In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: July 6, 2021

KRISTINE AKERS *and* MATTHEW AKERS, *as parents of* A.A., *a minor,*	*	PUBLISHED
	*	No. 15-597V
Petitioners,	*	
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Diphtheria-tetanus-acellular pertussis (DTaP); Hepatitis B (Hep B); Inactivated polio virus (IPV); Haemophilus influenzae type B (Hib); Rotavirus; Pneumococcal conjugate (PCV); Seizure Disorder; Infantile Spasms; West Syndrome; Focal Cortical Dysplasia (FCD); Entitlement Denial.
Respondent.	*	

William E. Cochran, Jr., Black McLaren et al., PC, Memphis, TN, for petitioners.[1]
Voris E. Johnson, United States Department of Justice, Washington, DC, for respondent.[2]

DECISION[3]

On June 12, 2015, Kristine & Matthew Akers ("petitioners") filed a petition on behalf of their minor daughter A.A., in the National Vaccine Injury Compensation Program.[4] Petition (ECF No. 1). The petition relates to A.A.'s receipt of the scheduled four-month diphtheria-

[1] Mr. Cochran is the attorney of record; Michael McLaren also participated in the entitlement hearing. Tr. 2.

[2] Mr. Johnson is the attorney of record; Ilene C. Albala, accompanied by Justine E. Walters, presented respondent's case at the entitlement hearing. Tr. 2.

[3] Pursuant to the E-Government Act of 2002, *see* 44 U.S.C. § 3501 note (2012), because this decision contains a reasoned explanation for the action in this case, I am required to post it on the website of the United States Court of Federal Claims. The court's website is at http://www.uscfc.uscourts.gov/aggregator/sources/7. **This means the decision will be available to anyone with access to the Internet.** Before the decision is posted on the court's website, each party has 14 days to file a motion requesting redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). "An objecting party must provide the court with a proposed redacted version of the decision." *Id.* **If neither party files a motion for redaction within 14 days, the decision will be posted on the court's website without any changes.** *Id.*

[4] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

tetanus-acellular pertussis ("DTaP"), hepatitis B ("Hep B"), inactivated polio virus ("IPV"), haemophilus influenzae type B ("Hib"), rotavirus, and pneumococcal conjugate ("PCV") vaccines on December 10, 2012.

The analysis of this case was significantly complicated by the evolving nature of A.A.'s seizures, as well as the increased understanding of their nature and source within the brain. The first MRIs did not reveal any particular abnormalities in A.A.'s brain. After A.A. grew older and she underwent more sensitive repeat MRIs and PET scans, as well as increasingly sophisticated and sensitive internal electrical monitoring including ECoG and SEEG, it was discovered that A.A.'s brain contained rather extensive abnormalities including focal cortical dysplasia ("FCD") which are associated with seizure disorders. Key events include the vaccinations at issue on December 10, 2012; seizure onset on December 12, 2012; the petition's filing on June 12, 2015; the first MRI suggestive of FCD in October 2016; A.A.'s first surgical resection on June 23, 2017; the entitlement hearing on February 6-8, 2018; the submission of post-hearing briefs in March 2019; and the subsequent filing of medical records reflecting that on January 8, 2019, A.A. had undergone a second surgical resection which was followed by the resolution of her seizures. After the entitlement hearing and the second surgical resection, petitioners filed several thousand pages of medical records and the parties submitted multiple additional expert reports.

After fully reviewing all of the evidence and testimony presented in this case in accordance with the applicable legal standards, I find that petitioners have not met their legal burden of establishing that A.A.'s December 10, 2012, vaccines caused or substantially contributed to A.A.'s seizure disorder. Accordingly, petitioners are not entitled to compensation.[5]

I. Background

A. Medical History from 2012 – 2015

A.A. and her family live in Michigan. She was born in early August 2012. Shortly after birth and before being discharged from the hospital, she was diagnosed with moderate to severe reflux. Pet. Ex. 15 at 253-55; Pet. Ex. 22 at 14, 28, 49. She received the first Hep B vaccination at the hospital. Pet. Ex. 15 at 50.

A.A. received regular pediatric care. *See generally* Pet. Ex. 15. At the one-week well-child visit, her physical examination was normal, although she had blood-tinged mucus in her diaper and had gained only about one ounce of weight since her hospital discharge. *Id.* at 50-52. At the two-week well-child visit, A.A. was underweight and diagnosed with feeding problems. *Id.* at 48-50. At the one-month well-child visit, A.A. continued to experience feeding problems and Dr. Sloan provided samples of a different formula. *Id.* at 47-48.

[5] Pursuant to Section 13(a)(1), in order to reach my decision, I have considered the entire record, including all of the medical records, expert testimony, and literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

At the two-month well-child visit on October 9, 2012, A.A. had no complaints, normal weight, and normal developmental gains. She received her second Hep B vaccine as well as her first DTaP, IPV, pneumococcal, Hib, and rotavirus vaccinations. Pet. Ex. 15 at 45-46. There are no records or allegations that A.A. had any adverse response to these vaccinations.

At the four-month well-child visit on Monday, December 10, 2012, A.A. was recorded to be doing well. Her weight had dropped to the 39th percentile for her age without weight loss. The physical examination was normal with the exception of plagiocephaly.[6] At this encounter, A.A. received her third Hep B as well as her second DTaP, IPV, pneumococcal, Hib, and rotavirus vaccinations, which are at issue in this claim. Pet. Ex. 15 at 43-44. There is no record or allegation that A.A. developed inflammation at the injection site or a fever after these vaccinations.

Five days later, on Saturday, December 15, 2012, her parents brought A.A. to the emergency room at Beaumont Children's Hospital in Royal Oak, Michigan. The purpose was evaluation for possible seizures. A registered nurse recorded: "Mom states child had vaccinations on Monday [December 10, 2012] and one short episode like this with rolling eyes into back of head and twitching tongue with unresponsiveness on Wednesday [December 12, 2012] which lasted for maybe 5 – 10 seconds. Now child is responding appropriately, smiling, and following activity with moving her eyes and head." Pet. Ex. 19 at 9.

The attending physician recorded similarly that "On Monday (12/10/12) [A.A.] had her 4-month immunizations (all vaccines she has had in past). Tuesday, she did not want to drink after 1730. She didn't wake up until 1000 Wednesday. She drank well that day but wasn't herself, per mom. Thursday she was back to normal, however in the afternoon she had a 15 second episode where her eyes were looking off the side and her tongue twitched. Last night again there was a similar 15-second episode." Pet. Ex. 19 at 10. Then, on Saturday, December 15, 2012, A.A. had "2 seizure-like episodes" where her "eyes were rolled back with tongue twitching, this lasted for approximately 40 seconds" then resolved spontaneously". *Id.* There was no history of recent fever, upper respiratory infection (URI) symptoms, apnea, or respiratory problems. *Id.* There was no family history of seizures. On examination in the emergency room, A.A. was a smiling, active baby with a strong cry. *Id.* Her temperature was recorded to be normal and afebrile. *Id.* at 11. While in the emergency room, A.A. suffered another seizure lasting approximately 15 – 20 seconds. *Id.* at 12. Within the next hour, A.A. tolerated a bottle of formula and went to sleep. *Id.* A.A. was admitted for a neurology consult. Pet. Ex. 19 at 12. A computerized tomography (CT) scan was negative. *Id.* at 284. Lab work was unremarkable. *Id.* at 14, 39, 53.

Following admission, A.A. continued to exhibit short seizures. On December 16, 2012, a neurologist, Surya Gupta, M.D., conducted an initial evaluation. Pet. Ex. 15 at 236-37. On physical examination, A.A. had significant head lag and was unable to support her head when held. *Id.* at 237. Dr. Gupta prescribed phenobarbital, which proved to be the first of many seizure medications attempted for A.A. *Id.* at 237, 246.

[6] Plagiocephaly is an "oblique deformation of the cranium." Resp. Post-Hearing Response at n. 2 (citing *Stedman's Medical Dictionary* (28th ed. 2006) at 1503).

On December 17, 2012, A.A. underwent a three-minute electroencephalogram (EEG)[7] which was reported as normal with no epileptiform abnormalities. Pet. Ex. 5 at 52. Magnetic resonance imaging (MRI) at 1.5 Tesla strength[8] of her brain was unremarkable. *Id.* at 35.

