



## I. Procedural History

Petitioners timely filed the petition on February 8, 2016, followed by records of R.A.'s extensive medical care and a statement of completion on April 7, 2016. During an initial status conference on April 26, 2016, respondent indicated that he would defend the case. I ordered petitioners to file an expert report, followed by respondent's responsive report and report pursuant to Rule 4(c). Scheduling Order (ECF No. 18).

On August 26, 2016, petitioners filed the first expert report of A.H.M. Mahbulul Huq, MBBS, Ph.D.<sup>4</sup>, who opined that R.A.'s course was consistent with a subtype of ALE with the associated biomarker of GAD antibodies, which was caused-in-fact by the Tdap and Menactra vaccines. Petitioner's Exhibit (Pet. Ex.) 29. On February 27, 2017, respondent filed the Rule 4(c) report and the first expert report of Michael Kruer, M.D.<sup>5</sup> Respondent's (Resp.) Ex. A. Dr. Kruer disagreed with the assessment of ALE and opined that R.A.'s "lack of response despite early, intensive immunotherapy indicates that another inflammatory process is far more likely to account for her symptoms." *Id.* at 5. During a Rule 5 status conference on March 30, 2017, I

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conclusion. This opinion will discuss the aspects of the record that were most relevant to the resolving the issue of entitlement.

<sup>4</sup> Dr. Huq is licensed to practice medicine in the state of Michigan. Pet. Ex. 44 at 2. He is board-certified in neurology (with a subspecialty in child neurology) and genetics. *Id.* He obtained a Bachelor of Medicine and a Bachelor of Surgery (MBBS) at Dhaka University/ Dhaka Medical School in Bangladesh in 1984, where he completed an internship in 1985. He obtained a Ph.D. in medical science at Tokushima University in Japan in 1991. He completed simultaneous residencies in pediatrics at the Children's Hospital of Michigan and neurology at Wayne State University from 1991 – 1992. He was a fellow in medical genetics at Baylor College of Medicine from 1993 – 1996. In 1998, he returned to Children's Hospital of Medicine where he is still a pediatric neurologist. Pet. 29 at 1; Pet. Ex. 44 at 1-3. Dr. Huq used to spend half of his time on research, which has been published in per-reviewed journals. He is now a full-time clinician seeing approximately 50 – 60 patients each week, in both inpatient and outpatient settings. Tr. 47-48. Dr. Huq has diagnosed and treated patients with ALE as well as FIRES. Dr. Huq is also a Professor-Clinician Educator in the departments of Pediatrics and Neurology at Wayne State University. Pet. 29 at 1; Pet. Ex. 44 at 1-3. Dr. Huq was offered and admitted without objection as an expert in pediatric neurology and clinical genetics. Tr. 51.

<sup>5</sup> Dr. Kruer is board-certified in neurology (with a subspecialty in child neurology), pediatrics, and neurodevelopmental disabilities. He obtained a Bachelor of Science from Arizona State University Barrett Honors College in 2001 and a medical degree with distinction in research from the University of Arizona College of Medicine in 2004. He had a residency in pediatrics at Phoenix Children's Hospital/ Maricopa Medical Center from 2005 – 2007. Afterwards, he had an overlapping clinical fellowship in neurodevelopmental disabilities and a post-doctoral fellowship in molecular neurogenetics at Oregon Health & Science University from 2007 – 2011. Dr. Kruer previously practiced and taught in South Dakota. Resp. Ex. E at 1-2. He is currently the Director of the Cerebral Palsy and Pediatric Movement Disorders Program at Barrow Neurological Institute in Arizona. Resp. Ex. E at 1. Dr. Kruer also sees a significant number of patients in both inpatient and outpatient settings. Tr. 159-61. He has treated "a great many... over a hundred" patients with encephalitis (not specifying which type(s)) and "more than a dozen" patients with FIRES. Tr. 162. Dr. Kruer is also an Associate Professor in the Child Health, Cellular and Molecular Medicine, and Neurology departments, as well as the Graduate Interdisciplinary Program in Genetics, at the University of Arizona College of Medicine College of Phoenix. Resp. Ex. E at 1; Tr. 159. He has also researched and published on topics including various forms of encephalitis. He is on the editorial board of the *Journal of Child Neurology* and conducts peer review for other journals in that filed. Resp. Ex. E at 2; Tr. 164. Dr. Kruer was offered and admitted without objection as an expert in child neurology, neurogenetics, and neuroimmunology. Tr. 165.

noted that Dr. Huq had set forth a reasonable opinion supporting causation-in-fact, but the parties disagreed on the timing and the underlying diagnosis. The parties requested to file additional expert reports and for a hearing to be scheduled. Scheduling Order (ECF No. 37).

On July 31, 2017, respondent filed Dr. Kruer's second report in which he opined that a more likely explanation for R.A.'s condition was febrile illness-related refractory epilepsy syndrome (FIRES). Resp. Ex. C at 3. Respondent filed the literature therein on November 16, 2017, Resp. Ex. C Tabs 1-14. On January 25, 2018, petitioners filed Dr. Huq's second report and cited literature. Pet. Ex. 31 and Tabs A-ZZ. During a pre-hearing status conference on April 5, 2018, I stated that I found persuasive the treating physicians and Dr. Huq's assessment that R.A. developed ALE, which Dr. Huq opined was caused-in-fact by the vaccines she received. I noted that I had previously adjudicated a case involving both autoimmune limbic encephalitis and FIRES, and that the latter typically depends on the absence of any other diagnosis. *McCulloch v. Sec'y of Health & Human Servs.*, No. 9-293v, 2015 WL 3640610 (Fed. Cl. Spec. Mstr. May 22, 2015). The parties indicated that informal resolution was unlikely. Pre-Hearing Order (ECF No. 65). On September 5, 2018, respondent filed a third report from Dr. Kruer. Resp. Ex. D. The parties filed simultaneous pre-hearing submissions (ECF Nos. 82-83), which I reviewed during another pre-hearing status conference on October 24, 2018. Pre-Hearing Order (ECF No. 84).

The entitlement hearing was held in Chicago, Illinois on November 14-15, 2018. *See* Hearing Transcript (ECF Nos. 89-90). On December 13, 2018, respondent filed several articles introduced during Dr. Kruer's testimony and Dr. Kruer's updated curriculum vitae. Resp. Ex. D Tabs 1-3; Resp. Ex. E. On March 6, 2019, respondent filed MRI images annotated by Dr. Kruer during his testimony. Resp. Trial Ex. 1. On April 5, 2019, petitioners filed Dr. Huq's third report addressing issues raised by Dr. Kruer at the hearing and additional medical literature. Pet. Ex. 45 and Tabs A-J. On April 10, 2019, petitioners filed a motion for interim attorneys' fees and costs which were awarded. Int. Fees Decision (ECF No. 106), at 2019 WL 2281744 (Fed. Cl. Spec. Mstr. April 23, 2019). Petitioners filed a post-hearing brief on June 4, 2019 (ECF No. 110), followed by respondent's response on October 31, 2019 (ECF No. 115) and petitioners' reply on November 21, 2019 (ECF No. 116). This matter is now ripe for adjudication.

## II. Legal Standard

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

A petitioner bears the burden of establishing entitlement to compensation from the Vaccine Program. There are two avenues to compensation. The first avenue requires the petitioner to demonstrate a Table injury (not alleged here). The second avenue requires the petitioner to prove that a vaccine listed on the Vaccine Table was the cause-in-fact of the injury.

To prove causation-in-fact, the petitioner must “show by preponderant evidence that the vaccination brought about the injury by providing 1) a medical theory connecting the vaccination and injury; 2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and 3) a showing of proximate temporal relationship between vaccination and injury.” *Althen v. Sec’y of Health & Human Servs.*, 418 F. 3d 1274, 1278 (Fed. Cir. 2005). There must be preponderant evidence for each *Althen* prong. *Caves v. Sec’y of Health & Human Servs.*, 100 Fed. Cl. 119, 132 (2011), *aff. per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012).

The preponderance of the evidence standard requires demonstrating that it is “more likely than not” that the vaccine caused the injury. *Moberly v. Sec’y of Health & Human Servs.*, 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec’y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). A petitioner must demonstrate that the vaccine was “not only [a] but for cause of the injury but also a substantial factor in bringing about the injury.” *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec’y of Health & Human Servs.*, 135 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec’y of Health and Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). Causation is determined on a case-by-case basis, with “no hard and fast *per se* scientific or medical rules.” *Knudsen v. Sec’y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). A fact-finder may rely upon “circumstantial evidence” which is consistent with the “system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants.” *Althen*, 418 F. 3d at 1280.

A petitioner often presents expert testimony in support of his or her claim. *Lampe v. Sec’y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Expert testimony in the Vaccine Program is usually evaluated according to the factors set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec’y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). A special master may use the *Daubert* framework to evaluate the reliability of expert testimony, but expert testimony need not meet each *Daubert* factor to be reliable. *Boatmon v. Sec’y of Health & Human Servs.*, 941 F.3d 1351 (Fed. Cir. 2019). The *Daubert* factors are “meant to be helpful, not definitive,” and all factors “do not...necessarily apply even in every instance in which the reliability of scientific testimony is challenged.” *Boatmon*, 941 F. 3d at 1359 (citing *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 151, 119 S. Ct. 1167, 143 L.Ed.2d 238 (1999)). Thus, for Vaccine Act claims, a “special master is entitled to require some indicia of reliability to support the assertion of the expert witness.” *Moberly* at 1324. Where both sides offer expert testimony, a special master’s decision may be “based on the credibility of the experts and the relative persuasiveness of their competing theories.” *Broekelschen v. Sec’y of Health & Human Servs.*, 219 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d 1357 at 1362).

Once a petitioner has proven causation by preponderant evidence, the burden shifts to respondent to show by a preponderance of the evidence that the injury is instead due to factors unrelated to the administration of the vaccine. *Deribeaux v. Sec’y of Health & Human Servs.*, 717 F.3d 1363, 1367 (Fed. Cir. 2013) (citing § 13(a)(1)(B)). Respondent has the burden of demonstrating that “a factor unrelated to the vaccination is the more likely or principal cause of injury alleged. Such a showing establishes that the factor unrelated, not the vaccination, was ‘principally responsible’ for the injury. If the evidence or alternative cause is seen in equipoise,

then the government has failed in its burden of persuasion and compensation must be awarded.” *Knudsen*, 35 F.3d at 551.

### **III. Summary of Relevant Facts**

#### **1. Before August 5, 2013 Tdap and Menactra Vaccines**

R.A. was born in 2002. She had normal growth and development. She received regular vaccinations including DTaP in October 2002; December 2002; January 2003; November 2003; and August 2007. Ex. 1 at 1; Ex. 2 at 4, 5, 14, 44-46. Her family history included hypothyroidism and an autoimmune hematologic disorder. Pet. Ex. 11 at 63; Pet. Ex. 13 at 134, 151. She lives with her family in the Chicago, Illinois metropolitan area.

#### **2. August 5, 2013 Tdap and Menactra Vaccines and Subsequent Primary Care and EMS Responses**

On August 5, 2013, when R.A. was eleven years old, she had an annual well child appointment. R.A. had not received any medical care in the past year. The examination was normal. R.A. was administered a tuberculosis test as well as her sixth Tdap vaccination and first Menactra vaccination. She was advised to follow up in one year. Pet. Ex. 2 at 44-46.

On August 8, 2013 in the morning, R.A. developed a fever reaching 103 degrees Fahrenheit, for which she started acetaminophen and amoxicillin. *See* Pet. Ex. 4 at 49-51; Pet. Ex. 2 at 47-49; Pet. Ex. 20 at 1.

On August 9, 2013 at 11:10 p.m., R.A. presented to urgent care solely for a chief complaint of fever. Pet. Ex. 4 at 49-50. She had no associated symptoms (denying, e.g., pain, sore throat, cough, earache, chest pain, cough, shortness of breath, and diarrhea). *Id.* at 50. The review of symptoms and physical exam were unremarkable. *Id.* at 50-51. The assessment was “Viral syndrome post-vaccine”. R.A. was discharged home with acetaminophen. *Id.* at 51.

On August 12, 2013, the primary care provider recorded R.A.’s chief complaint as: “C/o fever x 4 days. Was in the office for 11y check and given vaccines – Tdap, Menactra 7 PPD. Per dad, has been very lethargic over the past few days.” Pet. Ex. 2 at 47. The history of present illness was: “Fever: 4 day temp 102-103 first 2 daus [sic, days] & then below 101. Meds: Motrin, last night & has not had fever since then. Chills: no. Temp. comes down with fever medication. No other associated symptoms. Child has been less active, appetite decreased. Received vaccines 1 week ago, fever started 3 days later...” *Id.* The review of systems and physical exam were unremarkable. The diagnostic code was “fever, unspecified.” *Id.* at 49. The assessment was “? Viral illness”. *Id.* R.A. should continue alternating acetaminophen and amoxicillin, go to the emergency room if she got worse, and follow up with the primary care provider if her symptoms worsened or fever persisted for more than 3-4 days. *Id.*

That same day, August 12, 2013 at about 10:30 p.m., emergency medical services (EMS) were dispatched in response to an episode in which R.A. vomited in the bathroom and passed out. EMS recorded that R.A. had been having a fever of up to 103 degrees Fahrenheit, which

had gone down to 99 degrees Fahrenheit that day. EMS did not record R.A.'s temperature. R.A. appeared alert and oriented; she did not want to go to the hospital. EMS said to call again if R.A. began acting abnormal. Pet. Ex. 5 at 1-2.

Three hours later, on August 13, 2013 at 1:39 a.m., EMS were called back to the house. The parents reported that R.A. was "sleeping in bed when she began shaking and acting inappropriately." EMS observed R.A. to be "flushed, hot and dry... lying in bed... responsive to painful stimuli and mumbling incoherently... unable to respond to questioning... postictal." Pet. Ex. 5 at 3-8.

### **3. August 13, 2013: Advocate Sherman Hospital**

R.A. was brought via ambulance to the emergency department (ER) at Advocate Sherman Hospital (ASH) in Elgin, Illinois for "altered mental status and possible seizure". Pet. Ex. 3 at 434. R.A. was agitated and unable to follow commands. *Id.* She was sedated for a lumbar puncture, from which cerebrospinal fluid (CSF) analysis yielded unremarkable glucose, protein, and white blood cell counts, with no oligoclonal bands. *Id.* at 459. R.A. was administered vancomycin, ceftriaxone, acyclovir, versed, and ketamine. It was then decided to transfer R.A. to another hospital with greater resources. *Id.* at 434-35.

### **4. August 13 - 29, 2013: Advocate Lutheran General Hospital**

That same day, R.A. was transferred to Advocate Lutheran General Hospital (LGH) in Park Ridge, Illinois, where she was admitted to the Pediatric Intensive Care Unit (PICU). R.A. was agitated, did not know where she was, and was unable to recognize people. Pet. Ex. 11 at 7. R.A. was given another 2 mg of versed. One hour after admission, R.A. had a 4-minute tonic-clonic seizure, which resolved with oxygen and 5 mg of pentobarbital. Shortly after the seizure, R.A. underwent an EEG which was: "abnormal... due to the presence of disorganization and slowing of the background activity... suggestive of diffuse cerebral dysfunction, pointing towards an encephalopathic pattern. Right hemispheric sharp activity does point to some potential epileptogenic activity." *Id.* at 168-69. A pediatrician assessed "seizures and altered mental status, concern for encephalitis"; prescribed additional antibiotics, additional antivirals, and levetiracetam; and referred to neurology. *Id.* at 11.

That same day, pediatric neurologist Natalie Sgarlata, M.D. conducted an initial evaluation, recorded that the EEG "showed encephalopathy and small right frontal sparks", and ordered further work-up. Pet. Ex. 11 at 41-43. R.A. also underwent an MRI of the brain, which was unremarkable. *Id.* at 48. An infectious disease specialist, Elaine Rosenfeld, M.D., recorded: "concern for encephalitis". *Id.* at 45-49. On a follow up visit, Dr. Rosenfeld recorded that R.A.'s initial presentation was not typical for NMDAR encephalitis, which usually involves "psychotic symptoms and/or abnormal movements." Dr. Rosenfeld ordered a work up for both bacterial and viral etiologies. *Id.* at 86-88. This included CSF analysis for NMDAR antibodies, which were eventually found to be negative. Pet. Ex. 23 at 644-45.

