic condition either as a function of the generally accepted diagnostic criteria for ADEM or the specific legal requirements of this program.

vi. Dr. Kinsbourne's Testimony is Credible and Reliable

Implicit in respondent's counsel's questioning during the hearing is an argument by respondent that Dr. Kinsbourne's qualification to opine in this case should be doubted relative to Dr. Kruer. Respondent stresses that Dr. Kinsbourne has been retired from clinical practice for a considerable amount of time. (Tr. 95-96.) Although this point is clearly reasonable in a general sense, it is of reduced significance in the specific

context of this case. The nature and circumstances of Drs. Kinsbourne's and Kruer's opinions in this case inform this conclusion.

Especially because, as described above, I have found that A.E.'s treating physicians did ultimately reach a diagnosis of ADEM, this case in many ways presents a contrast of Dr. Kruer versus the treating physicians rather than Dr. Kruer versus Dr. Kinsbourne. Dr. Kinsbourne has not presented any assessment of diagnosis and causation that is distinct from those of the treating physicians. Nor, for that matter, has respondent meaningfully disputed through Dr. Kruer that the MMR and varicella vaccines are capable of causing ADEM as a matter of general medicine. (Tr. 210.) Rather, the role of Dr. Kinsbourne's opinion in this evaluation has largely been related to (1) assessing and further explaining the record notations demonstrating why the treating physicians felt A.E.'s presentation was potentially consistent with ADEM and (2) providing further explanation linking A.E.'s presentation to the relevant diagnostic medical literature that has been filed in this case.

While Dr. Kruer has stressed that the last ten years "have been an exciting time" in pediatric neurogenetics, that discussion focused in significant part on advancements in whole exome sequencing that have allowed for the discovery of additional neurogenetic disorders. (Tr. 132-34.) Significantly, however, in light of the fact that A.E. never had such testing performed, Dr. Kruer's reports and testimony regarding these more recent advances were never more specific than to identify the fact of this method of testing as being available and hypothetically revealing. With regard to the more concrete and specific diagnostic considerations of ADEM, Dr. Kruer did prefer newer diagnostic criteria from 2013 by the International Pediatric Multiple Sclerosis Study Group (and subsequent update by Pohl, et al) to Dr. Kinsbourne's reliance on the criteria developed in 2007 Brighton Working Group Collaboration; however, Dr. Kruer described the newer criteria only as a more concise and conceptual evolution of the relevant criteria. (Tr. 145-46.) Although Dr. Kruer indicated that his own reliance material was "authoritative" and "up-to-date," he did not indicate that the Bright Working Group criteria are wrong or antiquated, that the different sets of diagnostic criteria render different results, or that Dr. Kinsbourne's reliance on the Brighton criteria is unreasonable. (*Id*.)

Where both parties offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder ex rel. Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 742-43 (2009) (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)); *see also Isaac v. Sec'y of Health & Human Servs.*, No. 08–601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. Appx. 999 (Fed. Cir. 2013) (citing *Cedillo v. Sec'y of Health*

& Human Servs., 617 F.3d 1328, 1339 (2010)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly ex rel. Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1325–26 (2010) ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

In determining whether a particular expert's testimony was reliable or credible, a special master may consider whether the expert is offering an opinion that exceeds the expert's training or competence. *Walton v. Sec'y of Health & Human Servs.*, No. 04–503V, 2007 WL 1467307, at *17–18 (Fed. Cl. Spec. Mstr. Apr. 30, 2007) (otolaryngologist not well suited to testify about disciplines other than her own specialty). While (in keeping with the liberality with which evidence offered in Vaccine Program cases is treated) all testimony of the experts offered at the entitlement hearing was heard and considered, a special master may properly evaluate, and give appropriate weight to, whether certain testimony is beyond a particular expert's purview. *See e.g., King v. Sec'y of Health & Human Servs.*, No. 03–584V, 2010 WL 892296, at *78–79 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (petitioner's expert far less qualified to offer opinion on general causation issues pertaining to autism than specific issues pertaining to the petitioner's actual medical history, given the nature of the expert's qualifications).