By December 19, 2012, A.A. continued to have seizures, but "to a lesser extent since starting phenobarbital". Pet. Ex. 15 at 239. She was "now having them every 2-3 hours, with 15-30 second duration". *Id.* This prompted a second opinion with another neurologist, Gary Trock, M.D., who noted A.A.'s drop in weight percentile without weight loss (prior to the four-month vaccinations and onset of seizures), mild hypotonia[9], and slight head lag. *Id.* Dr. Trock's assessment was a seizure disorder, with: "Etiology not clear. May have underlying encephalopathy[10], given refractory nature, the minor findings on exam, and the slight fall off in weight percentile. Structural lesions not apparent on MRI also possible." *Id.* at 241. Dr. Trock prescribed continued phenobarbital with the addition of levetiracetam. *Id.*

Also on December 19, 2012, A.A. underwent a 24-hour EEG which was moderately abnormal and suggestive of a left hemisphere partial seizure disorder and a left hemisphere structural lesion. Pet. Ex. 5 at 53-54. This was the first documentation of a potential structural lesion which to that time had not been seen on MRI.

On December 21, 2012, A.A. was discharged from the hospital with instructions to follow up with Dr. Trock. *See* Pet. Ex. 19 at 34. Over the next several days, Dr. Trock spoke with the parents who reported that A.A. was having seizures every 1 – 3 hours, but she was happy and playful in between those episodes. *Id.* at 77.

On December 25, 2012, A.A. was readmitted to Beaumont – Royal Oaks Hospital for seizures that had increased and changed to include staring spells and stiffness in her extremities. Pet. Ex. 19 at 297. She was evaluated by the director of the pediatric epilepsy program, Daniel Arndt, M.D., who became her primary neurologist over the subsequent years. At this initial consult, Dr. Arndt recorded the history including that A.A. received her four-month vaccinations on December 10, 2012 "with no associated febrile reaction or vaccine encephalopathy (outside of

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[7] An electroencephalogram (EEG) is defined as: "A recording of the potentials on the skull generated by the currents emanating spontaneously from nerve cells in the brain. The normal dominant frequency of these potentials is about 8 to 10 cycles per second and the amplitude about 10 to 100 microvolts. Fluctuations in potential are seen in the form of waves, which correlate well with different neurologic conditions and so are used as diagnostic criteria." *Dorland's Medical Dictionary Online*, at https://www.dorlandsonline.com (hereinafter "*Dorland's*").

[8] Magnetic resonance imaging (MRI) is defined as "a method of visualizing soft tissues of the body by applying an external magnetic field that makes it possible to distinguish between hydrogen atoms in different environments." *Dorland's*. Tesla (T) is defined as a standard unit of "magnetic flux density" and was named after the physicist Nikola Tesla (1856 – 1943). *Id*.

[9] Hypotonia is defined as "a condition of diminished tone of the skeletal muscles, so that they have diminished resistance to passive stretching and are flaccid." *Dorland's*.

[10] Encephalopathy is defined as "any degenerative disease of the brain" with different subtypes based on recognized etiology. *Dorland's*. Petitioners did not allege and the record does not support that A.A.'s injury represents an encephalopathy, as evidenced by this notation by Dr. Arndt.

postictal agitation/lethargy)", followed by the onset of seizures the next day. Pet. Ex. 19 at 305. Dr. Arndt's assessment was breakthrough seizure and focal epilepsy, which was "multifocal, primary focus L anterior temporal > inferior/ lateral frontal." *Id.* at 312. Dr. Arndt "suspect[ed] developmental/ structural etiology – likely focal cortical dysplasia[11] (current imaging not definitive)" although a genetic etiology was also possible. *Id*. He also recorded: "CT/MRI so far without conspicuous focal cortical malformation or focal cortical dysplasia, needs 3T MRI and PET. Unable to access 3T epilepsy MRI currently here at Royal Oaks (npt, <6 months). Will follow up on this." *Id.* During this hospitalization, Dr. Arndt started A.A. on intravenous lorazepam and topiramate. *Id.* On December 30, 2012, A.A. was discharged with a referral for further evaluation at the Cleveland Clinic. *Id.* at 226-28, 321-24, 333.

On January 2, 2013, A.A. was brought to the Cleveland Clinic, during which she had a seizure which prompted admission to the epilepsy unit. Pet. Ex. 21 at 1-3. Another MRI of the brain failed to identify any focal lesions. *Id.* at 33. A PET scan[12] showed diffuse cortical hypometabolism with left hemisphere asymmetry, slightly more pronounced in the left frontal region, left posterior lateral temporal region, and left mesial temporal structure. *Id.* at 32-33. A video EEG showed seizure activity in the left temporal parietal area with frequent epileptiform discharges and evidence of cerebral dysfunction in the left hemisphere along with a diffuse epileptic encephalopathy. *Id.* at 72-74. At this point in time, A.A.'s seizures still appeared to be arising predominantly from the left hemisphere. A.A. was discharged from the Cleveland Clinic without a definitive impression, but a plan to increase topiramate. *Id.* at 29, 32-33.

In February 2013, at a six-month primary care visit, A.A. was recorded to have developmental delays, an inability to track with her eyes, and poor tone. Her parents "want[ed] to delay vaccines as these seizures started the day after her 4-month vaccines". The primary care provider accepted the parents' decision. However, she recorded: "I don't think this is vaccine related." Pet. Ex. 15 at 37-40. A.A. started physical therapy and occupational therapy. *See generally* Pet. Ex. 6.

[11] Focal is defined as pertaining to "the chief point of a morbid process." *Dorland's.* Cortical is defined as pertaining to the cortex, which is defined as "an external layer, such as the bark of a tree or the rind of a fruit" or alternatively, "the outer layer of an organ or other body structure, as distinguished from the internal substance." *Id.* Dysplasia is defined as any "abnormality of development" or "in pathology, alteration in size, shape, and organization of adult cells". *Id.* In this case, the parties' central dispute was whether FCD can be entirely asymptomatic, requires a trigger, or is inherently epileptogenic. This is discussed at greater length in the analysis section below.

[12] Tomography, also known as body section radiography, "mov[es] an x-ray source in one direction as the film is moved in the opposite direction, thus showing in detail a predetermined plane of tissue while blurring or eliminating detail in other planes". *Dorland's*. Positron emission tomography ("PET") is one method which depends on the subject being administered a naturally-occurring substance, typically glucose, containing positron-emitting isotopes. *Id.*

In February 2013, a repeat 24-hour EEG was moderately abnormal; the findings were felt to be consistent with infantile spasms[13] with hypsarrhythmia.[14] Pet. Ex. 19 at 570. In April 2013, Dr. Arndt started A.A. on adrenocorticotropic hormone (ACTH) injections and vigabatrin. Pet. Ex. 19 at 736.

In March 2013, a clinical geneticist at Beaumont recorded that: "[petitioner Adrienne Akers] expresses understanding that [A.A.]'s seizure disorder is very unlikely to have been caused by vaccination but that it is possible that [A.A.] may (or may not) have had a pre-existing pre-disposition to epilepsy made manifest following vaccination." Pet. Ex. 2 at 49. During this appointment, the geneticist's differential diagnosis included chromosomal abnormality (microscopic or submicroscopic), syndromic infantile spasms (tuberous sclerosis complex, Aicardi syndrome, other) syndromic hypothalamic hamartoma, GLI3-related disorders (Pallister-hall syndrome), and SLC1A-related seizure disorder. *Id.* He considered testing specifically for mutations in the SCN1A gene. *Id.* However, in August 2013, this geneticist advised that he had been "unable to secure a unifying genetic diagnosis" for A.A.'s condition. *Id.* at 16.

In September 2013, a neuro-geneticist at the Cleveland Clinic recorded that the temporal association between A.A.'s four-month vaccinations and the onset of seizures "raise[d] the concern of a sodium channelopathy, however infantile spasms are not typically seen in these conditions." Pet. Ex. 27 at 9. Therefore, he planned to evaluate for other conditions as well. *Id.* In January 2014, a comprehensive epilepsy gene panel found that two genes, GAMT and EFCH1, contained "variants of unknown significance". Pet. Ex. 13 at 164. The neuro-geneticist wrote:

> A variant in the EFHC1 gene typically presents with a seizure disorder very different from [A.A.'s] and is likely not causing [her] symptoms. A variant in the GAMT gene does not cause symptoms when present in isolation: a 2nd mutation or deletion in the gene was not identified. Thus it is likely not the cause of [her] symptoms.

Id. At the next appointment, the neuro-geneticist suggested other explanations for A.A.'s condition. Pet. Ex. 21 at 57. But in December 2014, whole-exome sequence analysis and mitochondrial genome testing were negative. *See generally* Pet. Ex. 24.