On August 13, 2013, at approximately 9:00 p.m., R.A. had another tonic-clonic seizure lasting approximately four minutes which prompted the start of lorazepam. Pet. Ex. 11 at 39. Approximately three hours later, R.A. went into continuous tonic-clonic seizures constituting status epilepticus.<sup>6</sup> She was given lorazepam, propofol, and phenobarbital to no avail. After R.A. had been in status epilepticus for approximately ninety (90) minutes, she was started on intravenous pentobarbital to induce burst suppression.<sup>7</sup> R.A. was started on continuous EEG monitoring. R.A. maintained a fever throughout this time and was placed on a cooling blanket. In the evening, the pentobarbital drip was briefly discontinued, but was restarted<sup>8</sup> following the reappearance of epileptic bursts and seizures. Pet. Ex. 11 at 13-19; Pet. Ex. 23 at 299-301.

A second EEG was “markedly abnormal... due to the presence of significant disorganization of the background activity with periods of lower amplitude activity interrupted by higher amplitude bursts of activity, reminiscent of a burst suppression pattern, albeit brief periods of suppression compared to the bursts. Some right hemispheric sharp activity and spike activity is noted pointing to some epileptiform potential. Ongoing electrographic seizures were not noted.” Pet. Ex. 11 at 166-67.

At this point, R.A.’s parents and the LGH treaters agreed to contact Lurie Children’s Hospital (Lurie) in Chicago, Illinois for at least a second opinion. Pet. Ex. 11 at 20-21.

An August 14, 2013 blood serum sample showed anti-microsomal antibodies of 6,240 unit/mL and anti-thyroglobulin antibodies of 3,423 unit/mL (significantly elevated above the reference range for both, of less than 60 unit/mL). Pet. Ex. 11 at 249. An August 16, 2013 blood serum sample showed glutamic acid decarboxylase (GAD) antibodies at 250.0 IU/mL (significantly elevated above the reference range of less than 5.0 IU/mL). *Id.* at 253.

Also on August 16, 2013, a repeat lumbar puncture and CSF analysis showed elevated protein of 93 mg/dL and 15 cells. Pet. Ex. 23 at 358. A cohort of treating providers agreed that the CSF results were “suggestive of inflammatory process.” Pet. Ex. 11 at 28. They continued to consider autoimmune encephalitis, more specifically the Hashimoto’s and limbic forms. *Id.* The treaters recognized “reports of some [forms of autoimmune encephalitis?] responding to steroids and some needing more aggressive immunosuppression.” *Id.* “In view of the fact that [R.A.] is already in pentobarb[ital] coma, considering urgency of situation, will start plasmapheresis to remove existing antibodies while continuing steroid at the same time” despite: “Lack of very clear evidence for either form of therapy from literature is lacking due to small number of cases.” *Id.* At that time, CSF testing for NMDAR antibodies remained pending; CSF

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<sup>6</sup> Status epilepticus is “any prolonged series of similar seizures without return to full consciousness between them; the two major types are *convulsive s. epilepticus*, which is life-threatening, and *non-convulsive s. epilepticus*, which is serious but not usually life-threatening.” *Dorland’s* at 1767.

<sup>7</sup> Respondent provides: “In patients with persistent seizures, pentobarbital at sufficient doses produces an EEG that demonstrates varying periods of high voltage followed by inactivity. This ‘burst-suppression’ pattern is felt to be characteristic of an inactivated brain and thus is felt to be neuroprotective in ‘shutting down’ the brain by coma in a patient whose seizures cannot be stopped by conventional medications.” Resp. Rep’t (ECF No. 82) at n. 5.

<sup>8</sup> As discussed below, R.A. remained on a pentobarbital drip for approximately two months until October 2014.

testing for “other neuronal antibodies” including GAD was ordered. *Id.*

On August 22, 2013, R.A. had completed five courses of plasmapheresis and was started on IVIG. Pet. Ex. 11 at 108-10. The working diagnosis continued to be “thyroid [antibody] associated encephalopathy or other autoimmune encephalopathy”. *Id.* at 123-32. Repeat EEGs remained abnormal. *Id.* at 150, 663.

On August 23, 2013, a repeat brain MRI showed: “1. Interval abnormal signal elicited from the hippocampal formations bilaterally as well as the amygdala... Findings are most suspicious for limbic encephalitis. Consider an autoimmune etiology as most likely cause.” Pet. Ex. 11 at 203-04. On August 26, 2013, R.A. was started on rituximab. Pet. Ex. 23 at 537. On August 27, 2013, the primary care provider’s office submitted a VAERS report concerning R.A.’s vaccinations and subsequent course. Pet. Ex. 2 at 3.

On August 29, 2013, R.A. was transferred with a working diagnosis of “anti-GAD related autoimmune encephalitis” from LGH to Lurie. Pet. Ex. 23 at 541-46.<sup>9</sup> The LGH medical team concurred with the family’s request to seek a second evaluation at Lurie “in view of the rarity of the current diagnosis and lack of a definitive treatment for autoimmune encephalitis.” *Id.* at 524. When LGH received the results of “a few outstanding labs” (including the CSF analysis for GAD antibodies), those would be forwarded to Lurie. *Id.*

#### **5. August 29, 2013 – March 17, 2014: Lurie Children’s Hospital and Rehabilitation Institute of Chicago**

Upon R.A.’s admission to the Lurie PICU, Jena Krueger, M.D., a neurologist, conducted an initial consult and recorded:

Work up thus far has been remarkable for (+) anti-microsomal, anti-thyroglobulin and anti-GAD [antibody], in the setting of an evolving MRI. Exam is confounded by sedation, but remarkable for absent brainstem findings. Etiology of seizures unclear. The leading possibility is an inflammatory or autoimmune process. Possibly FIRES syndrome. An infectious or post-infectious process also possible, although initial CSF WBC unremarkable. A metabolic/genetic or structural etiology is also possible, although it would not account for the positive antibodies.

Pet. Ex. 13 at 152-56. Another neurologist, Mark Wainwright, M.D., Ph.D., added:

Imp[ression]/ Rec[ommendation]: 1. Acute onset of RSE [refractory status epilepticus] in the setting of a febrile illness in a previously healthy child with exam now confounded by [pentobarbital]-induced coma. 2. Leading differential is an antibody-mediated epilepsy based on anti-thyroid and GAD antibodies.

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<sup>9</sup> During the LGH hospitalization, R.A. was also evaluated and ruled out for a host of infectious diseases including Erlichiosis, Rocky Mountain Spotted fever, Lyme disease, influenza A/B, RSV, adenovirus, metapneumovirus, parainfluenza virus, mycoplasma, arboviruses, brucella, bartonella, fungal, measles, toxoplasmosis, CMV, malaria) were negative. Pet. Ex. 11 at 78, 79, 115, 236-241, 249-252, 262-280.

Alternatively, the antibodies may be a secondary response to a primary CNS injury caused by either (a) CNS vasculitis or (b) underlying metabolic illness unmasked by febrile illness. FIRES is also in the differential but this is descriptive not mechanistic.

Pet. Ex. 13 at 157. R.A.'s case was also discussed with a third neurologist, John Millichap, M.D., who would later manage her outpatient care. *Id.* at 157.

An infectious disease specialist, Leena Bhattacharya, M.D., recorded that R.A. had undergone "an extensive and comprehensive infectious disease workup at OSH including rare cases of encephalopathy." She did not recommend "any further infectious disease work-up at this time." Pet. Ex. 13 at 123-26.

At Lurie, R.A. remained in a pentobarbital-induced coma and on a cooling blanket for fever control. She was given additional antivirals, antibiotics, seizure suppressants, steroids, IVIg<sup>10</sup>, and rituximab.<sup>11</sup> She was started on a ketogenic diet on August 30, 2013, but did not achieve ketosis due to the continued steroids. On September 11, 2013, R.A. received what would be the first of six monthly treatments of cyclophosphamide.<sup>12</sup> However, none of these treatments were associated with meaningful improvement; she continued to have seizure activity. *See generally* Pet. Ex. 13 at 10-18.

On October 2, 2013, the Food and Drug Administration (FDA) granted Dr. Wainwright's investigational new drug (IND) application for allopregnanolone, a neuro-steroid which, as stated in R.A.'s medical records, was "being studied in adult TBI [traumatic brain injury] related seizures, had anecdotal evidence of good response in RSA [refractory status epilepticus], and works on the non-synaptic GABA receptor." Pet. Ex. 13 at 855. Dr. Wainwright was granted permission to use allopregnanolone for treatment of R.A.'s "super-refractory status epilepticus due to autoimmune limbic encephalitis" with the "primary objective" of "weaning off pentobarbital". *Id.* at 836-38.

From October 4- 9, 2013, R.A. received the course of allopregnanolone. She was taken out of the pentobarbital-induced coma. She exhibited psychiatric features including memory loss, hallucinations, delusions, intermittent events of staring up, reaching hands to grab imaginary objects, and unprovoked laughter. These symptoms were recorded consistently until at least mid-November 2013. The symptoms prompted treatment with risperdal, consultation with psychiatry, and an EEG which did not find an ictal correlate. Pet. Ex. 13 at 21, 31-32, 33-35, 58-59, 56-57, 347-49, 472, 681-82. R.A. continued to have intermittent seizures which were treated with Ativan as needed. On October 31, 2013, she was fitted with a laparoscopic gastrojejunostomy [GJ] tube. *Id.* at 15.

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<sup>10</sup> As discussed below, IVIg is an immune suppressant which targets B cells and antibodies.

<sup>11</sup> As discussed below, rituximab is an immune suppressant which targets B cells and antibodies.

<sup>12</sup> As discussed below, cyclophosphamide is an immune suppressant which targets T cells.

While R.A. was hospitalized at Lurie, a Mayo Clinic laboratory determined that her CSF sample was negative for GAD65 antibodies. The lab report provides: “The patient’s serum was previously evaluated in this laboratory and reported positive. Serum is often more sensitive for detecting GAD65 antibody as a marker for autoimmune neurological disorders.” Pet. Ex. 23 at 644-45. This was subsequently noted by Lurie treaters. For example, on September 25, 2013, Craig M. Smith, M.D. noted that the Mayo Clinic’s findings and maintained the assessment of “refractory status epilepticus and limbic encephalitis likely secondary to an autoimmune process given her anti-microsomal, anti-thyroglobulin, and anti-GAD antibodies.” *Id.* at 932-33.

Repeat serum testing confirmed elevated but stable anti-GAD65 antibodies in October 2013, November 2013, and February 2014. Pet. Ex. 13 at 1287, 1253; Pet. Ex. 19 at 131. Dr. Wainwright recorded that he “[w]ould not expect these antibodies to become negative in the near future and it is possible that these antibodies will always remain positive.” Pet. Ex. 19 at 310.

From November 2013 to March 2014, R.A. moved between Lurie and the Rehabilitation Institute of Chicago. Her diagnoses remained “autoimmune limbic encephalitis (due to anti-microsomal, anti-thyroglobulin and anti-GAD antibodies)” and “refractory seizures”. Pet. Ex. 13 at 1699-1700, 1915. On March 17, 2014, R.A. was discharged home. Pet. Ex. 9 at 42-44. The plan was to continue on anti-seizure medications, ketogenic diet, and steroids. She would proceed with IVIg treatments already scheduled for the next few months, then switch to mycophenolate daily and rituximab infusions every six months. *Id.* at 44, 79.

#### **6. March 17, 2014 – On: Subsequent History**

Upon discharge, R.A. was able to ambulate short distances with mobility aids, although that was “less safe due to decreased safety awareness, limited awareness of surroundings and impulsivity, as well as unpredictable nature of [her] seizures.” She required assistance with many activities of daily living. She also had limitations with eating, attention to tasks, and thought organization. Pet. Ex. 9 at 42-55. In 2014 and 2015, R.A. had several additional in-patient stays at Lurie for repeated seizures and their consequences, including falls from her wheelchair. *See* Pet. Ex. 2 at 150-56; Pet. Ex. 13 at 2163-66; Pet. Ex. 2 at 192-96; Pet. Ex. 3 at 590; Pet. Ex. 5 at 5; Pet. Ex. 4 at 24-27; Pet. Ex. 5 at 7; Pet. Ex. 3 at 624-26. She received regular PT, OT, and speech therapy. Pet. Ex. 2 at 65-68; *see generally* Pet. Ex. 14.

Dr. Millichap and the pediatric epilepsy team at Lurie continued to follow R.A. as an outpatient. They maintained an assessment of autoimmune limbic encephalopathy with secondary intractable epilepsy and focal seizures. *See, e.g.*, Pet. Ex. 2 at 108, 132-39. R.A. remained on multiple antiseizure medications and a ketogenic diet. *Id.* at 75-76. Mycophenolate was weaned in December 2014. Pet. Ex. 19 at 1337, 1682. The last dose of rituximab was in September 2015 (according to subsequent records), after which she continued to receive steroid and IVIg infusions approximately once per month.

#### **7. March 31 – April 1, 2016: Mayo Clinic**

The parents brought R.A. to the Mayo Clinic in Rochester, Minnesota for another opinion. *See generally* Pet. Ex. 40.

A pediatric neurologist, Adam D. Wallace, M.D., reviewed the thousands of pages of outside records and conducted the initial consult. *Id.* at 19-28. Dr. Wallace's impression was that R.A.'s "initial course was likely a manifestation of severe bilateral hippocampal inflammation which likely led to her super refractory status epilepticus requiring about two months of intermittent pentobarbital infusion", which then resulted in a "subsequent epilepsy". *Id.* at 27. Dr. Wallace noted the findings of elevated thyroid and GAD antibodies, which "both are increasingly thought of as non-specific markers of inflammation." *Id.* Dr. Wallace's impression was that R.A.'s initial course represented autoimmune limbic encephalitis, with less likely considerations including "an acute presentation of a genetic epilepsy leading to bilateral hippocampal damage" and a metabolic mitochondrial disease. *Id.* Dr. Wallace "quer[ie]d whether at this point her autoimmune process might be 'burnt out' given the length of time since her initial inflammatory insult. This would be supported by the fact that her development/neurocognitive status has steadily continued to improve over the years and her epilepsy, albeit difficult to manage, seems to be getting slightly better." *Id.* If the autoimmune process was indeed "burnt out", it might be appropriate to withdraw the continued, "relatively moderate treatment regimen for immunosuppression". *Id.* Dr. Wallace also suggested "wean[ing] off the ketogenic diet eventually given the unknown efficacy of the treatment and [R.A.'s] recent increasing interest in 'non-keto' foods." *Id.* at 28.

The Director of Pediatric Epilepsy at the Mayo Clinic, Elaine C. Wirrell, M.D.<sup>13</sup>, supervised Dr. Wallace and agreed with his notes. Pet. Ex. 40 at 30. Dr. Wirrell added that R.A.'s initial presentation "certainly [involved] some features suggestive of an autoimmune process" including a preceding febrile-type illness, confusion, elevated protein and cells in the CSF, negative cultures, and elevated autoantibodies. *Id.* However, R.A. had not shown "a marked response to multiple immunotherapy trials." *Id.* at 31. Dr. Wirrell considered other etiologies including "febrile infection-related epilepsy syndrome [FIRES], potentially some genetic or metabolic etiologies; however, those I think would be less likely." *Id.*

A repeat MRI of the brain showed findings that were non-specific, but consistent with "limbic encephalitis related to autoimmune epilepsy and the resultant sequelae with mesial temporal sclerosis." Pet. Ex. 40 at 84. Dr. Wallace recorded that the MRI showed "atrophy affecting mostly the bilateral hippocampi and the lack of any acute signs of inflammation." *Id.* at 53. Drs. Wallace and Wirrell then referred to a third neurologist, Jan-Mendelt Tillema, M.D., primarily to recommend an ongoing treatment regimen. *Id.* at 27-28, 30-31.

Dr. Tillema concurred with the impression of autoimmune encephalitis involving "a very aggressive and difficult to control prolonged status epilepticus" which was "aggressively and rather early on treated with IV steroids and subsequent immunosuppressive [sic?] in a very appropriate stepwise fashion". Pet. Ex. 40 at 43. Dr. Tillema had an "extensive discussion" with R.A.'s parents about how the initial course resulted in structural injury to the hippocampi, causing cognitive impairment. *Id.* at 43-44. He did not predict a "significant return of function." *Id.* at 44. Dr. Tillema did not have "high concern for ongoing autoimmunity at this time." *Id.* at

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<sup>13</sup> Dr. Wirrell has served as an expert for respondent in the Vaccine Program. See, e.g., *Ellis v. Sec'y of Health & Human Servs.*, No. 13-336V, 2018 WL 4846547, \*26 (Fed. Cl. Spec. Mstr. Sept. 6, 2018); *Frette v. Sec'y of Health & Human Servs.*, No. 14-1105V, 2017 WL 7421013, \*10 (Fed. Cl. Spec. Mstr. Dec. 29, 2017).