With that standard in mind, I would not place Dr. Kinsbourne's opinion on equal footing with Dr. Kruer with regard to clinical judgments, such as the validity of neurogenetic testing or MRI interpretation, that are directly affected by medical advancements of the last several decades. However, petitioner has not presented Dr. Kinsbourne to opine on these points. Dr. Kruer's testimony is effectively unrebutted regarding neurogenetic conditions more broadly and Dr. Kinbourne deferred to A.E.'s medical records regarding interpretation of her MRI results. In contrast, respondent has not substantiated that advancements in medicine since Dr. Kinsbourne's retirement have left him unable to interpret medical records, recognize core neurologic signs or symptoms of encephalopathy, or review and appreciate relevant medical literature regarding diagnostic standards. And significantly, Dr. Kinsbourne has testified that he does have prior experience (albeit remote) in the clinical setting treating the specific condition at issue. (Tr. 5-6.)

Accordingly, Dr. Kinsbourne is qualified to offer the opinion that he has presented in this case and I see no reason to doubt that his opinion as offered in this case is credible and reliable. This is consistent with my prior experience with Dr. Kinsbourne. In a prior case involving infantile spasms, I was critical of Dr. Kinsbourne for presenting a theory beyond his expertise and questioned the quality of his testimony.[30] *Kottenstette v. Sec'y of Health & Human Servs.*, No. 15-1016V, 2020 WL 4197301 (Fed.

[30] Of note, I was not the special master who presided over that hearing. Rather, due to that special master's retirement, I addressed that case for the first time on remand.

Cl. Spec. Mstr. June 2, 2020), *review denied, decision aff'd*, No. 15-1016V, 2020 WL 4592590 (Fed. Cl. July 27, 2020). However, in another case, I accepted his opinion testimony regarding the basic neurologic injury of radial neuritis and explained that I found him to be a "conscientious" reviewer of the medical records. *Kirby v. Sec'y of Health & Human Servs.*, No. 16-185V, 2019 WL 6336026 (Fed. Cl. Spec. Mstr. Nov. 1, 2019), *review granted, decision rev'd on other grounds*, 148 Fed. Cl. 530 (2020).

c. Petitioner Has Satisfied the *Althen* Test with Respect to ADEM

i. *Althen* Prong One

Under *Althen* prong one, petitioners must provide a "sound and reliable" medical theory, demonstrating that the vaccine received can cause the type of injury alleged. *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019). In this case there is no dispute as to *Althen* prong one. In his first report, Dr. Kinsbourne opined that both the MMR and varicella vaccines can cause ADEM. (Ex. 12, pp. 5-6; see also Tr. 86-87.) During the hearing, Dr. Kruer likewise agreed that these two vaccinations can cause ADEM as a matter of general medicine. (Tr. 210.) Two of A.E.'s treating physicians also indicated that ADEM can be vaccine-caused. (Ex. 1, pp. 6-7 (Chen, infectious disease); Ex. 66, p. 8 (Legido, neurology).) Dr. Chen specifically identified the MMR vaccine as a rare cause of ADEM. (Ex. 1, pp. 6-7.) Accordingly, petitioners have satisfied *Althen* prong one.

ii. *Althen* Prong Two

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show [s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder,* 88 Fed. Cl. at 746 n.67 ("there is nothing ... that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted").

Here, for all the reasons discussed above there is preponderant evidence that A.E. did have ADEM rather than any unspecified neurogenetic condition. This conclusion is based both on the opinions of A.E.'s treating physicians as well as the

above assessment of the parties' expert presentations. Further, there is preponderant evidence that A.E.'s presentation, including her prolonged fever, is itself consistent with onset of ADEM. Additionally, both Dr. Kruer and Dr. Kinsbourne agreed that ADEM can be caused by an antecedent event, including vaccination. (Tr. 86-87, 121, 202-03, 210.) Dr. Kinsbourne further provided an affirmative opinion that A.E.'s own presentation is consistent with a logical sequence of cause and effect demonstrating A.E.'s ADEM to be vaccine-caused. A.E.'s treating physicians likewise concluded that A.E.'s ADEM may have been vaccine caused. Dr. Chen and Dr. Legido both specifically considered that possibility and Dr. Legido ultimately concluded in finalizing A.E.'s diagnosis that the etiology of A.E.'s ADEM could not be distinguished as between infection or vaccination. (Ex. 66, p. 8.) Notably, however, no specific infectious agent was ever confirmed. In any event, because A.E.'s clinical history presents a logical sequence of cause and effect consistent with vaccine causation, petitioners would not bear a burden of eliminating infection as an alternative cause.[31] *Walther*, 485 F.3d at 1151 (stating that "the petitioner generally has the burden on causation, but where there are multiple independent potential causes, the government has the burden to prove that the covered vaccine did not cause the harm."). Accordingly, in light of all of the above, petitioners have satisfied *Althen* prong two.