Throughout 2013 and 2014, Dr. Arndt, the Director of Pediatric Epilepsy at Beaumont Children's Hospital, continued to manage A.A.'s neurological condition. In February 2014, A.A. had a recurrence of seizure activity possibly in association with tapering down her

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[13] Infantile spasms, also referred to as West syndrome and jackknife seizures, are defined as "a syndrome of severe *myoclonus* appearing in the first 18 months of life and associated with general cerebral deterioration; it is marked by severe flexion spasms of the head, neck, trunk, and extension of the limbs." *Dorland's*. Myoclonus is defined as "shock-like contractions of a portion of muscle" which may "occu[r] as part of an epileptic aura or seizure". *Id.*

[14] Hypsarrhythmia is defined as "an electroencephalographic abnormality sometimes observed in infants, with random high-voltage slow waves and spikes that arise from multiple foci and spread to all cortical areas. It is seen most commonly in cases of jackknife seizures." *Dorland's*. It is noted that "jackknife seizures" are synonymous with infantile spasms, which are defined in the preceding footnote.

medications. Pet. Ex. 19 at 1270. Dr. Arndt made various adjustments to her medications to her in an effort to treat her recurrent seizure activity as well as behavioral issues. Pet. Ex. 5 at 14-18, 21-24; Pet. Ex. 13 at 6-8; 103-04. In May 2014, A.A. was readmitted to Beaumont Children's Hospital due to a concern for new seizures. Pet. Ex. 13 at 67-72.

In September 2014, when A.A. was appropriately two years old and additional development of myelination had taken place, she underwent a repeat MRI at the Mayo Clinic. Pet. Ex. 89 at 3-4. The radiologist's impression was that A.A.'s brain contained "non-specific," "multifocal areas of T2 hyperintensity involving the subcortical and periventricular white matter of the supratentorial structures new since the prior exam" on January 4, 2013. *Id.* at 4. Following additional EEGs, on January 27, 2015, A.A. underwent surgery for placement of a vagus nerve stimulator.[15] *Id.* at 2004-36.

B. Initial Procedural History

On June 12, 2015, petitioners filed their claim alleging that the four-month DTaP, Hep B, IPB, Hib, rotavirus, and PCV vaccinations either caused or significantly aggravated A.A.'s development of a seizure disorder. Petition at Preamble. On September 23, 2015, respondent advised that he would defend the claim. Resp. Status Report (ECF No. 10).

In April 2016, petitioners filed the first expert report of a geneticist Richard Boles, M.D.[16], who opined that certain known variants in the EFCH1 gene are associated with a variety of epilepsy phenotypes. Dr. Boles opined that A.A.'s particular EFCH1 gene variant is not pathogenic but can create susceptibility. He opined that the vaccines A.A. received were a "plausible" trigger for the development of "EFCH1-related neurological disease." Pet. Ex. 32 at 8. Petitioners also filed the first expert report of a neurologist, Marcel Kinsbourne, M.D.,[17] who

[15] A 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*.

[16] Dr. Boles obtained a Bachelor of Science degree in Biochemistry with Honors from the University of Arizona in 1983. Pet. Ex. 30 at 1. He obtained a medical degree from the University of California at Los Angeles (UCLA) Medical School in 1987. *Id.* He completed an internship and a residency in pediatrics at the Harbor-UCLA Medical Center. *Id.* Dr. Boles then served simultaneously as a genetic fellow at Yale University School of Medicine and an attending pediatrician in the Yale-New Haven Hospital Emergency Room from 1991 – 1993. *Id.* at 2. Dr. Boles has since developed an academic and clinical specialty in genetics. He was affiliated with University of Southern California (USC) Keck School of Medicine and Children's Hospital Los Angeles from 1993 – 2014. *Id.* at 2-3. In 2014, Dr. Boles transitioned to the volunteer faculty at USC and opened a private practice, in which he follows approximately 200 patients who have unusual disorders, nearly all neurological, probably over half involving seizures. Dr. Boles also began working for various private biotechnology companies. In both his private practice and consulting work, Dr. Boles evaluates DNA sequences for predispositions towards neurological conditions such as epilepsy. Tr. 46-48. Dr. Boles is licensed to practice medicine in the state of California and is currently board-certified in clinical biochemical genetics. Pet. Ex. 30 at 1-2; Tr. 45. Dr. Boles was offered and admitted without objection as an expert in medicine, pediatrics, clinical genetics, and clinical biochemical genetics. Tr. 49.

[17] Dr. Kinsbourne obtained a Bachelor of Arts degree from the University of Oxford in 1952 and a medical degree from the University of Oxford School of Medicine in 1955. Pet. Ex. 33 at 1. He has obtained licenses to practice medicine in England, Canada, and the United States and is board-certified in pediatrics. *Id.* He had nine years of post-graduate training, then became a professor and clinician in the field of pediatric neurology. Pet. Ex. 33 at 2-3;

supported vaccine causation in this case in part because "[n]euroimaging had failed to detect any structural lesion that could have been considered as causal." Pet. Ex. 32 at 5. Dr. Kinsbourne opined that the EFCH1 gene variant created a "susceptibility" after which the vaccines acted as a "second hit" or "trigger" to cause clinical epilepsy. *Id.* Dr. Kinsbourne opined that the four-month vaccines specifically DTaP, can activate pro-inflammatory cytokines, which can serve as a trigger for infantile spasms. *Id.* at 7-8.

In response, respondent filed the first report of neurologist Gerald M. Raymond, M.D.,[18] who agreed that A.A. had infantile spasms, questioned the relevance of the gene variant, and disputed vaccine causation. Resp. Ex. A. Respondent also filed his report pursuant to Vaccine Rule 4(c) in which he formally opposed compensation of petitioners' claim. Resp. Rept. (ECF No. 32). On November 30, 2016, I held a status conference pursuant to Vaccine Rule 5, during which I encouraged informal resolution. I also ordered supplemental expert reports as well as an entitlement hearing to take place in February 2018. *See* Scheduling Order (ECF No. 36); *see also* Pre-Hearing Order (ECF Nos. 39, 52).

C. Subsequent Medical History Including MRI Findings of FCD in 2016

Petitioners subsequently filed updated medical records which shed additional light on A.A.'s condition. Specifically, in March 2016, Dr. Arndt recorded his opinion that A.A.'s seizure disorder did not have a "genetic or metabolic phenotype." Pet. Ex. 86 at 5. He

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Tr. 196. Dr. Kinsbourne highlighted his experience at the Eunice Kennedy Shriver School as the director of the behavioral neurology department, where he conducted research and consulted on thousands of patients, "includ[ing] a fair amount of epilepsy" from 1980 – 1991. He was an attending neurologist at Massachusetts General Hospital during this same time period. Pet. Ex. 33 at 3; Tr. 197. Dr. Kinsbourne testified that since the early 1990s, he hasn't "formally engaged in treatment programs for children with epilepsy" but he has seen occasional patients on private referral. Tr. 247. He testified that he has maintained his board certifications. Tr. 200. He has also continued to publish and serve as a peer reviewer including in the field of neurology. Tr. 201. In 1995, Dr. Kinsbourne became a professor of psychology at the New School for Social Research. Pet. Ex. 33; Tr. 197. Dr. Kinsbourne testified that this encompassed "matters related to the brain, neuroscience, cognitive neuroscience, and of course, neurology." Tr. 197. Dr. Kinsbourne retired from the New School and from his "formal medical work" in 2014. Tr. 197-98. Dr. Kinsbourne has significant experience as an expert in the Vaccine Program. Tr. 199. Dr. Kinsbourne was offered and admitted without objection as an expert in neurology and pediatric neurology. Tr. 203. He agreed on cross-examination that he was not an immunologist and that petitioners had retained Dr. Gershwin to opine on that subject. Tr. 248.

[18] Dr. Raymond obtained a Bachelor of Science degree in Biology from Fairfield University in 1980 and a medical degree from the University of Connecticut in 1984. Resp. Ex. B at 1. He was an intern, then as a resident in pediatrics at Johns Hopkins University, after which he was a resident in neurology at Massachusetts General Hospital. *Id.* After a fellowship in developmental neuropathology in Belgium, he had a fellowship in genetics and teratology at Massachusetts General Hospital. *Id.* Dr. Raymond has taught and practiced neurology and genetics at several teaching hospitals including Johns Hopkins University, the University of Minnesota and Kennedy Krieger Institute. *Id.* at 1-2. In 2017, Dr. Raymond accepted a primary appointment as professor of neurology and pediatrics at Penn State Medical Center. Tr. 283. Dr. Raymond has been licensed to practice medicine in several states. Resp. Ex. B at 14. At the time of the entitlement hearing, he was board-certified in neurology (with special competency in child neurology), and clinical genetics. *Id.*; Tr. 285. Dr. Raymond described his focus as "the genetic underpinnings for [a patient's] neurologic condition". Tr. 286. He has clinical experience evaluating pediatric patients with FCD and epilepsy. Tr. 287. Dr. Raymond was offered and accepted without objection as an expert in neurology, genetics, and pediatrics. Tr. 287.

recommended removing the vagal nerve stimulator so that A.A. could undergo a repeat MRI, with a stronger 3T scanner, to evaluate A.A.'s brain for suspected FCD. *Id.* He suspected that FCD was present in the right parietal lobe[19] as well as the cingulate gyrus.[20] *Id.* If that was borne out, A.A. would be a candidate for surgical resection. *Id.* at 1-3, 5.