43. He noted that the Mayo Clinic brain MRI showed “significant volume loss” and the initial CSF results “showed no inflammation” and “protein and cell counts absolutely within the normal range.” *Id.* The CSF antibody testing was pending. *Id.* Dr. Tillema wrote: “The interesting part is that [R.A.] has had persistent GAD-65 antibodies at levels that are significant, without any clear worsening of the clinical status. I agree that evaluating the CSF GAD-65 levels seem reasonable and if negative there, I agree with the route that has been started of trying to continue to peel [sic] some of the immunosuppressive therapy off.” *Id.* That plan was specifically to continue weaning off steroids and consider weaning IVIg over the next year. *Id.* at 44.

The Mayo Clinic CSF analysis was negative for GAD65 antibodies. Pet. Ex. 40 at 58. The “epilepsy, autoimmune interpretation” provides: “No informative autoantibodies were detected in this evaluation. However, a negative result does not exclude autoimmune epilepsy, idiopathic or paraneoplastic. Sensitivity is enhanced by testing both serum and spinal fluid.” *Id.* at 59. The Mayo Clinic also found serum GAD antibodies at 0.37 nmo/L (elevated above the reference range of less than or equal to 0.02 nmol/L). *Id.* at 58. Dr. Tillema reviewed those results and maintained the diagnoses of: “#1 Intractable epilepsy. #2 Auto-immune encephalitis, GAD-65 positive.” *Id.* at 47.

### **8. April 1, 2016 – On: Subsequent History**

Following the Mayo Clinic consultation, Dr. Millichap at Lurie continued to manage R.A.’s care.<sup>14</sup> Although the Mayo Clinic neurologists had suggested a genetics evaluation to assess for an underlying genetic condition, that was not ordered by Dr. Millichap. Pet. Ex. 40 at 27, 30. Dr. Millichap did not expressly address genetic testing in his records. He did agree with the Mayo Clinic’s recommendation of surgical insertion of a vagal nerve stimulator<sup>15</sup>, which was performed in June 2016. Pet. Ex. 43 at 147-53.

R.A. continued to have intermittent seizures. She continued on anti-seizure medications, ketogenic diet, and steroid and IVIg infusions. She still had tracheostomy and gastrostomy tubes. She received physical, occupational, speech, and vocational therapy. She had an individualized education plan (IEP) and attended school approximately three hours per day, three days per week accompanied by a home health nurse. *See generally* Pet. Exs. 35, 43.

At the entitlement hearing, Mr. Saurabh Agarwal testified that his daughter R.A. was a typically functioning and progressing eleven-year-old girl prior to receiving the Tdap and meningococcal vaccinations on August 5, 2013. R.A. has cognitive impairments particularly

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<sup>14</sup> The Lurie Children’s records, at Pet. Ex. 43, do not address the Mayo Clinic’s suggestion of further genetics testing for assessment of an underlying/ comorbid genetic condition. Mr. Agarwal testified that Dr. Millichap reviewed the Mayo Clinic records, but Dr. Millichap “said it’s not really going to help and even the guys at Mayo, they are mentioning it, is really, I cannot really justify in [R.A.’s] case to have it so the insurance will pay.” Tr. 33-34. Dr. Millichap said that if R.A.’s parents really wanted the genetic testing, they would have to pay out-of-pocket. *Id.* at 34. The parents did not see a need and did not pursue the genetic testing. *Id.*; *see also id.* at 44-45.

<sup>15</sup> A vagal/ vagus nerve stimulator “deliver[s]... electrical current to the left vagus nerve in the neck by means of an electronic pulse generator implanted in the chest, just under the clavicle; used in the treatment of epilepsy”. *Dorland’s* at 1774.

with short-term memory. R.A. does not remember what she has for breakfast, what she does at school each day, or what happened in the previous chapters in a book. Tr. 34-35. Mr. Agarwal and R.A. used to spend significant time together studying mathematics; since the onset of her injury, over the course of four years, the only thing R.A. has been able to learn and retain is how to calculate the area of a triangle. Tr. 35. R.A. attends school, where she is enrolled in a special needs class. Tr. 39-40. R.A. has difficulty recognizing people and things. Tr. 35-36. She cannot navigate on her own: “Even if we tell [R.A.] there’s an exit sign up there, she wouldn’t be able to find the door. She won’t be able to find the handle.” Tr. 36. R.A. has a daily average of 2.5 seizures, of “all different kinds” and originating from various parts of her brain. Tr. 37. The parents, particularly Mrs. Agarwal, spend significant time preparing a ketogenic diet and administering R.A.’s medications throughout the day. Tr. 37-38. They have also made modifications to improve the home’s accessibility for R.A. Tr. 38-39. Separate from the determination of entitlement in this case, the medical records and the testimony establish that the Agarwal family has been exceptionally devoted to R.A., who will very likely need continuing care for the rest of her life.

#### **IV. Analysis**

##### **1. Nature of R.A.’s Injury**

The parties first request that I resolve the nature of R.A.’s injury. Petitioners, via their expert Dr. Huq, contended that R.A. developed autoimmune limbic encephalitis (ALE) associated with GAD antibodies. Respondent, via his expert Dr. Kruer, disputed the injury from the outset. Beginning in his second report Dr. Kruer contended that a more likely explanation was febrile illness-related refractory epilepsy syndrome (FIRES), which he contended was a fundamentally different condition.

In light of the experts’ disagreement, respondent contended that petitioners have the initial burden of establishing that R.A. developed the injury alleged before the inquiry can turn to causation. Resp. Pre-Hearing Brief at 14. Petitioners disagreed, contending that it is not clear that ALE associated with GAD antibodies and FIRES “differ significantly in their pathology.” Pet. Pre-Hearing Brief at 34. However, petitioners maintained that they have established that R.A. suffered from ALE associated with GAD antibodies.

##### **A. Legal Standard**

The Federal Circuit established the test for actual causation of an off-Table injury in *Althen*, 418 F.3d at 1278. In that case: “There was no dispute as to whether the petitioner, Margaret Althen, actually suffered from a central nervous system demyelinating disorder. Therefore, the Federal Circuit was not presented with a case in which the diagnosis itself was questioned, but one in which causation of the injury by the vaccine was the issue in dispute.” *Doe v. Sec’y of Health & Human Servs.*, 94 Fed. Cl. 597, 611 (2010) (citing *Althen*, 418 F.3d at 1282), *aff’d*, *Lombardi v. Sec’y of Health & Human Servs.*, 656 F.3d 1343 (Fed. Cir. 2011).

Special masters are generally not tasked with diagnosing injuries. In *Lombardi*, the Federal Circuit explained: “The function of a special master is not to ‘diagnose’ vaccine-related injuries, but instead to determine ‘based on the record evidence as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the petitioner’s injury.’” *Lombardi*, 656 F.3d at 1343, citing *Andreu v. Sec’y of Health & Human Servs.*, 569 F.3d 1367, 1382 (Fed. Cir. 2009).

However, the Federal Circuit has determined that in certain instances, “if there is a dispute as to the nature of a petitioner’s injury, the special master may opine on the nature of the petitioner’s injury.” *Contreras v. Sec’y of Health & Human Servs.*, 844 F.3d 1363, 1368 (Fed. Cir. 2017), citing *Hibbard v. Sec’y of Health & Human Servs.*, 698 F.3d 1355 (Fed. Cir. 2012); see also *Locane v. Sec’y of Health & Human Servs.*, 686 F.3d 1375 (Fed. Cir. 2012); *Broekelschen v. Sec’y of Health & Human Servs.*, 618 F.3d 1339 (Fed. Cir. 2010)).

In *Hibbard*, the Federal Circuit reasoned: “If a special master can determine that a petitioner did not suffer the injury that she claims was caused by the vaccine, there is no reason why the special master should be required to undertake and answer the separate (and frequently more difficult) question whether there is a medical theory, supported by ‘reputable medical or scientific explanation,’ by which a vaccine can cause the kind of injury that the petitioner claims to have suffered.” 698 F.3d at 1365.

The case law also suggests that while the special master is not required to reach a specific diagnosis, the special master may appropriately evaluate at least the nature of petitioner’s injury and whether that aligns with petitioner’s theory. For example, in *Broekelschen*, the petitioner’s expert adopted certain treating physicians’ diagnosis of transverse myelitis, a condition that is inflammatory in nature. The petitioner’s expert then offered a causation opinion for that injury. He did not offer a theory that would support other treating physicians’ diagnosis of anterior spinal cord artery syndrome, which is *vascular* in nature. The Federal Circuit affirmed the special master’s approach of first determining the petitioner’s injury before evaluating the theory of causation. 618 F.3d 1339, 1346.

In contrast, in *Contreras*, the Court of Federal Claims held that the special master erred by first evaluating whether the petitioner had transverse myelitis, Guillain-Barré syndrome, or both. The parties had agreed that because both of those injuries are inflammatory/ demyelinating in nature and had similar causes, the special master did not have to reach an exact diagnosis in order to assess causation. 107 Fed. Cl. 280, 288 (2012), *aff’d*, 844 F.3d 1363.

Relevant to this inquiry, the Vaccine Act provides that a special master must consider the record as a whole including any medical diagnosis contained therein. § 300aa-13(b)(1). However, no diagnosis in the medical records is “binding on the special master.” *Id.* Rather, “[i]n evaluating the weight to be afforded to any such diagnosis... the special master... shall consider the entire record and the course of the injury, disability, illness, or condition until the date of the judgment of the special master.” *Id.* The special master shall also consider any expert opinions and additional medical scientific evidence in the record. *Id.*

## B. ALE associated with GAD Antibodies

*Encephalitis* refers to inflammation of the brain parenchyma with associated neurologic dysfunction and is usually defined on the basis of selected clinical, laboratory, and neuroimaging features. Pet. Ex. 29-KKK<sup>16</sup> at 1. *Limbic* encephalitis (LE) involves injury to the medial temporal lobes, also termed the limbic areas, of the brain. Pet. Ex. 29 at 7; Tr. 58.

### i. Prodrome

Dr. Huq opined that the limbic encephalitis prodrome, e.g., the first clinical sign(s) and symptom(s), can include “the subacute development in days to weeks of seizures from temporal lobe, short-term memory loss, and psychiatric symptoms... However, in some cases, a single clinical feature (e.g., seizures, amnesia, delirium, psychosis) can be prominent or isolated.” Pet. Ex. 29 at 7.

Dr. Huq observed that on August 8, 2013, R.A. developed a fever reaching 104 degrees Fahrenheit. This fever persisted and was accompanied by fatigue, lethargy, and decreased appetite for the next few days. On August 12, 2013 in the late evening, R.A. continued to have a fever and she vomited and passed out, then began to experience seizures. Dr. Huq opined that R.A.’s prodrome included altered mental status, opining: “she was agitated, did not know where she was, and unable to recognize people.” Pet. Ex. 29 at 2; *see also* Tr. 53-54. This is consistent with the medical records of R.A.’s presentation to ASH on August 13, 2013, transfer to the LGH PICU that same day, and continued course up to her development of status epilepticus and pentobarbital-induced coma on August 14, 2013.<sup>17</sup> Dr. Huq also noted that when R.A. was brought out of the pentobarbital-induced coma in October 2013, she displayed prominent psychiatric manifestations including memory loss, hallucinations, delusions, and unprovoked laughter. Pet. Ex. 29 at 4; *see also* Tr. 53-54, 106. Dr. Huq opined that this course is consistent with limbic encephalitis. Pet. Ex. 29 at 4, 7-8; Tr. 64-66.

Dr. Kruer did not raise the issue in his reports, but newly argued at the hearing that R.A. did not have the limbic encephalitis “typical prodrome” of “neuropsychiatric symptoms” such as “memory impairment, personality change, behavior abnormalities,” and “hallucinations”; as a treating physician, it gets [his] attention if none of that is seen”. Tr. 191, 243. Dr. Kruer did not

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<sup>16</sup> Venkatesan et al., *Autoimmune Encephalitis and its Relation to Infection*, 15 *Curr. Neurol. Neurosci.* 3 (2015) [Pet. Ex. 29-KKK].

<sup>17</sup> On cross-examination, respondent’s counsel asked wasn’t it true that Dr. Rosenfeld, an infectious disease specialist, noted that R.A.’s “presentation was not typical because this presentation was generally seen with psychotic symptoms and abnormal movements at the time of presentation?” Tr. 106. Dr. Huq seemed to agree that R.A. did not have “psychiatric” or “psychotic” symptoms at the initial presentation. Tr. 106. On review, respondent’s counsel was referring to the following notation by Dr. Rosenfeld: “During summer infectious etiology of encephalitis include mosquito and tick born infections, viral infections. Also must consider year-round infectious such as HSV, non-infectious etiologies such as autoimmune disorders, such as *NMDAR encephalitis*, although patient’s presentation not typical; usually seen psychotic symptoms and/or abnormal movements at time of presentation.” Pet. Ex. 11 at 86 (emphasis added). Dr. Rosenfeld then ordered CSF analysis for *NMDAR antibodies* (which was negative). *Id.* at 87. This record does not shed much light on whether R.A.’s prodrome was consistent with limbic encephalitis.

cite any particular literature for this proposition, but he did submit some that are relevant. One article<sup>18</sup> provides that patients with limbic encephalitis “have memory and cognitive disturbance, temporal lobe seizures, behavioral and personality changes, as well as sleep disturbance.” Resp. Ex. A-12 at 2. Another article<sup>19</sup> provides that limbic encephalitis is “characterized by confusion, agitation, memory loss, and seizures”. Resp. Ex. C-9 at 3. A third article<sup>20</sup> provides that limbic encephalitis “has a subacute onset characterized by deterioration of episodic memory and seizures usually occur later.” Resp. Ex. C-10 at 7. In contrast to Dr. Kruer’s characterization of the prodrome, this literature tends to describe a “subacute” onset of a wider spectrum of neuropsychiatric symptoms as well as seizures. And significantly, Dr. Huq presented and Dr. Kruer acknowledged an article by Malter et al.<sup>21</sup> which describes a type of autoimmune limbic encephalitis associated with GAD antibodies, seen in younger female patients “whose condition was initially dominated by seizures, rather than cognitive features.” Tr. 148-49, 281-82, citing Pet. Ex. 29-OO at 472.

I have previously accepted that an initial presentation of limbic encephalitis dominated by seizures can make it particularly difficult to assess the patient for psychiatric symptoms. *McCulloch*, 2015 WL 3640610 at \*13. But in this case, Dr. Huq observed that R.A.’s medical records reflect psychiatric symptoms described as “altered mental status.”

Upon review, I find that R.A.’s prodrome including both seizures and altered mental status is consistent with limbic encephalitis especially the subtype associated with GAD antibodies, which has been reported in a cohort of younger female patients whose condition is initially dominated by seizures rather than cognitive features (discussed further below).

## ii. Further Classification of LE

Limbic encephalitis is most commonly caused by infections such as herpes simplex, which were ruled out in R.A.’s case. Pet. Ex. 29 at 3, 7; Tr. 58-59. Limbic encephalitis can also be autoimmune in nature (termed ALE). ALE is sometimes, but not always, associated with an underlying cancer (termed paraneoplastic), which was not discovered in the case of R.A. Pet. Ex. 29 at 6, 7. ALE is associated with CSF inflammation such as increased protein and cells, which were found in R.A.’s case. *Id.*

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<sup>18</sup> Suleiman & Dale, *The Recognition and Treatment of Autoimmune Epilepsy in Children*, 57 Dev. Med. Child Neurol. 431, 432 (2015) [Resp. Ex. A-12].

<sup>19</sup> Nosadini et al., *Immune Therapy in Autoimmune Encephalitis: A Systematic Review*, 15 Expert Rev. Neurother. 1391 (2015) [Resp. Ex. C-9].

<sup>20</sup> Rivas-Coppola et al., *Chronological Evolution of Magnetic Resonance Imaging Findings in Children with Febrile Infection-Related Epilepsy Syndrome*, 55 Ped. Neurology 22 (2016) [Resp. Ex. C-10].

<sup>21</sup> Malter et al., *Antibodies to Glutamic Acid Decarboxylase Define a Form of Limbic Encephalitis*, 67 Ann. Neurol. 470 (2010) [Pet. Ex. 29OO]; cited in Zuliani, *Central Nervous System Neuronal Surface Antibody Associated Syndromes: Review and Guidelines for Recognition*, 83 J. Neurol. Neurosurg. Psychiatry 638 (2015) [Pet. Ex. 29-PP].

Dr. Huq opined that even with a clinical diagnosis of ALE, it is important to further understand the etiology, to understand what treatment will be effective. He identified different subtypes. Pet. Ex. 29 at 7. First, ALE “may be associated with antibodies against cell surface proteins (e.g., N-methyl-d-aspartate [NMDA] receptor autoantibodies, anti-CASPR2, anti-LGI, GABA<sub>B</sub>R, AMPAR, GlyR, mGluR1, mGluR4 antibodies)”. *Id.* Dr. Huq opined that the autoantibodies against cell surface proteins are likely to be pathogenic. *Id.* “Accordingly, treatment designed to remove or deplete antibodies from the body such as plasmapheresis or Rituximab are often successful.” *Id.* In this case, R.A. underwent an extensive workup which was negative for antibodies against cell surface proteins.