iii. *Althen* Prong Three

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan*, 539 F.3d at 1352. Here, there is no debate as to what constitutes a medically acceptable temporal relationship. The experts both agreed that onset of ADEM within four weeks of an antecedent event is medically reasonable. (Tr. 78-81 (Kinsbourne), 203 (Kruer).) Accordingly, A.E.'s varicella and MMR vaccinations having been administered on April 27, 2012, onset of vaccine-caused ADEM should be evidenced by about May 25, 2012.

Dr. Kinsbourne identified both fever and ataxia as presenting symptoms for ADEM. (Tr. 51-52; 121-22.) As addressed above, Dr. Kruer disagreed that A.E.'s fever was attributable to ADEM, but did agree that fever can be a prodrome of ADEM. (Tr. 140.) Although there are some inconsistencies in the notations addressing onset of A.E.'s fever course and other neurologic symptoms, the earliest record places onset of illness broadly at 17 days prior to June 7, 2012, or approximately May 21, 2012, with "high" fever beginning three days prior, or about June 4, 2012. (Ex. 2, p. 277.) At this visit there is also the report of a symptom of likely ataxia (i.e. a notation of "balance off"). (Ex. 2, p 277; Tr. 13-14.) No separate onset is recorded for the loss of balance. (Ex. 2,

[31] Even if a viral illness had operated in conjunction with A.E.'s vaccinations to cause ADEM, petitioners would still be able to meet their burden of proof. *Shyface*, 165 F.3d at 1353 (explaining that although the Shyfaces did not prove that the DPT vaccine was the only or predominant cause of his death, the requirements of the Vaccine Act are met *prima facie* upon proof of the substantial factor criterion.).

p. 277.) At the next appointment fever onset is placed at 28 days prior to June 20, 2012, or approximately May 23, 2012. (*Id.* at 279.)

This places the likely onset of A.E.'s ADEM occurring no later than May 23, 2012, which is about 26 days following her April 27, 2012 vaccinations and within the four-week timeframe discussed by both experts. Accordingly, petitioners have satisfied *Althen* prong three.

d. Respondent Has Not Met His Burden of Establishing that A.E.'s Injury Was Caused by Any Factor Unrelated to Vaccination

Once petitioners have met their *prima facie* burden, respondent may still defeat petitioners' claim by coming forward with preponderant evidence that A.E.'s injury was due to factors unrelated to vaccination. § 300aa-13(a)(1)(B). This raises two separate questions.

First, respondent raises an argument to the extent of contending that A.E.'s condition is better explained diagnostically as an otherwise unspecified neurogenetic condition. As presented in this case the presence of ADEM and a neurogenetic condition are mutually exclusive explanations of A.E.'s clinical presentation. In that regard I have considered this possibility of an alternative neurogenetic condition in the context of whether A.E. was properly diagnosed with ADEM. Because I have concluded there is preponderant evidence that A.E. suffered ADEM, respondent necessarily fails to establish that there is preponderant evidence that her injury is otherwise explained by a neurogenetic condition. In any event, A.E.'s treating physicians apparently did not believe genetic testing to be warranted by her presentation and A.E. never underwent any genetic testing in the course of her extensive treatment history, leaving Dr. Kruer's suggestion of an unspecified alternative neurogenetic condition hypothetical. Conditions or other factors that are "idiopathic, unexplained, unknown, hypothetical, or undocumentable" cannot defeat a petitioner's claim. § 300aa-13(a)(2); *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994).