After removal of the vagal nerve stimulator, in October 2016 (nearly four years after the subject vaccinations and the onset of seizures), A.A. underwent a repeat brain MRI, which used a stronger 3T scanner. Pet. Ex. 56 at 86-88. This MRI identified an area of potential FCD in the right high anterior parietal lobe within the depth of the sulcus.[21] *Id.* at 86. Adjacent to the possible FCD, there were white matter T2 hyperintensities. *Id.* Heterotopic[22] neurons were seen in the subependymal layer adjacent to the right lateral ventricle.[23] *Id.* The right hemisphere, especially superiorly compared to the left hemisphere, had asymmetric sulcation.[24] The right high anterior frontal lobe[25] showed additional but questionable areas of cortical thickening. Both hemispheres had some scattered white matter T2 hyperintensities. The hippocampal formations had slight asymmetry, with the right being slightly smaller than the left, but without significant signal abnormality or volume loss. *See* Pet. Ex. 56 at 86-88. This MRI provided a significant change in the understanding of A.A.'s condition, which both parties and their experts incorporated into their positions towards the vaccine injury claim.

D. Subsequent Procedural History

Petitioners filed a second report from Dr. Boles, who opined that the EFCH1 gene is associated with cortical development. Pet. Ex. 61. Petitioners also filed a second report from Dr. Kinsbourne, who opined that FCD creates a hyperexcitable neural network and a lowered seizure threshold. However, Dr. Kinsbourne opined that individuals with FCD can develop seizures at varying ages and sometimes not at all, which in his view, supported that a trigger was necessary. He opined that vaccines, specifically DTaP, can serve as this trigger. He opined that with FCD, the earlier onset of seizures can cause a worsened course and sequelae such as developmental delay. Pet. Ex. 64.

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[19] The parietal lobe is defined as: "the upper central lobe of the cerebral hemisphere". *Dorland's*.

[20] Cerebral gyri are elevated areas on the surface of the cerebral hemispheres which are separated by cerebral sulci (singular: sulcus) which are long grooves or furrows. This structure is caused by the in-folding of the cortex. *Dorland's*. The cingulate gyrus is "an arch-shaped convolution closely related to the surface of the corpus collosum, from which it is separated by the callosal sulcus." *Id.*

[21] As sulcus (plural: sulci) is a long groove or furrow in the cerebral hemisphere. *Dorland's*.

[22] Heterotopia is the misplacement of gray matter (nerve fibers and nerve cells), within white matter (axons). *See Dorland's*; *see also* Tr. 205.

[23] A cerebral ventricle is a cavity filed with cerebral spinal fluid. There are four cerebral ventricles including two lateral ventricles (one in each hemisphere). *Dorland's*.

[24] Sulcation is defined as "the formation of sulci". *Dorland's*.

[25] Adjacent to the parietal lobe, the frontal lobe is anterior (nearest to the front) in the cerebral hemisphere. *Dorland's*.

In response, respondent filed a second report from Dr. Raymond and the initial report of another neurologist, Michael H. Kohrman, M.D.[26] Drs. Raymond and Kohrman opined that FCD is intrinsically epileptogenic and that there is no need for a trigger to cause seizures. Rather, the specific histopathology and extent of FCD is predictive of the course. Resp. Exs. FF, BBBB.

Respondent also filed the first expert report of an immunologist, Christine McCusker,[27] who challenged the theory, introduced by Dr. Kinsbourne, that vaccines including DTaP can cause or contribute to infantile spasms in the context of FCD. Dr. McCusker opined that vaccines cause the release of cytokines, but generally only at the site of administration. Resp. Ex. FF at 4. She opined that the same cytokines found in the immune system are constitutively expressed by cells in the brain, where they play distinct roles in normal brain homeostasis, and in this respect are not 'pro-inflammatory'. *Id.* at 3.

To respond to Dr. McCusker, petitioners retained an expert immunologist, M. Eric Gershwin, M.D.[28] He opined that: "Dr. McCusker is quite correct that if [A.A.] had a normal

[26] Dr. Kohrman obtained bachelor's and master's degrees in chemistry from Stanford University, followed by a medical degree from Rush Medical College in 1981. Resp. Ex. CCCC at 1. He completed an internship and a residency in pediatrics at the University of Chicago, followed by a fellowship in pediatric neurology at the University of Illinois. *Id.* Dr. Kohrman has taught and practiced neurology at several teaching hospitals. *Id.* at 2. In 2016, he became the director of child neurology at Akron Children's Hospital and a professor at the affiliated school Northeastern Ohio Medical University. Resp. Ex. CCCC at 2; Tr. 451. Dr. Kohrman is licensed to practice medicine in several states and is board-certified in pediatrics, neurology (with special competency in child neurology), clinical neurophysiology, epilepsy, and sleep medicine. *Id.* at 3. Dr. Kohrman testified that for approximately thirty years, his clinical focus has been pediatric neurology. Tr. 454. For approximately sixteen or seventeen years, 95% of his patients have pediatric epilepsy and most of those patients have what is called drug-resistant or refractory epilepsy. Tr. 454. He sees pediatric patients with FCD "on a regular basis… if not daily, weekly." Tr. 454-55. Dr. Kohrman has also published extensively on epilepsy and serves as the editor-in-chief of the Journal of Pediatric Epilepsy. *See generally* Resp. Ex. CCCC; Tr. 456. Dr. Kohrman was offered and accepted without objection as an expert in child neurology and epileptology. Tr. 456-57.

[27] Dr. McCusker obtained a Bachelor of Science degree in Microbiology with honors from the University of Toronto in 1985 and a Master of Science degree in Medical Sciences from McMaster University in 1988. Resp. Ex. HH at 1. She was in a PhD program in immunology at McMaster University from 1987 – 1990, before transferring to the medical school, from which she obtained a medical degree from in 1993. *Id.* at 1-2; Tr. 334. Dr. McCusker then joined McGill University/ Montreal Children's Hospital, where she was a resident in pediatrics, a clinical fellow in Allergy and Immunology, and then joined the faculty where she is currently an associate professor as well as the division director of pediatric allergy and immunology. Resp. Ex. HH at 2-3; Tr. 335. She is licensed to practice medicine in both Canada and the United States, and is board-certified in pediatrics, allergy and immunology. Resp. Ex. HH at 3; Tr. 340. Dr. McCusker was offered and accepted without objection as an expert in pediatrics and pediatric immunology. Tr. 340.

[28] Dr. Gershwin graduated with a Bachelor of Science degree in mathematics from Syracuse University in 1966 and a medical degree from Stanford University in 1971. Pet. Ex. 91 at 1. He completed an internship and residency at Tufts-New England Medical Center, then served as a clinical associate in immunology at the National Institutes of Health. *Id.* at 2. In 1975, Dr. Gershwin joined the University of California Davis (UC Davis) School of Medicine to start its immunology program. *Id.*; Tr. 105. With the exception of a sabbatical year in immunology and molecular biology at the Hall Institute for Medical Research in Australia, Dr. Gershwin has been on the UC Davis faculty since 1975. He is currently the Jack and Donald Chia Professor and a Distinguished Professor of Medicine in the divisions of Rheumatology/ Allergy and Clinical Immunology at UC Davis. Pet. Ex. 191 at 1-2. Dr. Gershwin is licensed to practice medicine in the state of California. He is board-certified in internal medicine, rheumatology,

central nervous system[,] then the vaccination[s] should not have led directly to this acute change in her neuropathology. However, in the presence of her mutation and especially cortical dysplasia, her brain will be more susceptible to damage. In other words, one should consider the target tissue as being more vulnerable to cytokine-mediated inflammatory injury than the normal brain." Pet. Ex. 90 at 2.

On October 4, 2017, I held a status conference in anticipation of the entitlement hearing set to take place on February 6 – 8, 2018. *See* Pre-Hearing Orders (ECF No. 57).

E. Subsequent Medical History Including the First Surgical Resection in 2017

After the pre-hearing status conference, petitioners filed updated medical records. These reflect that following the March 2017 3T MRI of the brain that was suggestive of FCD, A.A. was brought to the Cleveland Clinic for further workup. This included repeat brain MRIs which were consistent with FCD. Pet. Ex. 89 at 1-8; Pet. Ex. 101 at 42-43. It was agreed that A.A. would undergo surgery to correlate the MRI findings and potentially remove the affected tissue. Pet. Ex. 101 at 1.