Dr. Huq opined that R.A. developed a different subtype of ALE with the associated finding of antibodies against glutamic acid decarboxylase (GAD) 65, an enzyme that catalyzes the production of the major neurotransmitter GABA. Pet. Ex. 29 at 6.<sup>22</sup> Dr. Huq opined in his first report (and throughout his subsequent reports and testimony) that GAD antibodies are not pathogenic. *Id.* at 5, 6, 9.

Dr. Huq acknowledged that GAD antibodies are found in individuals who are healthy, have type I diabetes, or have various autoimmune neurological conditions including stiff-person syndrome, cerebellar ataxia, limbic encephalitis, and epilepsy. Pet. Ex. 29 at 8-9. Dr. Huq opined that these antibodies might indicate a susceptibility for autoimmune disease or the presence of autoimmune disease at a “subclinical” level. *Id.* at 9-10; Tr. 96-99. The next step is to identify the specific autoimmune disease. Tr. 146. Dr. Huq acknowledged that he could not determine whether R.A. had some level of GAD antibodies prior to the onset of symptoms. Pet. Ex. 29 at 6; Tr. 112. However, she had no family history or indicators of diabetes. Pet. Ex. 29 at 8; Tr. 113. Dr. Huq opined, based on R.A.’s lack of “any kind of pancreatic problem” and her abnormal brain MRIs, that her GAD antibodies were originating in the central nervous system. Tr. 61-62.

### iii. Significance of Antibodies in CSF versus Serum

Dr. Kruer newly argued at the hearing that R.A. did not truly have ALE associated with GAD antibodies because those were only detected in serum, not in CSF. Tr. 214-15, 219-22, 241-42. Dr. Kruer opined: “I think the current thinking indicates that where the [antibodies] are produced is actually exceedingly important. And so, the principle is that if an individual develops neurological autoimmunity and one is hypothesizing that the antibody or T-cell that’s involved is causing the symptoms,<sup>23</sup> it stands to reason that the antibody or those cells should be found in the central nervous system.” Tr. 213-14. Dr. Kruer opined that “a lot of the earlier literature.... didn’t distinguish” where antibodies were found; “It’s only more recently that that concept has really started to gain more momentum.” Tr. 271. Dr. Kruer did not refer to any medical literature or any of R.A.’s medical records in support of this proposition.

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<sup>22</sup> The medical records, medical literature, and experts refer variously to “GAD” and “GAD65”. This opinion will refer to “GAD”.

<sup>23</sup> As discussed further below, not Dr. Huq, but only Dr. Kruer, argued that GAD antibodies play a pathogenic role in this type of ALE.

Dr. Huq did not directly respond to this argument raised late in the proceedings, but he did submit a recent review of autoimmune encephalopathies authored by several neurologists at the Mayo Clinic<sup>24</sup> which provides: “some neural-specific autoantibodies are better detected in the CSF... while others are more easily detected in the serum”. Pet. Ex. 29-X at 255. This article does not address where GAD antibodies are better detected. However, that is addressed in R.A.’s medical records. In August 2013, a Mayo Clinic laboratory did not detect GAD antibodies in the CSF, only in the serum. The lab report provided: “Serum is more sensitive for GAD65 antibody as a marker for autoimmune neurologic disorders”. Pet. Ex. 23 at 644-45. This lab report was conveyed to R.A.’s treating providers at Lurie, who maintained the assessment of ALE associated with GAD antibodies. In spring 2016, R.A. was actually brought to the Mayo Clinic for a second opinion. Again, repeat testing did not detect GAD antibodies in the CSF, only in the serum. The lab report provided: “No informative autoantibodies were detected in this evaluation. However, a negative result does not exclude autoimmune epilepsy, idiopathic or paraneoplastic. Sensitivity is enhanced by testing both serum and spinal fluid.” Pet. Ex. 40 at 58. The Mayo Clinic neurologists maintained the impression of ALE associated with GAD antibodies, even after receiving this result. *Id.* at 30. Dr. Kruer did not address these lab reports and he did not submit any literature to rebut them. Accordingly, the available evidence on this issue does not preponderate in Dr. Kruer’s favor. The detection of GAD antibodies, even if only in the serum, is supportive of the diagnosis of ALE.

#### iv. Role of GAD Antibodies in ALE

Dr. Huq opined in his first report (and throughout his subsequent reports and testimony) that antibodies directed against GAD are not the inciting pathogenic event for ALE. Pet. Ex. 29 at 6, 9. He explained that GAD is located inside the membrane, within the cytoplasm of cells. Only tissue damage will release GAD, rendering it accessible to antibodies. Therefore, the antibodies against GAD are simply a biomarker. *Id.* at 6; Tr. 108.

Dr. Kruer initially seemed to misunderstand or disregard Dr. Huq’s opinion, arguing in his first responsive report that GAD antibodies “have not been shown to produce disease if transferred to animals nor to directly affect neuronal or glial physiology.” Resp. Ex. A at 4.

At the entitlement hearing, Dr. Kruer newly opined that GAD antibodies actually are pathogenic because they can “exert an effect on enzyme activity”, Tr. 222, introducing a 2005 article by Raju et al.<sup>25</sup> He also introduced a 2013 article by McEwan et al.<sup>26</sup> for the proposition that “antibodies can actually enter cells. And that, in fact, there’s an intracellular receptor, a protein whose specific job it is to recognize antibodies within cells.” Tr. 223. Dr. Kruer further opined that the focus of the article, TRIM21 “is the specific protein within antibodies that get

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<sup>24</sup> Flanagan et al., *Autoimmune Dementia and Encephalopathy*, 133 *Handb. Clin. Neurol.* 247 (2016) [Pet. Ex. 29-X].

<sup>25</sup> Raju et al., *Analysis of GAD65 Autoantibodies in Stiff-Person Syndrome Patients*, 175 *J. Immunol.* 7755 (2005) [Resp. Ex. D-2].

<sup>26</sup> McEwan et al., *Intracellular Antibody-Bound Pathogens Stimulate Immune Signaling via Fc-Receptor TRIM21*, 14 *Nat. Immunol.* 327 (2013) [Resp. Ex. D-3].

into cells. So, the presence of a protein whose job it is to recognize antibodies within a cell is very strong support for that concept.” Tr. 224-25. Dr. Kruer testified that this represented a shift from the earlier thinking in immunology that antibodies are “active in the humoral but not in the intracellular environment.” Tr. 225. I have since reviewed the article, which describes: “Antibodies can be carried into *cells when attached to infecting virus particles*. Once inside the cell, antibody-coated viruses are bound by the cytosolic antibody receptor TRIM21...” Resp. Ex. D-3 at 1 (emphasis added). The article goes on to describe how once the antibody is inside the cell, TRIM21 activates immune signaling. This article does not establish that antibodies which *are not attached to infecting virus particles* can enter cells. Additionally, this article is not about antibodies specific to GAD.

Dr. Huq was permitted to submit a supplemental report responding to this and other points newly raised by Dr. Kruer at the hearing. Dr. Huq cited to his earlier filing of a 2015 article by Gresa-Arribas et al.<sup>27</sup> who write that “the pathogenic significance of GAD-65 antibodies is controversial... but several lines of evidence suggest otherwise. First, GAD65-ab-positive neurological syndromes do not respond well to immunotherapy compared to those associated with antibodies against neuronal surface antigens; second, there is no correlation between antibody titres and disease severity; and third, there are no convincing animal models of the neurological disorders.” Pet. Ex. 29-AA at 2. “An important step towards proof of pathogenicity would be the demonstration that GAD-ab bind to live neurons, and after internalization reach the intracellular GAD isoforms.” *Id.* In other words: “If we postulate that GAD65 antibodies are pathogenic, they should reach the antigen, which is intracellular, and for this the antibodies need to be internalized.” *Id.* at 9. Gresa-Arribas et al. tested this theory in controlled lab experiments. *Id.* They observed that GAD antibodies were able to react with GAD in neuronal cells if the membrane was first “permeabilized”. *Id.* However, GAD antibodies were not able to reach GAD in intact neuronal cells. *Id.* at 12.<sup>28</sup>

Upon review, the available evidence does not establish that GAD antibodies are pathogenic in causing this subtype of ALE.

#### **v. Pathogenesis of ALE associated with GAD Antibodies**

Dr. Huq opined that for ALE associated with GAD antibodies, the more likely pathogenic mechanism is T-cell cytotoxicity, based on postmortem observations of abundant T cell infiltrates in the brain parenchyma in close apposition to neurons. The working understanding is that cytotoxic T cells (also termed CD8+ T cells) attack the limbic area of the brain, which releases GAD. That generates antibodies specific to GAD, which are a biomarker of the T-cell

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<sup>27</sup> Gresa-Arribas et al., *Antibodies to Inhibitory Synaptic Proteins in Neurological Syndromes Associated with Glutamic Acid Decarboxylase Immunity*, 10 PLoS One, e01212364 (2015) [Pet. Ex. 29-AA].

<sup>28</sup> See also Hackert et al., *Anti-GAD65 Containing Cerebrospinal Fluid Does Not Alter GABA-ergic Transmission*, 10 Front. Cell Neurosci. 130 (2016) [Pet. Ex. 45-E]; Stemmler et al., *Serum from a Patient with GAD65 Antibody-Associated Limbic Encephalitis Did Not Alter GABA-ergic Neurotransmission in Cultured Hippocampal Networks*, 6 Front. Neurol. 189 (2015) [Pet. Ex. 45-I].

mediated autoimmune process. Pet. Ex. 29 at 6, 9-10<sup>29</sup>; *see also* Pet. Ex. 31 at 3-4; Pet. Ex. 45 at 3-4; Tr. 59-62, 68-69, 107-08.

Dr. Kruer did not rebut this explanation. He actually provided a reference<sup>30</sup> which supports Dr. Huq's theory, stating: "Cumulatively, there is no evidence for the pathogenicity of GAD65-specific antibodies. Instead, although also not formally proven yet, T cells might also play an important role in the pathogenesis of the disease. It is striking that transgenic mice with monoclonal T GAD65-specific CD4+ T cells develop a lethal encephalomyelitis-like disease and that T-cell infiltrates dominated by CD8+ T lymphocytes were also seen in the temporal lobes of 3 patients with GAD antibody-positive limbic encephalitis, in the absence of immunoglobulin and complement deposition." Resp. Ex. A-2 at 1. Accordingly, the medical community's current understanding seems to be that a T-cell mediated process causes this type of ALE with the subsequent biomarker of GAD antibodies.

#### vi. Treatment of ALE associated with GAD Antibodies

Dr. Kruer opined that R.A.'s course of status epilepticus (beginning on August 14, 2013) which was resistant to anti-seizure medications, steroids, and immunosuppressant treatments (including the start of rituximab on August 26, 2013 and cyclophosphamide on September 11, 2013), necessitating maintenance of a pentobarbital induced coma, was not consistent with ALE. Resp. Ex. A at 2, 5; Resp. Ex. C at 3. Dr. Kruer opined that early aggressive immunosuppressant therapy is associated with better outcomes. Resp. Ex. A at 5.<sup>31</sup> On cross-examination, Dr. Kruer acknowledged that his cited literature did not address this type of ALE associated with GAD antibodies. Tr. 265-70. Dr. Kruer also acknowledged several articles submitted by Dr. Huq which provide that ALE with GAD antibodies is resistant to steroids and many immunosuppressants. Tr. 271-73.<sup>32</sup> Dr. Kruer emphasized that one such article, by Zuliani et al., provided that patients with ALE associated with GAD antibodies "do not usually respond well to immunotherapies *but were not treated aggressively at onset*." Tr. 273, discussing Pet. Ex. 29-PPP (Dr. Kruer's emphasis added). Dr. Kruer opined that aggressive immunotherapy administered "early enough, before irreversible injury has occurred" would be beneficial even for ALE with GAD antibodies. Tr. 195.

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<sup>29</sup> Citing Zuliani [Pet. Ex. 29-PP]; Costa et al., *T-Cell Reactivity to Glutamic Acid Decarboxylase in Stiff-Man Syndrome and Cerebellar Ataxia Associated with Polyendocrine Autoimmunity*, 129 Clin. Exp. Immunol. 471 (2002) [Pet. Ex. 29-LL]; Knight et al., *A Distinct Immunogenic Region of Glutamic Acid Decarboxylase 65 is Naturally Processed and Presented by Human Islet Cells to Cytotoxic CD8 T Cells*, 179 Clin. Exp. Immunol. 100 (2015) [Pet. Ex. 29-II].

<sup>30</sup> Bradl and Lassman, *Excerpt Re: GAD65 Antibody-Associated Neurologic Syndromes*, in *Autoimmune Neurology*, Handbooks of Clinical Neurology Vol. 133 (Pittock and Vincent, eds. 2013) [Resp. Ex. A-2].

<sup>31</sup> Citing Suleiman & Dale (2015) [Resp. Ex. A-12] and Nosadini et al. (2015) [Resp. Ex. C-9].

<sup>32</sup> Citing Malter et al. (2010) [Pet. Ex. 29-OO]; Bien & Schaffer, *Autoantibodies and Epilepsy*, 52 *Epilepsia* 18 (2011) [Pet. Ex. 29-B]; Zuliani et al. (2012) [Pet. Ex. 29-PPP].

In contrast, Dr. Huq explained that because this type of ALE is T-cell mediated, immunosuppressants designed to remove B cells and antibodies are unlikely to be helpful. Pet. Ex. 29 at 7; Pet. Ex. 31 at 4. The recent review of autoimmune encephalopathies filed by Dr. Huq provides:

The prognosis is variable and dependent on the underlying antibody, the presence of a diagnosis, and treatment delay (which worsens prognosis). In general, patients with autoantibodies to cell surface antigens (paraneoplastic or otherwise) tend to have a better prognosis while patients with autoantibodies to intracellular antigens have a worse prognosis...

Corticosteroids are often tried as the initial treatment in paraneoplastic and other ADE [autoimmune dementias and encephalopathies], but the type of autoantibody helps guide other treatments. In patients with autoantibodies to cell surface receptors (NMDAR, LGI, or CASPRA2 antibodies), we tend to focus on antibody-depleting or modifying therapy and targeting of B cells (plasma exchange/ intravenous immunoglobulin (IVIg), rituximab) while in those with antibodies to intracellular antigens (e.g., ANNA-1) we focus on treatments targeting predominantly T cells (e.g., cyclophosphamide)...

As we learn more about the pathogenesis and immune mechanisms involved in ADE [autoimmune dementias and encephalopathies], we suspect more targeted therapies will become available... As each neural autoantibody-mediated disorder may have a different pathogenesis, we suspect we will see more focused therapies targeted at the specific autoantibody resulting in benefits for patients.

Pet. Ex. 29-X at 250, 262, 265.

Dr. Huq also submitted a 2010 study by Malter et al. arising from the Department of Epileptology at the University of Bonn, Germany, which involved fifty-three (53) subjects with limbic signs and symptoms (median latency of 12 months, range 0 – 12 months), brain MRI revealing medio-temporal encephalitis, and unclear etiology. Pet. Ex. 29-OO at 470-71, 73. Nine subjects were found to have antibodies against GAD, while ten other subjects were found to have antibodies against voltage-gated potassium channel (VGKC) proteins. *Id.* at 473. Malter et al. compared clinical outcomes in these two “largest defined LE subgroups”. *Id.* The patients received standard immunotherapies (e.g., steroids, IVIG, plasmapheresis, cyclophosphamide) as well as anti-seizure drugs. *Id.* On follow-up, compared to the patients with VGKC antibodies, the patients with GAD antibodies never became seizure-free, were taking more anti-seizure drugs, and had worse memory outcomes. *Id.* Malter et al. recognized that their patients were later in the disease course and recommended undertaking “trials of more aggressive immunotherapy in patients diagnosed promptly” with this type of ALE. *Id.* at 475.<sup>33</sup> Dr. Huq

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<sup>33</sup> See also Bien & Scheffer [Pet. Ex. 29-B] at 21 (citing Malter et al. for the proposition that in ALE associated with anti-GAD antibodies, “seizures are generally resistant to anticonvulsants in [sic? and?] immunotherapy treatment resulting in a chronic disorder dominated by temporal lobe epilepsy”); Zuliani et al. [Pet. Ex. 29-PPP] at 3 (citing Malter et al. for the sentence: “GAD-Abs have been identified in younger females with a form of LE presenting mainly with temporal lobe epilepsy and MRI evidence of temporal lobe inflammation; these patients did not usually

testified that R.A. was clinically similar to these patients. Tr. 65-66.