Second, some of the medical records suggested that A.E. may have been experiencing an illness or infection around the time her neurologic symptoms first presented. Her treating physicians specifically considered whether her condition, if ADEM, could have been explained by such infection. Ultimately, that possibility was not entirely ruled out, but no infectious etiology was found to support the suspicion. (Ex. 44, p. 174.) The Federal Circuit has rejected the contention that the presence of a viral infection can *per se* be considered a factor unrelated to vaccination. *Knudsen*, 35 F.3d at 548-50. Rather, respondent bears a burden of proving not only that there was a viral infection, but also that the infection was principally responsible for causing petitioner's injury. *Id*. Ultimately, Dr. Legido indicated that the etiology of A.E.'s ADEM could not be distinguished as between infection and vaccination. (Ex. 66, p. 8.) In any event, Dr. Kruer's causal opinion was primarily premised on his assertion that A.E. did not have ADEM. (Tr. 136.) To the extent there is preponderant evidence that A.E. did suffer ADEM, Dr. Kruer did not opine that her ADEM would have been caused by infectious

illness. Accordingly, there is not preponderant evidence that A.E.'s ADEM was caused by a factor unrelated to vaccination.

e. This is a Close Case

Finally, I note that this is a very close case in which petitioner's treating physicians appear to have struggled to reach a diagnosis. I also note that, as explained above, the initial burden of proof rests with petitioner and respondent is not obligated to prove an alternative diagnosis. Dr. Kruer was a cogent witness and many of the points he raised were reasonable, though simply outweighed by other record evidence in the context of a difficult diagnostic picture in which subjective clinical judgments were key.

On the whole, Dr. Kruer applied a framework that he described as constituting a "common sense" approach, where he looked for classic or typical indicators of ADEM even while acknowledging that ADEM has a heterogenous clinical presentation. (Tr. 84-85 (Kinsbourne), 136-37 (Kruer).) As noted above, Dr. Kruer summarized his approach by explaining "ADEM is a specific entity that's been shown over time to be diagnostically specific, and it has to pass the common sense test. It has to look like ADEM, it has to present like ADEM, it has to act like ADEM, it has to have the imaging consistent with ADEM." (Tr. 207.) Without doubting that this represents sound clinical judgment, in a close case in this legal setting it is far more difficult to accept such a judgment as being consistent with petitioner's preponderant burden of proof. This is especially so because, as described above, both experts agreed that ADEM has a clinically heterogenous presentation and because A.E.'s own treating physicians ultimately concluded that she suffered ADEM. Dr. Kinsbourne was persuasive in opining on the whole that A.E.'s presentation, though somewhat atypical, still fit within diagnostic tolerances. This case presented a series of close questions; however, as explained above, petitioners did come forward with record evidence supporting their claim on each critical point.

The closeness of this case is also reflected in the fact that there remains a significant degree of uncertainty even in Dr. Kruer's own opinion. During the hearing, Dr. Kruer was specifically asked how he would proceed if A.E. were his own patient and his response was very measured:

> So I don't think it's completely – I don't think it's obvious, by any stretch, what specific condition A.E. has. With that said, I am often in a position, either with wearing my hat as a neuroimmunologist or a neurogeneticist, that I am performing second or third opinions. In that context, if I had reviewed A.E.'s case, I would be very suspicious that ADEM was not the correct diagnosis, for all the reasons that I have outlined.

(Tr. 135.)

"The Vaccine Act does not contemplate full blown tort litigation in the Court of Federal Claims. The Vaccine Act established a federal 'compensation program' under

which awards are to be 'made to vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Knudsen*, 35 F.3d at 549. (quoting H.R.Rep. No. 99–908, 99th Cong., 2d Sess. 18, *reprinted in* 1986 U.S.C.C.A.N. 6344.) Accordingly, the Federal Circuit has suggested that this program represents a "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Althen*, 418 F.3d at 1280. I do stress that there is preponderant evidence supporting petitioners' claim. However, I also note that the outcome in this case is consistent with the Federal Circuit's guidance regarding the generous and remedial nature of this program.

VI. Conclusion

Accordingly, for all the reasons described above, petitioners are entitled to compensation for A.E.'s ADEM which was caused-in-fact by her MMR and/or varicella vaccinations received on April 27, 2012. A separate Damages Order will issue setting forth additional steps for the damages phase of this case.

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master