On June 23, 2017 at the Cleveland Clinic, A.A. underwent a craniotomy[29] on the right side of the brain, followed by intraoperative electrocorticography (ECoG)[30] which "mapped the malformation of cortical development stereotactically[31] to the post-inferior[32] parietal region behind the perirolandic strip."[33] Pet. Ex. 101 at 127. That tissue was removed. *Id.*

A neuropathologist recorded that this resected tissue measured 4.5 by 2.6 by 1.2 centimeters. Pet. Ex. 102 at 1. It showed "nodular white matter heterotopia, hyaline

allergy, and clinical immunology. *Id.* at 2; Tr. 106. He sees patients in both inpatient and outpatient settings, conducts peer review, and publishes his own research in medical journals. Tr. 106-08. Dr. Gershwin highlighted that he has been awarded an honorary doctorate degree by the University of Athens, home of the Hippocratic Oath, for lifetime achievement in immunology. Pet. Ex. 91 at 1; Tr. 109. He has been elected master of the American College of Physicians, which is a significant honor for an internist. Pet. Ex. 91 at 1; Tr. 109. He has also been funded by the NIH without interruption for approximately forty-five years. Tr. 91. Dr. Gershwin was offered and admitted without objection as an expert in internal medicine, rheumatology, allergy, and immunology. Tr. 109.

[29] Craniotomy is defined as any "operation" or "incision" into the cranium. *Dorland's*.

[30] Electrocorticography is defined as "electroencephalography [EEG] with the electrodes applied directly to the cortex of the brain." *Dorland's*.

[31] Stereotactic mapping can refer to "types of surgery… that use a system of three-dimensional coordinates to locate the site to be operated on." *Dorland's*.

[32] Post- means "after or behind." *Dorland's*. Inferior refers to "the lower surface of an organ or other structure." *Id.*

[33] Peri- means "near or around." *Dorland's*. "Rolandic" is most likely a reference to the fissure of Rolando, which is another term for the sulcus central cerebri, the "relatively deep, nearly vertical sulcus on the cerebral hemisphere which separates the frontal and the parietal lobe." *Id.*

protoplasmic astrocytopathy,[34] focal perivascular white matter atrophy, and focal perivascular chronic inflammation." *Id.* The neuropathologist commented: "Histologic sections show focal cortical disorganization associated with rare dysmorphic neurons.[35] Heterotopic nodules of gray matter are focally situated within white matter areas." *Id.*

During the surgery, ECoG showed epileptiform activity arising from within and at several locations surrounding the area to be resected. After the resection, the ECoG demonstrated continued spiking in the remaining tissue. Pet. Ex. 101 at 126-27; *see also id.* at 133-34 (ECoG report). Also after the resection, A.A. had increased seizures and was kept in the PICU for several days, after which she was discharged on June 28, 2017. *Id.* at 57-64.

Despite this first resective surgery, A.A. continued to have seizures, which Dr. Kotagal at the Cleveland Clinic hoped would lessen over time. Pet. Ex. 101 at 420-21. In July 2017, a brain MRI was stable and a 24-hour video EEG was "severely abnormal" with: "Several clusters of focal epileptic spasms from the R parietal/central region with morphology electrographically similar to presurgical epileptic spasms. Interictal findings also similar to presurgical state, but [interictal epileptic discharge] frequency & intensity significantly decreased." Pet. Ex. 121 at 25-27.

F. Subsequent Procedural History

In November 2017, petitioners also filed Dr. Kinsbourne's third report. He opined that A.A.'s FCD "is the main source of her seizure activity, not the mutation that may be its antecedent. [Dr. Kinsbourne would] offer no further discussion of EFCH1." Pet. Ex. 102 at 1. He also noted that A.A. had undergone the first surgical resection at the Cleveland Clinic. *Id.* at 6. Petitioners also filed their pre-hearing brief (ECF No. 64).

In December 2017, respondent filed Dr. Raymond's third report as Resp. Ex. HHHH, Dr. McCusker's second report as Resp. Ex. IIII, Dr. Kohrman's second report as Resp. Ex. JJJJ, and respondent's pre-hearing response (ECF No. 68). On January 11, 2018, petitioners filed their pre-hearing reply (ECF No. 72).

On January 12, 2018, the parties filed a joint pre-hearing submission (ECF No. 75). With regard to the facts, the parties stipulated to A.A.'s date of birth and her receipt of DTaP, Hep B, IPV, Hib, rotavirus, and PCV vaccines on December 10, 2012. *Id.* at 1. They did not stipulate to the precise onset of seizures, but they did stipulate that A.A. presented for evaluation of possible seizures on December 15, 2012. *Id.* They stipulated that A.A. was afebrile when she presented to the hospital, with no reports of a fever between the time of her vaccinations on December 10, 2012 and her arrival at the hospital on December 15, 2012. *Id.*, citing Pet. Ex. 19 at 9-12. They stipulated that A.A. was diagnosed with epilepsy and FCD. *Id.* at 1-2, citing Pet. Ex. 15 at 226-28; Pet. Ex. 101 at 440. The parties did not identify disputed material facts dispositive to

[34] Hyaline is defined as "glassy and transparent." *Dorland's*. Protoplasmic astroglia are defined as a type of neuroglial cells. *Id.* Cytopathy is defined as a disorder of a cell or its constituents. *Id.*

[35] Dysmorphic neurons are a key finding in FCD Type IIa. *See* Resp. Ex. MM and the analysis section below.

petitioners' theory of causation. *Id.* at ¶ 2.

With regard to material issues in the case, the parties stipulated that A.A. received vaccine[s] set forth on the Vaccine Injury Table; she received those vaccines within the United States; and she has suffered the residual effects of her epilepsy for more than six months. Joint Pre-Hearing Submission at 2. The parties stipulated that A.A.'s FCD "played a role in causing her seizure disorder." *Id.* They asked for resolution of the following disputed material issues:

1. Whether A.A.'s December 10, 2012, vaccinations also played a role in causing her seizure disorder.
2. Whether petitioners have put forth preponderant evidence of a reliable medical theory causally connecting A.A.'s December 10, 2012, vaccinations with her epilepsy.
3. Whether petitioners have put forth preponderant evidence of a logical sequence of cause and effect showing that A.A.'s December 10, 2012, vaccinations were the reason for her epilepsy.
4. Whether petitioners have put forth preponderant evidence showing a proximate temporal relationship between A.A.'s vaccinations and her epilepsy.

Joint Pre-Hearing Submission at 2-3.

An entitlement hearing took place in Detroit, Michigan, on February 6 – 8, 2018. *See* Transcript (Tr.) (ECF Nos. 85-88). Petitioner Kristine Akers (the mother of A.A.) offered credible fact testimony. Petitioners next called Dr. Boles, who repeatedly opined that the EFHC1 gene variant's exact mechanism was not known but it could be "altered brain development" such as FCD. *See generally* Tr. 44-100. Towards the conclusion of Dr. Boles's testimony, I held a sidebar. Afterwards, I summarized that the parties had "stipulate[ed] that the EFCH1 theory is no longer part of the case and that it's not necessary for the respondent's [experts, sic] to address that." Tr. 98. Additionally, I stated that I would not "hol[d] against the petitioners the fact that their experts addressed that issue before FCD was a medically known phenomenon to be in existence in this young child." *Id.*

Petitioners then called Dr. Gershwin, who testified by videoconference and was then excused. Tr. 180. Petitioners then called Dr. Kinsbourne, who testified in person and was then excused to travel home for a personal medical appointment. Tr. 189-93, 281. Petitioners reserved the right to have their experts, particularly Dr. Kinsbourne, offer any necessary rebuttal after the hearing.

Respondent then presented expert testimony from Drs. McCusker, Raymond, and Kohrman. Of note, Dr. Raymond stated multiple times that A.A.'s brain contained "extensive" areas of FCD. *See, e.g.*, Tr. 288, 301, 302, 303, 305, 307. Afterwards, Dr. Kohrman testified that there were "multiple," "discrete foci of heteropia and T2 abnormalities that most likely represented FCD, on both sides of A.A.'s brain. *See* Tr. 478-79. Petitioners objected that in Dr. Kohrman's report, while he stated that he had reviewed A.A.'s MRIs and PET scans, he did not

opine on any specific findings or go into detail about there being multiple foci. Tr. 485. I permitted the line of testimony, including the review of the MRIs and PET scans, as it was relevant to my understanding of the case, *see generally* Tr. 485-577 and Resp. Ex. UUU (Dr. Kohrman's annotated MRI images, filed after the hearing), but as noted below, I permitted petitioners to subsequently retain their own neuroradiologist to review the MRIs and PET scans.