Dr. Huq opined that new approaches to treatment continue to be developed. Pet. Ex. 31 at 4; Tr. 125-26. He submitted a 2015 case report by Widman et al.,<sup>34</sup> also based at the University of Bonn Department of Epileptology, of a male patient with epilepsy since the age of 18 and displaying clinical signs of ALE and high titers of GAD antibodies in serum and CSF. Pet. Ex. 31-YY at 1. The patient did not respond to IV steroids. *Id.* Widman et al. noted that in previous patients with limbic encephalitis associated with GAD antibodies, immunosuppressive therapy was not effective and when surgical intervention occurred, the temperomesial structures were found to contain cytotoxic T-lymphocytes. *Id.* at 3, 8. Accordingly, Widman et al. experimented involving “therapeutic Abs against the activated interleukin-2 receptor”, “aimed at reducing the amount of activated T-lymphocytes”. *Id.* The only such treatment available was Basilimixab, an intravenous drug approved in 1998 to prevent rejection in organ transplantation. Widman et al. obtained authorization for experimental use of Basilimixab to treat ALE with GAD antibodies. *Id.* In their patient, Basilimixab was associated with reduction to normal limits of both CD4+ and CD8+ T cells; the reduction below detectable levels of GAD antibodies; and a reduction in seizure frequency. *Id.* at 5-9. The patient then had a clinical relapse, which may have been caused by the formation of human anti-drug antibodies (HADAs). *Id.* at 9.

Widman et al. proposed a pathogenic role for cytotoxic CD8+ T cells in causing this subtype of ALE associated with GAD antibodies, via two possible pathways:

Experimental studies have shown that an attack of cytotoxic T-lymphocytes against neurons could result in a perforin-dependent electrical silencing, which is not necessarily linked to neuronal cell death. Thus, a chronic epilepsy by non-lethal cytotoxic attacks against GAD65 expressing GABAergic interneurons is possible. An alternative explanation... could be that primarily there is an attack by cytotoxic T-lymphocytes against e.g., GAD65 expressing GABAergic interneurons... and second, partly denatured GAD65 comes into contact with the humoral part of the immune system, resulting in the GAD65-Abs, also against linear epitopes of the enzyme, due to prior lysosomal denaturation. Therefore, a direct therapy against GAD65-ABs should fail, whereas an attenuated activation [sic? attack on?] cytotoxic T-lymphocytes should be helpful.

*Id.* at 8. Upon publishing their article in 2015, Widman et al. “anticipat[ed] the approval of a new homologous therapeutic AB... daclizumab hyp” which might be more effective and appropriate for long-term therapy. *Id.* at 10. They suggested a controlled study of daclizumab hyp for treatment of ALE with GAD antibodies. *Id.*

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respond well to immunotherapies but were not treated aggressively at onset”).

<sup>34</sup> Widman et al., *Treating a GAD65 Antibody-Associated Limbic Encephalitis with Basilimixab: A Case Study*, 6 *Frontiers in Neurology* 1, doi:10.3389/fneur.2015.00167 (2015) [Pet. Ex. 31-YY].

The above literature reflects that autoimmune encephalopathies are generally treated first with corticosteroids and that the specific understanding of the condition guides more specific treatment. In patients with pathogenic antibodies to cell surface receptors such as NMDAR (for which R.A. was tested, early in her course), the focus is on immune suppressants which target B cells and antibodies, including IVIg (which R.A. started on August 16, 2013) and rituximab (August 26, 2013). When a patient is detected to have antibodies against intracellular components such as GAD, the focus is on treatments targeting T cells such as cyclophosphamide (which R.A. started on September 11, 2013, nearly one month into status epilepticus). The literature reflects that ALE associated with GAD antibodies involves persistent seizure activity, resistance to treatment, and worse memory. The literature suggests that earlier detection and initiation of treatment focused on the T cell pathogenesis, possibly including new treatments, can be associated with better outcomes.

Dr. Huq opined: “It is logical to assume that [R.A.’s] initial super-refractory status epilepsy [sic? epilepticus?] led to significant brain damage which contributed to the pathogenesis of her subsequent intractable epilepsy via non-immune mechanisms... Once there is significant brain injury and neuronal loss, one can have continued seizures and intractability even without an active inflammatory process in [the] brain.” Pet. Ex. 31 at 5. Dr. Kruer agreed that it was “possible that R.A.’s disease course was biphasic; that is, there was an initial insult that caused irreparable brain damage, and that the brain injury R.A. sustained contributed to her persistent, refractory seizures.” Resp. Ex. C at 2. This is consistent with statements from physicians who subsequently examined R.A. For example, during the second opinion in 2016 at the Mayo Clinic, the neurologist Dr. Wallace, who agreed with the assessment of ALE, summarized that R.A. initially suffered “severe bilateral hippocampal inflammation which likely led to her super refractory status epilepticus requiring about two months of intermittent pentobarbital infusion”, resulting in a “subsequent epilepsy”. Dr. Wallace also suggested withdrawal of immunosuppressants because “at this point her autoimmune process might be ‘burned out’ given the length of time since her initial inflammatory insult.” Pet. Ex. 40 at 27-28. This is a logical explanation of how an inflammatory T-cell mediated process constituting status epilepticus, which persisted for nearly a month before the first dose of a drug targeting T cells (cyclophosphamide), could result in a subsequent epilepsy.

#### **vii. MRIs**

Dr. Kruer argued that the progression of R.A.’s MRIs (on August 30, September 11, October 24, and December 17, 2013) were not consistent with ALE, even the subtype associated with GAD antibodies. Resp. Ex. A at 2 (citing MRI images filed as Resp. Tr. Ex. 1). Dr. Kruer opined that the findings of mesial temporal and hippocampal sclerosis were consistent with ALE, but the “significant cortical and cerebellar atrophy” was not. Tr. 240-41. In support for this proposition, he cited Malter et al.’s finding that: “On follow-up brain MRI, there was a general tendency to regression of encephalitic mediotemporal signal and volume increases” in LE with GAD antibodies. Pet. Ex. 29-OO at 474-75. In other words, “there is an improvement”, unlike what is seen in R.A.’s MRIs. Tr. 227-28. Dr. Huq opined that these findings are in fact non-specific and can be seen after status epilepticus, prolonged febrile seizures, and ALE, and cites literature which bears this out. Pet. Ex. 45 at 4.<sup>35</sup>

<sup>35</sup> Citing Fujisao et al., *Hippocampal Damage and Atrophy Secondary to Status Epilepticus in a Patient with*

### viii. Treating Physicians

Dr. Kruer acknowledged that the treaters at LGH, Lurie, and the Mayo Clinic consistently diagnosed R.A. with ALE associated with GAD antibodies. He opined that this was a valid “working diagnosis” that “had its value” at the beginning of her course. Tr. 211. “It gave rise to a specific treatment plan that was aggressive and gave [R.A.] the best chance, with what was known at the time, for the best possible long-term outcome.” Tr. 211. But Dr. Kruer said that ALE became “chart lore... basically it’s true because... someone wrote it somewhere... it’s difficult to get things out of the medical chart... it will still be carried forward.” Tr. 210. He also testified: “As a treating physician, many of us are most keen on overturning diagnoses that would change a treatment course and tend to be more complacent with ones that don’t.” Tr. 211-12. Dr. Kruer testified that the ALE diagnosis “seemed to come over with [R.A.] from [LGH]” and was not overturned at Lurie. But then he agreed that the Lurie treaters “conduct[ed] an independent analysis of the clinical and radiological findings in [R.A.’s] case.” Tr. 260.

### C. FIRES

Dr. Kruer opined that in retrospect and with the benefit of reviewing all of R.A.’s medical records and relevant literature, he arrived at a more likely explanation: febrile illness-related epilepsy syndrome (FIRES). Resp. Ex. C at 3-6; Resp. Ex. D at 1-2; *see generally* Tr. 166-305.

Dr. Kruer opined that FIRES is a clinical entity that was first described in approximately 2010, although some earlier reports referred to similar conditions. Tr. 169. A consensus of international experts across multiple fields including epilepsy, neuroimmunology, and neurocritical care have participated in “careful vetting” leading to its current definition. Dr. Kruer’s reports were accompanied by articles published from 2011 – 2017.<sup>36</sup> At the entitlement hearing,

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*Schizophrenia*, 8 Front Neurol. Doi: 10.3389/fneur.2017.00024 (2017) [Pet. Ex. 45-B] at 4 (providing that “several neuroimaging studies have demonstrated acute swelling of the hippocampus after prolonged febrile seizures”); Ikeda et al., *Isoflurane Use in the Treatment of Super-Refractory Status Epilepticus is Associated with Hippocampal Changes on MRI*, 26 Neurocrit. Care 420 (2017) [Pet. 45-F] at 426 (concluding that signal change in the hippocampus may be either a marker of neurotoxicity or seizure-related damage, and that signal change outside the hippocampus is the result of refractory status epilepticus); Tanabe et al., *Hippocampal Damage after Prolonged Febrile Seizure: One Case in a Consecutive Prospective Series*, 52 Epilepsia 837 (2011) [Pet. Ex. 45-J] (presenting similar findings); Haberlandt et al., *Limbic Encephalitis in Children and Adolescents*, 96 Arch. Dis. Child 186 (2011) [Pet. Ex. 45-D] (a study of 10 patients, including images of “a characteristic MRI course” from a female pediatric patient with limbic encephalitis and GAD antibodies); Kotsenas et al., *MRI Findings in Autoimmune Voltage-Gated Potassium Channel Complex Encephalitis with Seizures: One Potential Etiology for Mesial Temporal Sclerosis*, 35 AJNR Am. J. Neurorad. 84 (2014) [Pet. Ex. 45-H] (indicating that “radiologic progression is common” due to “persistent CNS inflammation, damage done secondarily by recurrent seizures, or both”).

<sup>36</sup> Citing Kramer et al., *Febrile Infection-Related Epilepsy Syndrome (FIRES): Pathogenesis, Treatment, and Outcome: A Multicenter Study on 77 Children*, 52 Epilepsia 1956 (2011) [Resp. Ex. C-5]; Van Baalen et al., *Febrile Infection-Related Epilepsy Syndrome Without Detectable Autoantibodies and Response to Immunotherapy: A Case Series and Discussion of Epileptogenesis in FIRES*, 43 Neuropediatrics 209 (2012) [Resp. Ex. C-13]; Van Baalen et al. (2012) [Resp. Ex. C-14]; Howell et al., *Long-Term Follow-Up of Febrile Infection-Related Epilepsy Syndrome*, 53 Epilepsia 101 (2012) [Resp. Ex. C-3]; Nabbout, *FIRES and IHHE: Delineation of the Syndromes*, 53 Epilepsia 54 (2013) [Resp. Ex. C-8]; Caraballo et al., *Febrile Infection-Related Epilepsy Syndrome: A Study of 12 Patients*, 22 Seizure 553 (2013) [Resp. Ex. C-2]; Singh et al., *Cognitive Outcomes in Febrile Infection-Related Epilepsy Syndrome with the Ketogenic Diet*, 134 Pediatrics e1431 (2014) [Resp. Ex. C-11]; Nosadini et al. (2015) [Resp. Ex.

he introduced a 2018 article by Gaspard et al.<sup>37</sup>, who offer a “consensus definition of New-Onset Refractory Status Epilepticus (NORSE): *a clinical presentation, not a specific diagnosis*, in a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic, or metabolic cause. This includes patients with viral or autoimmune causes.” Resp. Ex. D-1 at 3 (emphasis added). Gaspard et al. then define FIRES as “a subcategory of NORSE that requires a prior febrile infection, with fever starting between 2 weeks and 24 hours prior to onset of refractory SE, with or without fever at onset of SE.” *Id.*

Dr. Kruer opined that ALE and FIRES have some superficial similarities, but key differences. First, FIRES has a typical prodrome of high fever, “leading physicians to initial[ly] suspect a viral illness, although often no source is found.” Resp. Ex. C at 3; *see also* Tr. 169.

Dr. Kruer opined that second, FIRES has a consistent clinical course. Tr. 169. The patient quickly develops focal onset seizures constituting status epilepticus which persists for weeks to months, which eventually burns itself out, but putatively causes brain damage, because it is followed by a second phase of persistent seizures, as well as cognitive and behavioral sequelae. Resp. Ex. C at 3, 5; Tr. 176-77, 187-88. Dr. Kruer opined that is “precisely what was observed in R.A.’s case.” Resp. Ex. C at 5.

Dr. Kruer opined that FIRES is also characterized by a lack of response to immunotherapy. Resp. Ex. C at 4; Tr. 169. Gaspard et al. notes that there have been uncontrolled reports of approximately 50% of patients with FIRES showing a dramatic response to the ketogenic diet. Resp. Ex. D-1 at 4. The diet is associated with reduction of plasma levels of pro-inflammatory cytokines. *Id.* However, ketogenic diet is used as a treatment not only for FIRES, but for drug-resistant epilepsy more generally. *Id.*<sup>38</sup> In this case, R.A. was started on a ketogenic diet during her hospitalization at Lurie but this was not associated with a clear improvement. The second opinion at the Mayo Clinic included “consideration to wean off the ketogenic diet eventually given the unknown efficacy of the treatment”. Pet. Ex. 40 at 28.

Dr. Kruer opined that “FIRES is thought to represent an inflammatory epilepsy fundamentally different from autoimmune encephalitis.” Resp. Ex. C. at 4; *see also* Tr. 174. As support for this proposition, he submitted a 2016 case report by Dr. Elaine Wirrell and

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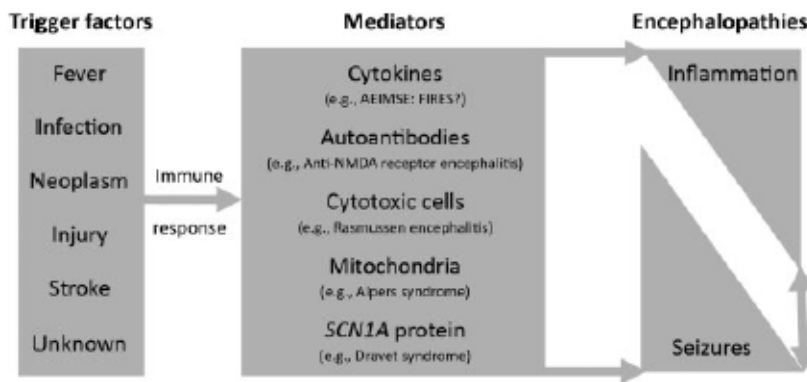
C-9]; Suleiman & Dale (2015) [Resp. Ex. C-12]; Appavu et al., *Ketogenic Diet Treatment for Pediatric Super-Refractory Status Epilepticus*, 41 *Seizure* 62 (2016) [Resp. Ex. C-1]; Kenney-Jung et al., *Febrile Infection-Related Epilepsy Syndrome Treated with Anakinra*, 80 *Ann. Neurol.* 939 (2016) [Resp. Ex. C-4]; Moynagh, *The Interleukin-1 Signalling Pathway in Astrocytes: A Key Contributor to Inflammation in the Brain*, 3 *J. Anat.* 265 (2005) [Resp. Ex. C-7]; Rivas-Coppola et al. [Resp. Ex. C-10]; Mirás Veiga et al., *Effectiveness of Electroconvulsive Therapy for Refractory Status Epilepticus in Febrile Infection-Related Epilepsy Syndrome*, 48 *Neuropediatrics* 45 (2017) [Resp. Ex. C-6].

<sup>37</sup>Gaspard et al., *Critical Review and Invited Commentary - New-Onset Refractory Status Epilepticus (NORSE) and Febrile Infection-Related Epilepsy Syndrome (FIRES): State of the Art and Perspectives*, 59 *Epilepsia* 745 (2018) [Resp. Ex. D-1].

<sup>38</sup> *See, e.g.*, Appavu et al. (2016) [Resp. Ex. C-1] (reporting on the efficacy of ketogenic diet for children with “super-refractory status epilepticus” attributed to various etiologies including autoimmune encephalitis).

colleagues at the Mayo Clinic<sup>39</sup>, describing a pediatric patient presenting with intractable seizures. Resp. Ex. C-4 at 939. The authors noted prior case reports “suggest[ing] that children with an autoimmune epileptic encephalopathy... can mimic FIRES.” *Id.* at 943. However, in their patient, both serum and CSF were negative for the antibodies associated with autoimmune encephalitis. *Id.* at 940. The patient was also resistant to immunosuppressants. Her condition was labelled as FIRES. It was observed that the medication Anakinra had been “approved for treating autoinflammatory diseases.” *Id.* at 940. Anakinra inhibits the biological actions of interleukin (IL)-1 $\beta$ , “a prototypical proinflammatory cytokine implicated in a variety of autoinflammatory disorders” demonstrated to have “ictogenic properties in various seizure models and contributes to the generation of febrile seizures in immature rodents.” *Id.* at 939. In the case report, Anakinra “successfully treat[ed] super RSE [refractory status epilepticus] in [the child with FIRES and maintain[ed] this seizure control over the subsequent 12 months.” *Id.* at 939. Dr. Kruer opined that Anakinra would never be used to treat autoimmune encephalitis, Tr. 174, but that is not stated in the article. Indeed, the significant takeaways from this article include that autoimmune epileptic encephalopathy and FIRES can have similar presentations, and that it is important to work up a patient for the former before settling on the latter. Also of note, this case report came from the Mayo Clinic and one of the authors is Dr. Elaine Wirrell, Director of the Pediatric Epilepsy Clinic. The same year the case report was published, R.A. went to the Mayo Clinic for a second opinion and Dr. Wirrell recorded that FIRES was a “less likely” explanation than autoimmune encephalitis in her case. *See* Pet. Ex. 40 at 30.

Dr. Kruer allowed that the pathogenesis of FIRES “has not been completely elucidated”. Resp. Ex. D at 1; *see also* Tr. 291 (Dr. Kruer’s testimony that FIRES includes inflammation but it’s not yet clear “what’s chicken, what’s egg”). This is consistent with the literature. For example, an article by Van Baalen et al. provides that that “febrile infections trigger FIRES, but the mediator of epileptogenesis remains hypothetical” and suggested the following possible factors:



**Figure 4** Model of the role of immunity and inflammation in epileptogenesis. Various factors (also combined) may trigger an initial immune (e.g., inflammatory) response that possibly mediated by a secondary pathogenic mechanism, generates seizures or inflammation, which in turn, activate further seizures and inflammation in various epileptic encephalopathies.

<sup>39</sup> Kenney-Jung, Wirrell, et al. *Febrile Infection-Related Epilepsy Syndrome Treated with Anakinra*, 80 Ann. Neurol. 939 (2016) [Resp. Ex. C-4].

Resp. Ex. C-14 at 215. In another article, Nababout suggests “A common pathophysiology based on a vicious circle with inflammation inducing seizures evolving to status epilepticus and status enhancing and keeping active the inflammatory pathways”. Resp. Ex. C-8 at 56. The 2018 review by Gaspard et al. provides:

A unifying mechanism that could account for all the specific features of cryptogenic NORSE and FIRES is still lacking. It is, however, tempting to speculate that it might be caused by a fulminant inflammatory response in the CNS. An intrathecal overproduction of proinflammatory cytokines and chemokines has been described in children with FIRES and was not observed in the CSF of controls with other inflammatory and non-inflammatory neurological conditions. Several of these molecules have proconvulsant activity. This accumulation could be the product of the activation of T cells, perivascular cells, and glia and could take several days, perhaps explaining the latency between the febrile episode and the onset of SE. However, it is currently unclear whether intrathecal inflammation is the cause or the consequence of the prolonged episode of refractory SE (RSE), as controls with RSE of noninflammatory origin were not studied. Furthermore, whether this cytokine storm is sufficient to explain a long-lasting severe episode of SE is also unclear, and additional mechanisms such as mitochondrial dysfunction or synaptic plasticity may occur. Individual predisposition may be determined by allelic variations in HLA subtypes or cytokine pathways, as in other postinfectious neurological disorders. Further studies to confirm these hypotheses are ongoing.

Resp. Ex. D-1 at 748.

Dr. Kruer opined that histopathology of FIRES brain tissue typically shows “gliosis but not signs of inflammation.” Tr. 171. However, this histopathology was not obtained in R.A.’s case. Dr. Kruer also cited an article by Rivas-Coppola et al.<sup>40</sup> for the proposition that unlike ALE, FIRES has a unique pattern of “global brain atrophy” within a month and “significant brain atrophy and cerebellar atrophy” on follow up for up to two years. Dr. Kruer opined that R.A.’s MRIs showed this unique pattern for FIRES. Resp. Ex. C at 3-4; Tr. 225-41 (citing Resp. Ex. C-10; Pet. Ex. 29-OO; Ct. Ex. 1). But as noted above, Dr. Huq opined, based on supporting literature, that these MRI findings can be non-specific and generally consistent with status epilepticus, prolonged febrile seizures, and ALE.

Dr. Kruer emphasized that R.A.’s treating physicians considered FIRES. Tr. 211-12. First at Lurie, the neurologist Dr. Krueger recorded: “The leading possibility is an inflammatory or autoimmune process. Possibly FIRES syndrome...” Pet. Ex. 13 at 156. However, this record was reviewed by the attending neurologist Dr. Wainwright, who added: “FIRES is in the differential but this is descriptive not mechanistic.” *Id.* at 157. Dr. Kruer agreed that the Lurie treaters independently analyzed the clinical and radiologic findings and then recorded a diagnosis of autoimmune encephalitis. Tr. 260-61.

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<sup>40</sup> Rivas-Coppola et al., *Chronological Evolution of Magnetic Resonance Imaging Findings in Children with Febrile Infection-Related Epilepsy Syndrome*, 55 *Ped. Neurology* 22 (2016) [Resp. Ex. C-10].

Dr. Kruer said that FIRES was also mentioned when R.A. went to the Mayo Clinic for a second opinion. However, those records indicate that Dr. Elaine Wirrell thought FIRES was “less likely” than ALE associated with GAD antibodies, and the latter diagnosis was maintained. Pet. Ex. 40 at 30. On cross-examination, Dr. Kruer agreed that “none of [R.A.’s treating physicians concluded that she had FIRES” and that their final diagnosis was ALE associated with GAD antibodies. Tr. 260-265.

Dr. Huq opined that saying that a patient has FIRES is equivalent to saying that the etiology is “unknown”, Pet. Ex. 31 at 1. In other words “the essence of FIRES is that you don’t have a diagnosis”. Tr. 66. Dr. Huq opined that FIRES probably encompasses a “heterogeneous” set of cases; as they are further worked up and studied, “at least some cases will turn out to be immune mediated or autoimmune in nature.” Pet. Ex. 31 at 1; *see also* Tr. 139-40. For example, Dr. Huq provided a 2017 article by Caputo et al.<sup>41</sup> reporting on a case of suspected FIRES associated with antibodies against an unidentified cell surface antigen, which was identified as GABA<sub>A</sub>R. Pet. Ex. 31-G at 183-84. After these antibodies were identified, Caputo et al. changed the diagnosis to autoimmune encephalitis. *Id.* Following treatments to remove the putatively pathogenic cell surface autoantibodies, the patient achieved a significant recovery. *Id.* Caputo et al. emphasized “a prompt recognition of the immune-mediated etiology and a proper treatment” in cases with FIRES-like onset. *Id.* at 185.

Dr. Huq has personally diagnosed and treated six or seven patients with FIRES or the older term, new-onset refractory status epilepticus (NORSE). Tr. 74, 103. Dr. Huq opined that his current approach is to do a “lot more testing” including a “complete antibody panel”. Tr. 73. “Previously, we didn’t have any option[s] and I retrospectively think that probably I misdiagnosed some cases as FIRES and if it now [sic?], probably I will be able to get a more specific diagnosis.” Tr. 73-74.

#### D. Conclusion

During R.A.’s extended course at several hospitals most significantly Lurie Children’s, where she was subsequently followed as an outpatient, and during a second opinion at the Mayo Clinic, she underwent a thorough workup for the nature of her condition including repeated EEGs, MRIs, serum and CSF analysis. She was seen by many sophisticated practitioners, primarily in the field of neurology. To be sure, several of the neurologists considered a genetic epilepsy, a metabolic disorder, or FIRES.<sup>42</sup> However, the neurologists – at least seventeen (17)

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<sup>41</sup> Caputo et al., *Febrile Infection-Related Epilepsy Syndrome (FIRES) with Super-Refractory Status Epilepticus Revealing Autoimmune Encephalitis due to GABA<sub>A</sub>R Antibodies*, 22 Eur. J. Paediatr. Neurol. 182 (2018) [Pet. Ex. 31-G].

<sup>42</sup> Pet. Ex. 13 at 156 (Lurie neurologist Dr. Krueger’s notation that “A metabolic/ genetic or structural etiology is also possible, although it would not account for the positive antibodies” and “Possible FIRES syndrome”); *but see* Pet. Ex. 13 at 157 (Lurie supervising neurologist Dr. Wainwright’s comment that “FIRES is also in the differential but this is descriptive not mechanistic”); Pet. Ex. 30 at 31 (Dr. Wirrell’s consideration of “FIRES, potentially some genetic or metabolic etiologies, however, those I think would be less likely”).

individuals, at three different medical institutions – were more certain and consistent in an assessment of ALE associated with GAD antibodies, as set forth in the lengthy footnote below.<sup>43</sup>

Dr. Huq concurred with the assessment of ALE associated with GAD antibodies. Dr. Huq also explained that a T cell-mediated process damages tissue, which releases GAD which is met with antibodies; those GAD antibodies are a later biomarker rather than the inciting pathogenic process. The T-cell pathogenesis of this condition explains the resistance to steroids as well as immunosuppressants designed to target B cells and antibodies. R.A. did receive a first dose of cyclophosphamide nearly a month into her course of status epilepticus, but it is not clear that treatment was administered soon enough to prevent “irreparable damage” as argued by Dr. Kruer, or whether that one dose was sufficient to inhibit the pathogenesis. The experts did agree that an initial insult could result in lasting cognitive deficits and resultant epilepsy, as endorsed by R.A.’s treating providers.

On the other side, Dr. Kruer argued that the repeated assessments of ALE represented “chart lore” which did not explain R.A.’s condition. However, Dr. Kruer did not recognize Dr. Huq’s opinion identifying a subtype associated with GAD antibodies; which are thought to be biomarkers of a T cell-mediated process. Dr. Kruer also raised several arguments for the first time at hearing, which did not bear out. For example, Dr. Kruer opined that R.A. did not have the expected prodrome of neuropsychiatric symptoms. The early medical records, identified in Dr. Huq’s first report, reflect that R.A. had altered mental status as well as seizures when she first presented to ASH, then LGH, then Lurie. R.A.’s presentation is consistent with what is described in the literature about ALE, especially the subtype associated with GAD antibodies. Furthermore, Dr. Kruer testified that serum findings are less specific than CSF findings, while the lab reports in this case, conducted at the Mayo Clinic, actually provide that testing of both is informative, and that serum is more sensitive for GAD65 antibody as a marker for autoimmune neurologic disorders. Additionally, Dr. Kruer testified that GAD antibodies are pathogenic because they can enter cells, but Dr. Huq submitted the article by Gresa-Arribas et al. who

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<sup>43</sup> Pet. Ex. 23 at 259, 352, 378 (“working diagnosis is autoimmune encephalitis”); Pet. Ex. 13 at 1167 (“all together, this is most consistent with an autoimmune epilepsy”); Pet. Ex. 13 at 493, 838, 1123 (“super-refractory status epilepticus likely secondary to an autoimmune process given her anti-microsomal, anti-thyroglobulin, and anti-GAD antibodies”); Pet. Ex. 13 at 1093 (“most likely an autoimmune mediated refractory epileptic encephalopathy related to GAD and thyroid antibodies”); Pet. Ex. 13 at 973 (“presumed etiology autoimmune encephalitis”); Pet. Ex. 13 at 101 (“super-refractory status epilepticus secondary to autoimmune limbic encephalitis (anti-GAD and anti-thyroid antibody positive)”); Pet. Ex. 13 at 1933 (“autoimmune limbic encephalitis and refractory epilepsy as a result of her presentation with refractory status epilepticus”); Pet. Ex. 13 at 2032 (“autoimmune limbic encephalitis”); Pet. Ex. 13 at 2072 (“autoimmune encephalitis ([secondary to] positive GAD, microsomal and thyroglobulin antibodies) as well as refractory epilepsy and trach/G-tube dependence”); Pet. Ex. 19 at 310 (“refractory status epilepticus from autoimmune limbic encephalitis (positive GAD, microsomal, and thyroglobulin antibodies)”); Pet. Ex. 19 at 1376 (“epilepsy due to autoimmune limbic encephalitis (+anti-microsomal, anti-thyroglobulin, and anti-GAD antibodies), with super-refractory status epilepticus”); Pet. Ex. 19 at 1458 (“intractable epilepsy with focal seizures secondary to autoimmune limbic encephalitis (anti-GAD and anti-thyroid antibody positive)”); Pet. Ex. 40 at 27 (“medically refractory multifocal epilepsy likely secondary to a history of autoimmune limbic encephalitis”); Pet. Ex. 40 at 30 (“There were certainly some features suggestive of an autoimmune process... DIAGNOSES[:] #1 Intractable epilepsy, possible autoimmune etiology); Pet. Ex. 40 at 43-44 (R.A. “has a history that indeed its with a refractory status epilepticus in the setting of autoimmune encephalitis... DIAGNOSES[:] #1 Intractable epilepsy[,] #2 Auto-immune encephalitis, GAD-65 positive”).

demonstrated that antibodies specific to GAD cannot enter cells unless the membrane is permeabilized.

Dr. Kruer argued that a more likely explanation for R.A.'s condition was FIRES. As I have noted in a previous case, FIRES describes a clinical subgroup of patients who develop fever followed shortly thereafter by refractory seizures or status epilepticus, for which no cause is identified and is associated with very poor outcomes. *See McCulloch*, 2015 WL 3640610 at \*15-16. In that case, respondent's expert opined that if a particular antibody were identified, he would remove the diagnosis from the category of FIRES, the hallmark of which is an unknown cause. *Id.* at 18. In the present case, the literature submitted does not support a significant change in the understanding of FIRES. For example, the 2018 article by Gaspard et al. provides that FIRES is a clinical descriptor, not a specific diagnosis. And the 2016 case report by Wirrell et al. recommends a thorough workup including for autoimmune encephalitis types before settling on FIRES and trying experimental treatments such as Anakinra. However, in this case, R.A. was found to have significantly elevated GAD antibodies which the literature and her treating physicians identified as representing a subtype of ALE. While that discovery did not improve R.A.'s course, it did reveal an etiology. Therefore, she no longer fit the descriptor of FIRES.<sup>44</sup> Finally, considering R.A.'s extensive evaluations by numerous neurologists at the well-regarded Lurie Children's Hospital as well as a second opinion by several specialists at the Mayo Clinic, all concurring on an assessment of autoimmune limbic encephalitis, it seems a bit extreme to characterize this as simply "chart lore".

Accordingly, petitioners have established that more likely than not, the appropriate explanation for R.A.'s injury is ALE associated with GAD antibodies.

## **2. *Althen* Prong One**

### **A. Legal Standard**

Under *Althen* prong one, the causation theory must relate to the injury alleged. Thus, a petitioner must provide a "reputable" medical or scientific explanation that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. It must only be "legally probable, not medically or scientifically certain." *Id.* at 549. However, the theory still must be based on a "sound and reliable medical or scientific explanation." *Id.* at 548. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field *bereft of complete and direct proof of how vaccines affect the human body.*" *Althen*, 418 F.3d at 1280 (emphasis added).

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<sup>44</sup> Even were FIRES is accepted as a diagnosis unto itself, the pathogenesis is not clearly understood. FIRES is resistant to immunosuppressants designed to remove antibodies. Dr. Kruer's literature suggests that FIRES can be mediated by cytokines, fever, inflammation, and T cells. Thus, Dr. Huq's opinion in support of vaccine causation, presented below, may very well apply to FIRES as well.

Drs. Huq and Kruer, and counsel in briefing this case, spent the bulk of their time disagreeing about R.A.'s diagnosis. This was a natural focus for Drs. Huq and Kruer, two well-qualified pediatric neurologists who are devoted to the prompt diagnosis and effective treatment of their patients. The theory of causation depended much more on immunology. Neither Dr. Huq nor Dr. Kruer are board-certified in immunology, but they agreed on many key concepts and submitted relevant literature.

## B. Autoimmunity

Dr. Huq opined that the normally functioning immune system recognizes, but does not respond to, the human body's own tissue. Tr. 77. In rare cases, this self-tolerance breaks down, resulting in autoimmune disease. *Id.* Dr. Huq opined that certain individuals are genetically predisposed to autoimmunity. Environmental factors also contribute both to the development of an autoimmune disease and its severity. Dr. Huq opined that each individual is uniquely susceptible, based on particular genetic makeup, to particular environmental factors and to the development of particular autoimmune conditions. Pet. Ex. 29 at 6<sup>45</sup>; Tr. 62-63, 132-36.