After the hearing, petitioners requested the opportunity to file supplemental expert reports. Pet. Status Report (ECF No. 82) and two status conferences took place, *see* Scheduling Orders (ECF No. 83, 89), in which I directed multiple detailed questions to the various experts. On May 7, 2018, petitioners filed Dr. Kinsbourne's fourth report as Pet. Ex. 137 and Dr. Gershwin's second report as Pet. Ex. 138. Petitioners also filed two reports from a neuroradiologist, Robert M. Kessler, M.D,[36] who reviewed A.A.'s MRIs and PET scans and responded to Dr. Kohrman's interpretation. Pet. Exs. 136, 139.

On July 6, 2018, respondent filed Dr. Kohrnman's third report as Resp. Ex. VVVV and Dr. McCusker's third report as Resp. Ex. WWWW.

On July 20, 2018, petitioners filed a motion for a referral to mediation. Pet. Mot. (ECF No. 100); *see also* Scheduling Order (ECF No. 101); Resp. Response (ECF No. 110). I denied the motion because in light of respondent's opposition, mediation was unlikely to be fruitful. *See* Order (ECF No. 111)

On October 15, 2018, petitioners filed Dr. Kinsbourne's fifth report as Pet. Ex. 150 and Dr. Gershwin's third report as Pet. Ex. 157. That same day, respondent filed Dr. Kohrman's fourth report as Resp. Ex. YYYY and Dr. McCusker's fourth report as Resp. Ex. AAAAA. On January 7, 2019, petitioners filed their post-hearing brief (ECF No. 113).

On March 8, 2019, respondent filed his response (ECF No. 117). On March 28, 2019, petitioners filed their reply (ECF No. 118). The matter *appeared* to be ripe for adjudication.

[36] Dr. Kessler obtained a Bachelor of Science degree with honors from Yale College in 1967 and a medical degree from Yale University School of Medicine in 1971. Pet. Ex. 137 at 1. He completed post-graduate training from 1971 – 1975, then served as a major in the U.S. Army Medical Corps from 1975 – 1977. *Id.* at 1-2. In 1977, Dr. Kessler joined the NIH where he specialized in nuclear medicine, first as a fellow, then as a staff physician, and then as chief of the Emission Tomography section until he left in 1984. *Id.* at 1-2. He served on the faculty, specializing in radiology, at the Vanderbilt University School of Medicine from 1984 – 1995. *Id.* at 2. He has been on the faculty specializing in the same field at the University of Alabama – Birmingham (UAB) School of Medicine from 1995 to the present. *Id.* at 1-2. Dr. Kessler is licensed to practice medicine in Tennessee and is board-certified in diagnostic radiology as well as nuclear medicine. *Id.* at 1. Petitioner retained Dr. Kessler and he submitted several reports (at Pet. Exs. 136, 139, 156) only *after* the entitlement hearing, thus he was not formally offered as an expert or subject to objection or cross-examination. In my discretion, I accept Dr. Kessler as an expert in diagnostic radiology.

G. Final Medical History Including the Second Surgical Resection in 2019[37]

Despite the first resective surgery in June 2017, A.A. continued to have seizures uncontrolled by medication. She returned to her pre-operative baseline, but then in December 2017 ("just before… Christmas"), she had an increase in seizures, prompting an increase in the medication Onfi, which led to urinary retention. Pet. Ex. 148 at 1. In March 2018, the Mayo Clinic neurologist Dr. Kotagal recorded that A.A. had: "Epileptic spasms in clusters, 4-5 clusters per day; sometimes has prolonged clusters for up to 30 minutes long despite Clonazepam/ Diastat. Absence seizures: staring 20-30 seconds, 2-3 times a day. Partial seizures: eyes deviate up and to the left (may occur during a spasm cluster) lasting 30 – 60 seconds, about 4 – 6 times a day." *Id.* Dr. Kotagal agreed that A.A. should be reevaluated to determine whether additional surgery on the right side of her brain was necessary. *Id.* at 2.

In April 2018, A.A. underwent another FDG-PET scan.[38] The impression was "Diffuse hypometabolism involving the entire RIGHT parietal, temporal, and the portion of the frontal lobe, without discrete focal abnormality". There was also an "incidental finding of focal hypermetabolism in the inferior posterior aspect of the LEFT frontal lobe of unknown etiology and uncertain clinical significance." Pet. Ex. 144 at 11-12.

In April 2018, A.A. also underwent a SPECT[39] brain scan. The impression was: "Abnormal study demonstrates asymmetric, focally increased tracer activity in the superoposteromedial aspect of the RIGHT parietal lobe, suspicious for an ictal epileptic focus." Pet. Ex. 145 at 172-73.

In May 2018, A.A. had another increase of seizures. She was started on prednisone, which seemed to help decrease seizure frequency and baseline activity. Pet. Ex. 175 at 360, 373.

On July 10, 2018, a pediatric neurologist at Beaumont Hospital's pediatric epilepsy monitoring unit, Dr. Laoprasert, met with A.A. and her parents, who helped provide the history. Pet. Ex. 175 at 168-72. At the time of this encounter, A.A. was one month short of five years old. *Id.* at 168. Dr. Laoprasert recorded the following semiology:

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[37] This recitation of the facts is derived mostly from petitioners' status report (ECF No. 125) identifying the key medical records filed after the hearing.

[38] PET scans dynamically image brain function. This is done by injecting small amounts of radioactive isotopes incorporated into a naturally occurring substance. The substance currently used is flurodeoxyglucose (FDG). The brain metabolizes glucose as a major source of energy. FDG-PET scan will detect the regions of the brain where glucose uptake is high (termed hypermetabolism) or low (hypometabolism). *See* Wu, *PET and SPECT in Epilepsy Surgery*, Cleveland Clinic, available at https://my.clevelandclinic.org/Documents/Epilepsy_Center/Web%20script%20Wu.pdf (last accessed June 21, 2021).

[39] Like PET, single-photon emission computed tomography (SPECT) is another tool for brain imaging. In contrast to PET, SPECT is mainly used to measure blood flow to the brain by injecting radio-labeled chemicals (ECD or HMPAO) which are picked up by the brain cells in proportion to the level of blood flow. The brain cells' uptake of these chemicals is proportional to the level of blood flow. Measuring this uptake during seizure activity helps to locate the regions of activation in the brain. *See* Wu, *PET and SPECT in Epilepsy Surgery*, *infra* footnote 38.

> Seizure Type 1. Focal Asymmetric Tonic. Description: Hypomotor period with behavioral arrest and right eye/head deviation, and later seizures showed eyes open forward without head/eye deviation and slight RUE higher than left, stiff, +/- bicycling. Onset 2 months. Last seizure: April 2013 (Age 8 months). Duration: 20 seconds. Frequency: Was 6-8 times per day, resolved.
>
> Seizure Type 2: Epileptic Spasms #1 (Infantile Spasms). Description: Ranges from subtle eye opening to bilateral extensor/flexor semiology to query subtle asymmetric focal clinical spasms with rightward fencer. Onset: 6 months of age. Last seizure: May 2013 (Age 9 months). Duration: Clusters, resolved after ACTH. Frequency: Resolved.
>
> Seizure Type 3: Epileptic Spasms #2. Description: Left leg and arm extend out, head down and to the left, rarely right side will be involved. Onset: 18 months. Last seizure: This morning (0345-0415). Duration: Variable, occurs in clusters (usually 5 – 8 minutes). Frequency: Multiple times per day.
>
> Seizure Type 4: Tonic Seizures. Description: Bends at the waist, falls either straight forward or to the left, left arm extension with stiffening. Onset: December 2015. Last seizure: last week. Duration: Random. Frequency: daily.
>
> Seizure Type 5: Laughing Probable Gelastic. Description: Laughing spells in the middle of the night inappropriately. Onset: 2015. Last seizure: last week. Duration: random. Frequency: Random, increased since surgery.
>
> Seizure Type 6: Absence. Description: Stares off to the left. Onset: Fall 2017. Last seizure: today. Duration: 30 seconds to a few minutes: Frequency: multiple times per day.

Id. at 168-69. Dr. Laoprasert commented that A.A. was a "5 year old right handed (pathologic) globally developmentally delayed female with a past medica[l] history of medically refractory previously multifocal epilepsy more suggestive of singular focus/ focal epilepsy now (right frontal/ insular) [status post] right parietal resection and hypotonia." *Id.* at 171.