Dr. Huq opined that various infections have been associated with, and thus considered to be triggers, for various autoimmune diseases including some types of encephalitis. Pet. Ex. 29 at 11. Dr. Huq opined that similar to infections, vaccines may also act as environmental factors. *Id.* at 11. He submitted an article by Castiblanco et al. discussing the difficulty of studying this issue: "Autoimmunity is a concern for many vaccines, though [autoimmune disease] presentation among immunized individuals is rarely observed. However, because of relatively low baseline incidence of many autoimmune conditions, large post-marketing and adequately powered studies are required to evaluate any increased risk of [autoimmune diseases] after vaccination. In fact, in most of the clinical trials evaluating vaccines, a systematic screening for [autoimmune diseases] is not performed." Pet. Ex. 29-GG at 55.

Dr. Huq opined that autoimmunity is a developing area of study and the mechanisms are not fully understood. In his first report, he opined: "There is no single mechanism explaining how a vaccine may induce autoimmunity with precision." Pet. Ex. 29 at 11. He opined that vaccines can trigger autoimmunity by means of a variety of mechanisms including cytokine production and molecular mimicry. These mechanisms can work concurrently and in conjunction with one another." *Id.*

Dr. Kruer agreed that autoimmunity is multi-factorial. He also agreed that both genetic susceptibility and environmental factors (such as infection and in some cases, vaccinations) can contribute to forming autoimmunity. Tr. 283.

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<sup>45</sup> Citing Castiblanco et al., *Genetics and Vaccines in the Era of Personalized Medicine*, 16 *Curr. Genomics* 47 (2015) [Pet. Ex. 29-G]; Costenbader et al., *Genes, Epigenetic Regulation, and Environmental Factors: Which is the Most Relevant in Developing Autoimmune Diseases?*, 11 *Autoimmune Rev.* 604 (2012) [Pet. Ex. 29-M]; see also Ceccarelli et al., *Genetic Factors of Autoimmune Diseases*, *J. Immunol. Res.* Doi: 3476023 (2016) [Pet. Ex. 29-H].

### C. Inflammatory Response

Dr. Huq explained that vaccines, by design, cause a rather non-specific innate immune response involving activation of cytokines (specifically identifying IL-1 $\beta$ , TNF- $\alpha$ , and IL-6). Pet. Ex. 31 at 2. I asked whether this represents “the first step” in forming immunological memory of that antigen and a more specific adaptive response for when it is encountered again. Tr. 94. Dr. Huq agreed. Tr. 95. He opined that in most individuals, the innate response to vaccination might include no noticeable symptoms or mild symptoms such as fever, flu-like symptoms, and/ or a little bit of pain. Tr. 95.

Dr. Huq opined that in rare cases, certain susceptible individuals that receive vaccinations can have a more significant innate response. Tr. 96. His theory seemed to include the innate response’s pro-inflammatory cytokines reaching the brain, as he agreed that IL-1 $\beta$  signals to the hypothalamus to generate fever, Tr. 91, and he opined that “significant fever” is observable evidence of innate immune response and activation of pro-inflammatory cytokines in the brain. Tr. 89, 95-96, 129.<sup>46</sup> He submitted two articles by Vezzani et al.<sup>47</sup> which provide that when IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 are present in the brain, they affect synaptic transmission and neuronal excitability, and also cause neuronal cell loss and injury to the blood-brain barrier (BBB).

Dr. Kruer agreed that the normal immune response to vaccines involves the innate immune system and activation of pro-inflammatory cytokines. Tr. 199-200, 288. Dr. Kruer also agreed that proinflammatory cytokines can affect synaptic transmission and neuronal excitability. Tr. 288. He also agreed that brain inflammation contributes to seizure thresholds in susceptible brain regions. Tr. 288. Dr. Kruer agreed that “Tdap and Menactra could certainly cause an immune response. I think that it’s possible that in some cases that could contribute to seizures, yes.” Tr. 168. Dr. Kruer agreed that inflammation is part of autoimmunity. Tr. 199.

### D. Immune Cell Cross-Reactivity

Dr. Huq also opined that autoimmunity can also develop due to structural or sequence similarity between a foreign antigen and a self-antigen, which is termed molecular mimicry. Pet.

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<sup>46</sup> Dr. Huq also suggested that fever itself may be pathogenic, given the “direct effect of heat on physiological processes” such as the function of ion channels. Pet. Ex. 31 at 5, citing Schuchmann et al., *Experimental Febrile Seizures are Precipitated by a Hyperthermia-Induced Respiratory Alkalosis*, 12 Nat. Med. 817 (2006) [Pet. Ex. 31-KK]; Thomas et al., *Heat Opens Axon Initial Segment Sodium Channels: A Febrile Seizure Mechanism?*, 66 Ann. Neurol. 219 (2009) [Pet. Ex. 31-QQ]. Fever may also “overlap” with the cytokines creating inflammation, to cause seizures. Pet. Ex. 31 at 5, citing Haspolat et al., *Interleukin-1beta, Tumor Necrosis Factor-Alpha, and Nitrite Levels in Febrile Seizures*, 17 J. Child Neurol. 749 (2002) [Pet. Ex. 31-S]; Kim et al., *Analysis of Plasma Multiplex Cytokines and Increased Level of IL10 and IL1Ra in Febrile Seizures*, 14 J. Neuroinflammation 200 (2017) [Pet. Ex. 31-X]; Matsuo et al., *Increased IL-1beta Production from dsRNA-Stimulated Leukocytes in Febrile Seizures*, 35 Pediatr. Neurol. 102 (2006) [Pet. Ex. 31-Z]; Sun et al., *DPP4 Regulates the Inflammatory Response in a Rat Model of Febrile Seizures*, 28 Biomed. Mater. Eng. S139 (2017) [Pet. Ex. 31-OO]; Vezzani (2013) [Pet. Ex. 31-SS]; Vezzani (2015) [Pet. Ex. 31-TT].

<sup>47</sup> Citing Vezzani et al., *The Role of Inflammation in Epileptogenesis*, 69 Neuropharmacology 16 (2013) [Pet. Ex. 31-SS]; Vezzani et al., *Neuromodulatory Properties of Inflammatory Cytokines and Their Impact on Neuronal Excitability*, 96 Neuropharmacology 70 (2015) [Pet. Ex. 31-TT].

Ex. 29 at 11.<sup>48</sup> Dr. Huq opined that there were several opportunities for molecular mimicry relevant to this case. First, he opined that tetanus toxoid (present in the Tdap vaccine) has structural similarity to human IL-1 $\alpha$  protein and IL-1 $\beta$  protein, and short peptide sequence homology to human beta 2-glycoprotein-I and laminin proteins. Dr. Huq opined that these structural similarities favored the role of tetanus toxoid in autoimmune conditions (including those impacting the central nervous system), with molecular mimicry as the mechanism. *Id.* at 11<sup>49</sup>; *see also* Tr. 79, 81, 127-29, 138-39.

Dr. Huq also identified similarities between the Menactra vaccine and glycoproteins in neural tissue. Pet. Ex. 29 at 12-13. Dr. Huq explained that Menactra contains conjugates of groups A, C, W135 and Y meningococcal capsular polysaccharide. Research indicates that group C is cross-reactive with group B, which is not contained in the vaccine. *Id.* at 12.<sup>50</sup> Vaccination for group C is also associated with a decrease in the incidence of meningococcal group B. *Id.* at 12<sup>51</sup>, which Dr. Huq opined further supports cross-reactivity, *see* Tr. 81. Group B meningococcal capsular polysaccharide is almost identical to the polysaccharide found on the surface of brain tissues. Thus, meningococcal capsular polysaccharides, including those in the Menactra vaccine, can potentially act as a trigger or autoimmune stimulus in humans by inciting cross reactivity with brain tissue thus causing immunopathology. Specifically, the antibodies generated in response to the meningococcal capsular polysaccharides can cross-react with glycoproteins in neural and extra-neural tissue. Pet. Ex. 29 at 12.<sup>52</sup> Dr. Huq opined that this

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<sup>48</sup> Cusick, Libbey, and Fujinami, *Molecular Mimicry as a Mechanism of Autoimmune Disease*, 42 Clin. Rev. Allergy Immunol. 102 (2012) [Pet. Ex. 29-P].

<sup>49</sup> Citing Blank et al., *Antiphospholipid Syndrome Infectious Origin*, 24 J. Clin. Immunol. 12 (2004) [Pet. Ex. 29-C]; Stojanovic et al., *The Context of Tetanus Toxoid Application Influences the Outcome of Antigen-Specific and Self-Directed Humoral Immune Response*, 53 Microbiol. Immunol. 89 (2009) [Pet. Ex. 29-HHH]; Stojanovic et al., *Role of Molecular Mimicry and Polyclonal Cell Activation in the Induction of Pathogenic Beta2-Glycoprotein I-Directed Immune Response in Balb/c Mice Upon Hyperimmunization with Tetanus Toxoid*, 56 Immunol. Res. 20 (2013) [Pet. Ex. 29-GGG]; Caronti et al., *Serum Anti-Beta2-Glycoprotein I Antibodies from Patients with Antiphospholipid Antibody Syndrome Bind Central Nervous System Cells*, 11 J. Autoimmun. 425 (1998) [Pet. Ex. 29-E]; Caronti et al., *Anti-Beta2-Glycoprotein I Antibodies Bind to Central Nervous System*, 156 J. Neurol. Sci. 211 (1998) [Pet. Ex. 29-F].

<sup>50</sup> Citing Robbins et al., *Capsular Polysaccharide Vaccine for Group B Neisseria Meningitidis, Escherichia Coli K1, and Pastereurella Haemolytica A2*, 108 Proc. Natl. Acad. Sci. U.S.A. 17871 (2011) [Pet. Ex. 29-X].

<sup>51</sup> Citing Cohn et al., *Changes in Neisseria Meningitidis Disease Epidemiology in the United States, 1998 – 2007: Implications for Prevention of Meningococcal Disease*, 50 Clin. Infect. Disease 184 (2010) [Pet. Ex. 29-K].

<sup>52</sup> Citing Finne, *Occurrence of Unique Polysialosyl Carbohydrate Units in Glycoproteins of Developing Brain*, 257 J. Biol. Chem. 11966 (1982) [Pet. Ex. 29-T]; Finne et al., *An IgG Monoclonal Antibody to Group B Meningococci Cross-React with Developmentally Regulated Polysialic Acid Units of Glycoproteins in Neural and Extraneural Tissues*, 138 J. Immunol. 4402 (1987) [Pet. Ex. 29-U]; Finne et al., *Occurrence of Alpha 2-8 Linked Polysialosyl Units in a Neural Cell Adhesion Molecule*, 112 Biochem. Biophys. Res. Commun. 482 (1983) [Pet. Ex. 29-V]; Finne et al., *Antigenic Similarities Between Brain Components and Bacteria Causing Meningitis: Implications for Vaccine Development and Pathogenesis*, 2 Lancet 355 (1983) [Pet. Ex. 29-W]; Saukkonen et al., *Antibodies to the Capsular Polysaccharide of Neisseria Meningitidis Group B or E. Coli K1 Bind to the Brains of Infant Rats In Vitro but not In Vivo*, 1 Microb. Pathol. 101 (1986) [Pet. Ex. 29-BBB]; Nedelec et al., *Evidence for Autoimmune Antibodies Directed Against Embryonic Neural Cell Adhesion Molecules (N-CAM) in Patients with Group B*

represented another opportunity for the development of autoimmunity in predisposed individuals such as R.A. *Id.* at 13; *see also* Tr. 79-84, 128-29, 138-39.

The 2012 article by Cusick, Libbey, and Fujinami, which Dr. Huq filed to introduce the concept of molecular mimicry, actually details various ways that T cells can contribute to the development of autoimmune disease. Pet. Ex. 29-P. They explain that the etiology of autoimmune disease is not fully elucidated, but is likely based on a combination of hereditary and environmental factors. *Id.* at 102. A foreign antigen is met by an immune response including proinflammatory cytokines such as type I interferon (IFN), interleukin (IL)-1 $\beta$ , IL-12, IFN- $\gamma$ , IL-17, and TNF- $\alpha$ , which facilitate inflammation. *Id.* This is critical for clearance of a virus or bacteria. *Id.* However, prolonged pro-inflammatory responses to infections have been associated with the initiation and exacerbation of autoimmune diseases. *Id.*

Cusick, Libbey, and Fujinami explain: “The immune system has a number of mechanisms that are able to detect foreign pathogens by utilizing the major histocompatibility complex (MHC). This locus encodes HLA genes and a variety of immune response (Ir) genes, thereby shaping the immune system that protects against pathogens.” Pet. Ex. 29-P at 103. They go on to state: “The HLA locus is extremely polymorphic leading to a heterogeneous population ensuring propagation of a species against novel pathogens. Unfortunately, this genetic heterogeneity adds to the complexity of identifying HLA genes implicated in autoimmune diseases.” *Id.* at 103. There are two main types of HLA antigens. *Id.* Class I (which are present on all cells) stimulate T cell receptors (TCRs) on the surface of CD8+ T cells, which leads to the killing of the specific cells. *Id.* Class II, for which TCRs are found on various cells of the immune system, can stimulate the production of B cells, antibodies, CD4+ helper T cells, and CD8+ cytotoxic T cells. *Id.*

Cusick, Libbey, and Fujinami explain that the hallmark of autoimmunity is the dysregulation of the immune system, especially T and B cells recognizing self-antigens as foreign. *Id.* at 105. The ability of T cells to evade central (thymic selection) and peripheral (Tregs) mechanisms of tolerance is evidenced by the large number of T cell-mediated human autoimmune diseases. *Id.* The difference between other non-specific mechanisms that initiate autoimmunity and molecular mimicry is that microbial mimics specifically direct the immune response towards a tissue or organ. *Id.* The medical community previously thought that T cell recognition was highly specific and that cross-reactivity was a rare phenomenon. *Id.* However, more recent studies have demonstrated that a given MHC class II peptide binding groove can accept different (self or foreign) antigens which share the same amino acid sequence. *Id.* at 105-06. This results in molecular mimicry, which remains a leading theory in the generation of autoimmunity. *Id.* at 106.

Cusick, Libbey, and Fujinami also describe that the medical community previously believed that T cell signaling was mediated by a single antigen receptor. *Id.* More recent evidence demonstrates that a single T cell is capable of expressing functional dual receptors, creating another opportunity for recognition of a foreign antigen to lead to activation against the self. What is more: “Normally, high avidity self-reactive T cells are thymically depleted, but it

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*Meningitis*, 29 J. Neuroimmunol. 49 (1990) [Pet. Ex. 29-TT].

has been hypothesized that the expression of a self-TCR on a T cell is lower when presented in the context of a second TCR, thereby providing a cover for high avidity self-TCRs from both central and peripheral tolerance.” *Id.* Cusick, Libbey and Fujinami mention yet a third mechanism, which involves a T cell expressing chimeric TCRs generated from either a single V $\alpha$  combining with two different V $\beta$ s or a single V $\beta$  combining with two different V $\alpha$ s, resulting in a T cell with the potential of expressing two different chimeric TCRs specific for a self-antigen and a foreign antigen. *Id.* at 108.

This article supports Dr. Huq’s theory that in rare cases involving susceptible individuals, an environmental stimulus such as vaccines can activate an innate immune response involving fever and inflammation. This innate immune response can also activate the adaptive immune response by both CD4+ and CD8+ T cells which can complicate the inflammatory process and gave rise to cross-reactivity through molecular mimicry or degenerate T-cell binding with neural tissue. Dr. Huq explained that this damage can result in seizures.

Dr. Kruer agreed that molecular mimicry is a well-accepted mechanism for the development of autoimmunity; that molecular mimicry is taught in medical school; it is discussed in peer-reviewed journals and textbooks; and it has been demonstrated in animal models. Tr. 283-84. He agreed that there is hexapeptide sequence homology between tetanus toxoid and beta 2 glycoprotein. Tr. 286. He agreed that tetanus toxoid induces anti-beta 2 glycoprotein antibodies in mice. Tr. 287.

Dr. Kruer’s main objection to the theory presented in this case was that it would not occur quickly enough to cause R.A.’s onset of fever four days after vaccination and seizures seven days after vaccination. This is better addressed below under *Althen* prong three.

### **E. Lasting Brain Damage**

Dr. Huq opined that seizures constituting status epilepticus can result in permanent brain damage and a lower threshold for further seizures, e.g., epilepsy, even after the inciting immune response is “burned out”. Pet. Ex. 31 at 6; *see also* Tr. 86, 89-91. Dr. Kruer agreed with this proposition, opining: “It is possible that R.A.’s disease course was biphasic; that is, there was an initial insult that caused irreparable brain damage, and that the brain injury RA sustained contributed to her persistent, refractory seizures.” Resp. Ex. C at 2.