In November 2018, a grid of sEEG electrodes was placed intraoparatively directly on A.A.'s brain to localize the focus of her continued seizures. Pet. Ex. 175 at 726-28, 1143-71; *see also* Pet. Ex. 179 at 14-15 (subsequent removal of the grid). A pediatric epileptologist, Dr. Laoprasert, recorded that the findings were "supportive of the diagnosis of structural epilepsy with probable epileptogenic region in the right fronto-insula[40] region." Pet. Ex. 175 at 1171. Dr. Laoprasert recommended resection of those parts of the brain. *Id.* However, Dr. Laoprasert also said that if A.A. continued to have seizures after this resection, a right function

[40] The insula is a portion of the cerebral cortex which lies deep in the lateral sulcus, underneath the frontal and parietal lobes. *Dorland's*.

hemispherectomy[41] due to diffuse epileptogenicity should be considered.

In December 2018, a pediatric neurosurgeon, Dr. Zakalik, agreed that: "Seizures are arising most from the right frontal lobe, including the motor strip, anterior insula, and cingulate gyrus. The planned resection is to remove all of frontal lobe in front of the parietal defect." Pet. Ex. 179 at 11. The Beaumont providers "hope[d] that this surgery will help the seizures, but there is no guarantee." *Id.* Dr. Zakalik noted that after the surgery, A.A. would be paralyzed on the left side but would hopefully regain function in her left leg. *Id.* Her left hand had not been quite useful since the first resection and already had weakness. *Id.* The parents decided that A.A. would undergo this second recommended surgery. *Id.*

On January 8, 2019, Dr. Zakalik performed the lengthy second surgery. He began by identifying the cavity from the first surgery on the right parietal lobe. Pet. Ex. 175 at 1756. He "went posterior to that and included part of the cortex… which was likely part of the parietal cortex." *Id.* "Over the next 6 hours, [Dr. Zakalik] proceeded in resecting the frontal lobe… The aim was to remove the frontal lobe including the cingulate gyrus… Eventually… [Dr. Zakalik] removed the entire large frontal lobe measuring 12 cm in length. The pathologist came back in to obtain this large specimen. [Dr. Zakalik] showed [the pathologist] the posterior part of the frontal lobe where the previous resection was." *Id.* at 1756-57. Dr. Zakalik then proceeded to remove the insula, which apparently was not examined. *Id.* at 1757.

The pathologist examined the specimen labeled "right frontal lobe – brain," though as noted above, Dr. Zakalik had also removed the cingulate gyrus and part of the parietal cortex. Pet. Ex. 176 at 2. The specimen was larger than Dr. Zakalik's estimate, at 14.8 by 6.3 by 2.8 centimeters. Pet. Ex. 176 at 2. The "posterior aspect" marked the boundary of the previous resection site. *Id.* at 2-3. It showed FCD, white matter heterotopia, and abundant gliosis[42] with reactive changes. *Id.* The neuropathologist commented: "Foci of probable cortical dysplasia are present. What is more prominent, however, is white matter heterotopi[a] (white matter neurons) seen in multiple regions… Subacute gliotic changes, likely due to grid[43] placement and removal, are present and do mask potential cortical dysplasia and tumor nodules, but white matter neurons are apparent even in the background of reactive changes. Areas of remote reactive changes, likely due to previous excision, are present. The white matter neurons are most apparent in the posterior aspect of the specimen but focal abnormalities are also seen in random sections of more anterior cortex." *Id.* The histopathology demonstrated numerous white matter neurons (e.g., heterotopia) as well as mild architectural distortion within the cortex. *Id.* It is reiterated that the insula was also believed to be a part of the epileptogenic region and that was also removed in the second surgery, but that apparently was not examined by the pathologist.

[41] Hemispherectomy is defined as "resection of a cerebral hemisphere." *Dorland's*.

[42] Gliosis is defined as "an excess of astroglia in damaged areas of the central nervous system." *Dorland's*.

[43] This is a reference to the grid of electrodes placed directly on A.A.'s to localize the focus of seizures in November 2018. *See* Pet. Ex. 175 at 726-28, 1143-71.

Shortly after this surgery, Dr. Laoprasert recorded that A.A. was recorded to be doing well with no breakthrough seizures. Pet. Ex. 178 at 1-21. In February 2019, she continued to be "very happy since surgery", and participating in physical, occupational, and speech therapies. *Id.* at 22-26. In April 2019, she continued to do well. *Id.* at 27-28. In May 2019, it was recorded that A.A. "had more than 100 sz's [seizures] a day prior to surgery", but she had "none since the surgery". Pet. Ex. 179 at 1. She was still taking the anti-seizure medications zonisamide and clobazam. She had left hemiparesis but it was improving; her cognitive function was also improving; and she was participating in physical and speech therapies. *Id.* at 1, 4. She would undergo repeat MRIs in one year. *Id.* Petitioners have not advised of any significant setbacks to A.A.'s condition.

H. Final Procedural History

After the completion of post-hearing briefs, in spring 2019, petitioners filed over three thousand (3,000) pages of updated medical records pertaining to A.A.'s second surgical resection. Pet. Exs. 175-77. Respondent filed a motion requesting (1) petitioners' clarification as to whether the additional records bore on the issue of entitlement; (2) an opportunity for respondent to respond, if necessary; and then (3) for the record to be closed. Resp. Mot. (ECF No. 121). On August 6, 2019, I held a status conference. I discussed that the newly filed records seemed to reflect a significant medical event potentially providing more detail about A.A.'s condition. I denied respondent's motion to close the record at that time without prejudice. *See* Scheduling Order (ECF No. 122). On August 26, 2019, petitioners filed a final batch of updated medical records pertaining to A.A.'s condition following the second surgery. Pet. Exs. 179-80; Supplemental Statement of Completion (ECF No. 123). Petitioners also duly identified the key medical records for further expert review. Pet. Status Report (ECF No. 124).

I then ordered both parties to file "any supplemental expert reports limited to the significance, if any, of the updated medical records towards understanding the nature of A.A.'s condition and by extension, vaccine causation." Scheduling Order entered August 6, 2019 (ECF No. 122) at 2. On November 25, 2019, petitioners filed one final report from Dr. Kinsbourne. Pet. Ex. 180. On November 25, 2019, respondent filed one final report from Dr. Kohrman. Resp. Ex. RRRRR. The matter is now ripe for adjudication.

II. Legal Standard[44]

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)

[44] Decisions of special masters and the U.S. Court of Federal Claims (some of which are referenced in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

(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 his or her entitlement to compensation from the Vaccine Program. The burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). A petitioner may prevail by proving either that (1) the vaccinee suffered an injury listed on the Vaccine Injury Table with onset beginning within a corresponding time period following receipt of a corresponding vaccine (a "Table Injury"), for which causation is presumed or that (2) the vaccinee suffered an injury that was actually caused by a vaccine. Under either method, however, the petitioner must also show that the vaccinee "suffered the residual effects or complications of the illness, disability, injury, or condition for more than six months after the administration of the vaccine." Section 11(c)(1)(D)(i).

In the present case, petitioners did not allege a Table injury. Rather, they alleged that the December 10, 2012 vaccines "caused-in-fact" A.A.'s development of a seizure disorder. Petition at Preamble; Pet. Post-Hearing Brief at 1. Thus, they bear the burden of establishing actual causation (causation in fact). They 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 the petitioner to demonstrate 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.

The 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).

If the petitioner makes a *prima facie* case supporting vaccine causation-in-fact, 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.

Under *Althen* prong one, the causation theory must relate to the injury alleged. 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).

The Federal Circuit has held that a petitioner is not required to establish that the vaccine received is the *sole* cause of the injury alleged. Rather, the petitioner is required to prove, by a preponderance of the evidence, that the vaccine can be "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1353 (Fed. Cir. 1999) (holding that both a DTP vaccine and an *e. coli* infection (sepsis) substantial factors that caused a child's death); *see also H.L. v. Sec'y of Health & Human Servs.*, 715 Fed. App'x. 990, 995 (Fed Cir. 2017) (affirming that petitioners had not established that a vaccine substantially contributed to the death of a child with pre-existing Leigh disease, a central nervous system disorder in which "there is often no trigger for decompensation").

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.

Within the Vaccine Program, consideration is given to contemporaneous medical records and the opinions of treating medical providers, who are "likely to be in the best position to determine whether 'a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" *Capizzano*, 440 F.3d at 1326 (citing *Althen*, 418 F.3d at 1280). A special master should "conside[r]" treaters' opinions with regard to possible causation, even when they rely "in part on the temporal proximity of… injuries to the administration of the vaccine". *Id.*; *see also Reilly v. Sec'y of Health & Human Servs.*, No. 09-489V, 2016 WL 3456844, at *15 (Fed. Cl. Spec. Mstr. May 31, 2016) (holding that treaters' opinions helped to establish that the DTaP vaccine did cause the onset of seizures in the setting of FCD).