### **F. Conclusion**

Dr. Huq described a “perfect storm”, in which an individual who is genetically predisposed to autoimmunity is confronted with an environmental stimulus such as vaccine(s) which, via inflammation and T-cell cross-reactivity, can cause a severe autoimmune response such as occurred in R.A. He opined that the Tdap and Menactra vaccines can cause an immune response including both inflammation and T cell cross-reactivity with neural tissue, which can both contribute to seizures. Pet. Ex. 31 at 6. Dr. Kruer agreed with many key propositions including that certain individuals are genetically predisposed to autoimmunity; that autoimmunity also depends on environmental factors, including in some cases vaccines; that the Tdap and Menactra vaccines can cause an immune response involving pro-inflammatory

cytokines, which in some cases can lead to seizures; and that there was evidence of molecular mimicry between tetanus toxoid and self-antigens.

Respondent criticized Dr. Huq for proposing a “cafeteria of mechanisms” that was “purely speculative”. Resp. Post-Hearing Response at 11. While Dr. Huq’s opinion encompassed several aspects of the immune response, he emphasized that autoimmunity is multifactorial and continues to be studied. After reviewing the significant record in this case, I referenced a helpful and concise reference text by Lauren Sompayrac, Ph.D., which happens to succinctly articulate Dr. Huq’s opinion. Dr. Sompayrac introduces the concept of autoimmune disease. He then summarizes the two leading proposed mechanisms of molecular mimicry and inflammation, each of which seem unlikely to work independently as the sole cause of autoimmune disease:

So the scenario most immunologists favor for the initiation of autoimmune disease is this: A genetically susceptible individual is attacked by a microbe that activates T cells whose receptors just happen to cross-react with a self-antigen. Simultaneously, an inflammatory reaction takes place in the tissues where the self-antigen is expressed. This inflammation could be caused either by the mimicking microbe itself, or by another, unrelated infection or trauma. As a result of this inflammatory reaction, [antigen-presenting molecules] are activated that can re-stimulate self-reactive T-cells. In addition, cytokines generated by the inflammatory response can upregulate class I MHC expression on normal cells in the tissues, making these cells even better targets for destruction by self-reactive CTLs [killer T cells, another term for cytotoxic CD8+ T cells].

Sompayrac, *How the Immune System Works* (5<sup>th</sup> ed. 2016) at 123. This envisions a substantial causal role for environmental factors, such as the Tdap and Menactra vaccines in this case and fits the current understanding of the ALE subtype associated with GAD antibodies, which is understood to be mediated by cytotoxic CD8+ T cells. Moreover, Drs. Huq and Kruer agreed that an initial insult can cause irreparable brain damage leading to persistent, refractory seizures, even when the initial process is burned out.

Accordingly, I find that petitioners have established a reputable scientific explanation of how the Tdap and Menactra vaccines can cause ALE associated with GAD antibodies, with resultant brain damage involving cognitive deficits and intractable epilepsy.

### **3. *Althen* Prong Two**

#### **A. Legal Standard**

Under *Althen* prong two, petitioner must prove “a logical sequence of cause and effect showing that the vaccination was the reason for [her] injury.” *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the “did it cause” test; i.e. in this particular case, did the vaccine(s) cause the alleged injury. *Broekelschen*, 618 F. 3d at 1345 (“Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner’s case”). Temporal association alone is not evidence of

causation. *See Grant v. Sec’y of Health & Human Servs.*, 9556 F.2d 1144, 1148 (Fed. Cir. 1992). This sequence of cause and effect is usually supported by facts derived from petitioner’s medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148.

## B. Discussion and Conclusion

Prior to the August 5, 2013 Tdap and Menactra vaccinations, R.A. was a healthy eleven-year-old girl with normal developmental milestones who had not sought any medical attention for any reason over the past year and who was doing very well in school. Pet. Ex. 2 at 44-46; *see also* Tr. 5-42. Dr. Kruer agreed. Tr. 297.

Dr. Huq opined that R.A. was predisposed to autoimmunity for several reasons. First, her family history includes hypothyroidism and an autoimmune hematologic disorder. Pet. Ex. 29 at 8, 10, 13; Tr. 112-13. Second, after R.A.’s vaccinations and onset of fever and seizures, R.A. was found to have elevated antibodies directed against GAD, thyroid protein, and thyroid enzyme (termed anti-microsomal antibodies). As discussed above, Dr. Huq opined that the inflammatory and T-cell mediated process most likely caused neuronal tissue damage resulting in the generation of antibodies against GAD. He opined that the antibodies directed against thyroid protein and thyroid enzyme may have been present beforehand and further suggested a predisposition to autoimmunity. Pet. Ex. 29 at 10, 13; Pet. Ex. 31 at 6; Tr. 62, 113-14, 132.

Dr. Huq noted that predisposition to autoimmunity is genetic, but: “No genetic polymorphisms affecting autoimmunity have been investigated in [R.A.’s] case.” Pet. Ex. 29 at 10. Of note, when R.A. presented for a second opinion in 2016, neurologists at the Mayo Clinic recommended genetic testing to possibly include either an epilepsy panel, microarray, or whole-exome sequencing to “assess for underlying/ comorbid genetic condition.” Pet. Ex. 40 at 27, 30. However, when R.A. returned home to Illinois, her neurology team at Lurie Children’s did not order or even discuss genetics testing in their records.

Dr. Huq opined that genetic testing can reveal certain mutations that are clearly associated with neurological disorders, such as those in the sodium channel (e.g., SCN1A) associated with Dravet syndrome (which has never been suspected in R.A.’s case). Tr. 136. Dr. Huq opined that in R.A.’s case, genetic testing at best might “give us a clue what made [R.A.] susceptible to the vaccination[s]... I don’t think that it will give us a monogenic epilepsy gene.” Tr. 142.

On the other hand, Dr. Kruer opined that if he were treating R.A., he would order genetic testing because she “did not seem to fit the clinical diagnosis of autoimmune encephalitis.” Tr. 266. But as discussed above, I have concluded that the evidence supports that R.A. does fit the description of ALE associated with GAD antibodies. Dr. Kruer also opined that the intention behind genetic testing is to potentially learn something new. Tr. 204; *see also id.* at 266. Dr. Kruer stated: “I’ll be honest, most of the time when we do a whole-exome, if we find an answer, it’s closure. It’s predictive value. It’s anticipating the future... There’s only a small, you know, proportion of the time that it introduces a completely new treatment... and I can’t necessarily say before I run the test, who’s going to be what. I’m routinely surprised.” Tr. 205. He predicted

the likelihood of finding “something new” to be about 10 to 20 percent. Tr. 204. In R.A.’s case, he could not contemplate a specific genetic diagnosis that would change either the prognosis or the treatment plan. Tr. 205, 266. The obvious corollary to Dr. Kruer’s estimate is that there was an 80 – 90% likelihood that genetic testing would *not* shed any additional light on R.A.’s case.

Based on the available evidence, I accept Dr. Huq’s opinion that R.A. was predisposed to autoimmunity based on her family history and the findings of elevated anti-microsomal and anti-thyroid antibodies. While genetic testing was suggested at the Mayo Clinic, neither that facility nor Dr. Kruer identified genetic factors that are known to be associated with R.A.’s condition, let alone whether those only *predispose* an individual as opposed to acting as the *sole cause* of the injury, as is held in the SCN1A/ Dravet syndrome cases.<sup>53</sup> I disagree with respondent’s argument that the *lack* of genetic testing, for some unspecified trigger, prevents a finding of a logical sequence of cause and effect in this case. See Resp. Post-Hearing Response at 13.

Dr. Huq observes that there was no other identified environmental trigger that could have caused R.A.’s condition. Pet. Ex. 29 at 1-15, 13-14; *see also* Pet. Ex. 31 at 6; Tr. 62, 92-94, 98; Pet. Post-Hearing Brief at 65-66. R.A. was healthy upon receiving the Tdap and Menactra vaccinations on August 5, 2013. Pet. Ex. 2 at 44-46. Afterwards, she reported a chief complaint of fever with no other symptoms to urgent care. Pet. Ex. 5 at 49-51. She followed up with her primary care provider, who again recorded a chief complaint of fever with no other symptoms suggestive of a viral illness. The diagnostic code was “fever, unspecified.” Pet. Ex. 2 at 47-49. After R.A. suffered the onset of seizures, during her hospitalization first at LGH then at Lurie, she underwent an extensive workup. No other bacteria, virus, neoplasm, trauma, or other environmental trigger was identified. No metabolic or structural etiology was identified. Dr. Kruer did not dispute this fact or suggest that some specific environmental trigger was missed.

Multiple treating physicians noted at least a temporal association between R.A.’s vaccines and her subsequent development of fever and seizures. See Pet. Post-Hearing Brief at 63-65 (quoting from medical records from eleven different treating physicians).

Dr. Huq also opined that R.A.’s development of fever was evidence of the innate immune response and activation of pro-inflammatory cytokines. Tr. 89. Specifically, the cytokine IL-1 $\beta$  signals to the hypothalamus to generate fever. Tr. 91. Dr. Kruer agreed that the vaccines R.A. received on August 5, 2013 are designed to generate pro-inflammatory cytokines. Tr. 292. He also opined that cytokine testing “kits” are available from scientific supply companies, but those are not clinically available, certainly not in 2013. Tr. 203.

As discussed above, Dr. Huq explained that the immune response to the vaccines led to status epilepticus which was considerably difficult to treat. He opined: “It is logical to assume that [R.A.’s] initial super-refractory status epilepsy [sic? epilepticus] led to significant brain damage which contributed to the pathogenesis of her subsequent intractable epilepsy via non-immune mechanisms.” Pet. Ex. 31 at 4. Dr. Kruer agreed: “It is possible that R.A.’s disease

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<sup>53</sup> See *Oliver v. Sec’y of Health & Human Servs.*, 2017 WL 747846 (Fed. Cl. Spec. Mstr. Feb. 1, 2017) (collecting cases at footnote 3), *review denied*, 133 Fed. Cl. 341, *affirmed*, 900 F.3d 1357, *en banc rehearing denied*, 911 F.3d 1381.

course was biphasic; that is, there was an initial insult that caused irreparable brain damage, and that the brain injury RA sustained contributed to her persistent, refractory seizures.” Resp. Ex. C at 2. Accordingly, petitioners have established *Althen* prong two.

#### 4. *Althen* Prong Three

##### A. Legal Standard

*Althen* prong three requires establishing a “proximate temporal relationship” between the vaccination and the injury alleged. *Althen* at 1281. That term has 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 v. Sec’y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is medically acceptable timeframe must align with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352.

##### B. Discussion and Conclusion

It is undisputed that R.A. received the Tdap and Menactra vaccinations on August 5, 2013. Pet. Ex. 1 at 1. Three days after vaccination, on August 8, 2013, she developed a fever. Four days after vaccination, on August 9, 2013, she presented to urgent care with a fever of 104 degrees Fahrenheit. Pet. Ex. 4 at 49-51. More than seven days after vaccination, on August 13, 2013, at approximately 1:30 a.m., R.A. had a generalized tonic-clonic seizure, prompting EMS transport and hospitalization. Pet. Ex. 3 at 435. She had several more tonic-clonic seizures, including at approximately 9:00 p.m., when she entered status epilepticus prompting a pentobarbital-induced coma. Elevated GAD antibodies were found in a serum sample obtained on August 16, 2013. Pet. Ex. 11 at 253. Elevated protein and cells were found in a CSF sample obtained that same day. Pet. Ex. 23 at 358.

Dr. Huq opined: “The timing of [R.A.’s] onset of symptoms from *cytokines and inflammatory response* from the vaccine is consistent with her presentation of fever at three days and subsequent development of seizures at one week and around two [to] three weeks, the MRI changes.” Tr. 121 (emphasis added).<sup>54</sup> Dr. Huq further opined that the vaccine-induced inflammatory response can both cause the initial seizures and also lead to a *cytotoxic T-cell mediated process*, Tr. 97-98, 121-22, which takes more time, Tr. 89, but probably starts within two weeks of the vaccinations, Tr. 122. Dr. Huq opined: “This is a well-accepted timeframe for an immune-mediated response.” Pet. Ex. 29 at 13.

Dr. Huq also opined: “Given the overlapping mechanisms of fever and inflammation and the role of inflammation in epileptogenesis, as well as [the] direct effect of heat on physiologic processes such as ion channel function, it is likely that fever triggered by vaccination had a role in causing initial seizures as well as causing an earlier onset of seizures.” Pet. Ex. 31 at 5.

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<sup>54</sup> Dr. Kruer in fact agreed that a foreign antigen is first met by an innate immune response including fever, and that can occur within as little as one day. Tr. 250.

“Priming from [prior exposure to] tetanus toxoid also likely had a role in accelerating inflammation and immune response and triggering initial seizures.” *Id.* Dr. Huq stated that “priming” not only represents formation of memory B and T cells, but other processes such as induction of inflammatory cytokines and epigenetic changes. *Id.* at 5-6. Dr. Huq noted that R.A. had received five prior vaccinations with tetanus toxoid. He opined: “That [R.A.] did not develop any autoimmune condition during an earlier administration of tetanus vaccination does not exclude the possibility that priming from tetanus toxoid contributed to the development of autoimmune encephalitis at a later age when a combination of other susceptibility factors pushed her above the threshold of clinical expression.” *Id.*

Dr. Kruer initially opined that the timing in this case was not medically acceptable because molecular mimicry would take 10 – 14 days, citing an article by Cornaby et al.<sup>55</sup> focusing on B cells and antibodies. Resp. Ex. A at 3-4. However, Dr. Huq consistently opined that this condition is mediated by inflammation and T cells. *See, e.g.*, Pet. Ex. 29 at 6, 7, 8; Pet. Ex. 31 at 3-4.

Dr. Kruer testified: “...[F]rom what we know about both humoral and cell-mediated immunity, that it takes, typically, from between seven to 14 days in order for an appropriate response to be mounted. If the initial reaction triggered cytokine production, and then that led to fever on day four, I believe, it was then only three additional days until she manifested the seizures. Three days is not enough time, according to current scientific understanding... to mount an antibody or a cytotoxic response.” Tr. 248-49.

However, Dr. Kruer agreed that the cytokine response leading to fever occurs as part of the early innate immune response to a vaccine and can happen as early as in the first day. Tr. 250. He also agreed that the innate immune response, which can give rise to inflammation, is the first step in triggering the adaptive immune response. *Id.* He also agreed that it could take as little as seven days to mount either a humoral [e.g., T cells] or cell-mediated [e.g., B cells and antibodies] response. Tr. 248. On cross-examination, he confirmed that it can take as little as seven days for autoimmunity to develop, “as a general principle”. Tr. 292-93. This fits the present case, in which R.A. developed fever approximately four days after vaccination and seizures seven days after vaccination.

Dr. Kruer also suggested that it would take longer to develop a new, adverse autoimmune response: “[I]f you were to hypothesize that this actually went awry at some point, you know, the rails went off the track, that implies that it’s not the same response. It now requires the process of affinity or avidity hypermutation, and it requires clonal [sic? clonal?] expansion in order to get a different result.” Tr. 252. After the memory response, “there’s a whole process of clonal [sic? clonal?] expansion where those T-cell receptors and B-cell receptors then undergo a process of mutation and refinement and all kinds of variants on that memory response... Now, those guys could end up being bad players. But it’s going to take time to do that is what I’m saying.” Tr. 254. Dr. Kruer did not cite to any literature in support for his opinion. I have reviewed his literature and have not independently found any support for his opinion.

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<sup>55</sup> Cornaby et al., *B Cell Epitope Spreading: Mechanisms and Contribution to Autoimmune Diseases*, 163 *Immunol. Lett.* 56 (2015) [Resp. Ex. A-4].

Accordingly, it is not evident that the timing of previous immune responses to an antigen will dictate the timing of a subsequent adverse response to the same antigen.

Past opinions in this program have recognized that the immune response to repeat exposure to vaccines can be more rapid than the response to the initial exposure to that vaccine; this is often referred to as an anamnestic response. While the timing of the autoimmune response is not entirely understood, there is preponderant evidence that the timing in this case was medically acceptable. Petitioners have established *Althen* prong three.

## **V. Conclusion**

After a careful review of the entire record before me, I find that petitioners have established that there is preponderant evidence that after receiving the Tdap and Menactra vaccinations on August 5, 2013, R.A. developed autoimmune limbic encephalitis (ALE) with the associated biomarker of GAD antibodies, and the residual effects of cognitive deficits and intractable epilepsy. Petitioners have also established causation-in-fact. Respondent has not raised an alternative cause. *See generally* Resp. Pre-Hearing Brief; Resp. Post-Hearing Response. Accordingly, petitioners, on behalf of R.A., are entitled to compensation. A separate damages order will be issued.

**IT IS SO ORDERED.**

**s/Thomas L. Gowen**

Thomas L. Gowen  
Special Master