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.

III. Analysis

A. Introduction to Cortical Development

To preface the classification of FCD, which involves *malformation* or *disorganization* of the cortex, it is helpful to understand how the cortex normally develops. There are three stages. First, cells proliferate in utero in the center of the nascent brain, in the ventricular and subventricular zones. Second, neurons migrate outwards and settle along a scaffold- or ladder-like structure of radial glial cells. This results in horizontal and vertical columns of neurons. Pet. Ex. 64 at 3-4; Tr. 211. The third stage involves final intracortical organization. The second and third stages are overlapping. Pet. Ex. 64 at 3-4; Tr. 211; *see also* Resp. Ex. FF at 2[45]. It is important to note that the majority of cortical development occurs between the point of conception and about 22- or 23-weeks' gestation; it is complete by about 30- to 32-weeks' gestation. Tr. 291-92, 473-74.

[45] Citing Barkovich et al., *Classification System for Malformations of Cortical Development*, 57 Neurology 2169 (2001) [Resp. Ex. KK] at 1; Barkovich et al., *A Developmental and Genetic Classification for Malformations of Cortical Development*, 27 Neurology 1873 (2005) [Resp. Ex. LL] at 1.

Dr. Kinsbourne opined that in the "circuit" described above, the vertical columns of neurons secrete the main activating substance of the brain, which is called glutamate. Tr. 208, 211. The horizontal columns of neurons secrete the main inhibiting substance of the brain, which is called GABA. Tr. 208, 211.[46]

The literature reflects and the expert neurologists agreed that with malformations of cortical development (MCD) including FCD, these "lesions have an embryological basis and may be produced at different stages of gestation, through mechanisms involving dysregulation of genetic control and or environmental insults. It is now understood that cortical development can be altered (1) at the level of neuroglial proliferation and differentiation, (2) during neuronal migration to the cortical plate, and (3) at the final stages of intracortical organization. Interference with each of these processes leads to variable degrees of abnormalities in cortical architecture and synaptic organization." Resp. Ex. II[47] at 549.

In FCD, the neurons do not migrate normally. A greater proportion of the neurons may settle along the vertical columns, resulting in greater production of the activating substance glutamate. Or fewer neurons may settle along the horizontal columns, resulting in less production of the inhibiting substance GABA. This leads to a "hyper-excitable circuit" and a lowered seizure threshold. Pet. Ex. 64 at 3-4; Tr. 208-09; *see also* Tr. 291-92, 297 (Dr. Raymond agreeing with this explanation from Dr. Kinsbourne).

B. Classification of FCD

FCD was first described in 1971, when Dr. David Taylor and colleagues published a study on individuals with intractable epilepsy who underwent surgical resection. Microscopic examination revealed cortical disorganization (introduced above in section III.A), large bizarre neurons, balloon cells, and other unusual pathology. *See* Resp. Ex. JJ[48] at 3, 5. The medical community devoted increased attention to FCD over time: "From 1971, after the initial study by Taylor and colleagues, to 1990 only a few papers were published. By comparison, from 1991 – 2007, the number of published papers on this topic has increased dramatically. This is due in part to the increased detection of cortical dysplasia lesions with modern neuroimaging. With

[46] The transcript reads "glutamine." This is likely an error. In a supplemental expert report, Dr. Kinsbourne quoted an article by Ben-Ari et al. for the proposition that: "The central hypothesis proposed here for secondary epileptogenesis is that the selective loss of specific GABAergic interneurons and the formation of new excitatory *glutamatergic* circuits synergistically augment excitability, which leads to the propensity to further seizures." Pet. Ex. 140 at 5 (citing Ben-Ari and Dudek, *Current Review: Primary and Secondary Mechanisms of Epileptogenesis in the Temporal Lobe: There is a Before and After*, 10 Epilepsy Currents 118 (2010) [Pet. Ex. 143] at 1 (emphasis added).

[47] Palmini & Holthausen, *Chapter 58: Focal Malformations of Cortical Development: A Most Relevant Etiology of Epilepsy in Children*, in Handbook of Clinical Neurology, Vol. III – Pediatric Neurology Part I (2013 Dulac et al., eds.) [Resp. Ex. II].

[48] Lerner et al., *Critical Review and Invited Commentary: Assessment and Surgical Outcomes for Mild Type I and Severe Type II Cortical Dysplasia: A Critical Review and the UCLA Experience*, 50 Epilepsia 1310 (2009) [Resp. Ex. JJ] (citing Taylor et al., *Focal Dysplasia of the Cerebral Cortex in Epilepsy*, 34 J. Neurol. Neurosurg. Psychiatry 369 (1971) [not filed]).

increased detection, it became apparent that… the prevalence of cortical dysplasia in epilepsy surgery patients was higher than originally appreciated." *Id.* at 3.

Dr. Andre Palmini is a leading researcher who published the first iteration of a classification scheme for FCD in 2004,[49] which Palmini and other members of the International League of Epilepsy (ILAE) updated in 2011.[50] They provide that the hallmark finding of FCD is cortical disorganization; that finding alone is classified as FCD Type I. Resp. Ex. MM at 4-6, 14; *see also* Resp. Ex. II at 550. FCD Type IIa has cortical disorganization plus dysmorphic neurons. Resp. Ex. MM at 6-7, 13. Type IIb has cortical disorganization and dysmorphic neurons, plus balloon cells. Resp. Ex. MM at 7-8, 13.[51]

Palmini and the ILAE task force recommended that following any surgery on suspected FCD: "the reporting pathologist will identify a corresponding distinct abnormality" and "provide robust and consistent objective criteria for any cortical abnormality with findings that are reproducible and reliable between laboratories." Resp. Ex. MM at 2.

Additionally, and with relevance to this case, in a critical review and invited commentary on FCD published in the journal Epilepsia in 2009, Lerner noted that cortical disorganization (classified as FCD Type I) is "often associated with… other histopathological findings that denote more severe abnormal cortical development." Resp. Ex. JJ at 5. In Lerner's studied cohort,[52] 99% of FCD Type I cases also had "excessive heterotopic white matter neurons," which were "attributed to abnormal neuronal migration or secondary to overproduction of cortical neurons in the periventricular proliferative zone during cerebral development." *Id.*

Palmini has written that FCD has "emerged as the most prevalent etiology for difficult-to-treat epilepsy in children. Although reported figures vary, in some series up to 75% of children operated on for refractory epilepsy had [FCD]." Resp. Ex. II at 549. FCD is "responsible for the majority of medically refractory partial epilepsies." *Id.* at 550. Palmini wrote in 2013 that experience over the last two decades has shown that "in comparison to patients harboring other epilepsy etiologies, such as hippocampal sclerosis, those with FCD are younger at seizure onset, have a higher seizure frequency, and are operated for their epilepsy at a younger age." *Id.* at 551. Palmini cited Lerner's research for the proposition that most children with FCD type II have seizure onset before age 5 and tend to be operated on before age 10, while children with FCD type I tend to have these curves shifted rightward for about 5 or more years.

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[49] Palmini et al., *Terminology and Classification of the Cortical Dysplasias*, 62 Neurology S2-S8 (2004) [Ct. Ex. 1]. The Court located this article after it was cited by both parties and much of the submitted literature.

[50] Palmini et al., *The Clinicopathologic Spectrum of Focal Cortical Dysplasias: A Consensus Classification Proposed by an Ad Hoc Task Force of the ILAE Diagnostic Methods Commission*, Epilepsia 52(1):158-74 (2011) [Resp. Ex. MM].

[51] The ILAE task force also recognizes FCD associated with hippocampal sclerosis, epilepsy-associated tumors, vascular malformations, or epileptogenic lesions acquired in early life. Resp. Ex. MM at 2. These are not at issue in the present case.

[52] Lerner studied histopathological findings from a total of 97 patients with FCD who underwent surgery at the University of California, Los Angeles between 2000 – 2007. Resp. Ex. JJ at 3.

Id. (citing Lerner (2009 [Resp. Ex. JJ]). However, Palmini noted that other researchers, Hildebrandt and Blümcke, had identified a specific subsyndrome of FCD-I associated early onset childhood epilepsy. *Id.* Hildebrandt and Blümcke "also found a correlation between lesion size and epilepsy severity, in that *the larger the lesions* the earlier the epilepsy onset, the higher the seizure frequency, and the younger the age at operation." *Id.* (emphasis in the original).

Palmini also wrote that a significant percentage of patients have FCD lesions in the Rolandic or premotor regions. Resp. Ex. II at 551. These lesions are mostly type II and they usually manifest as medically refractory partial motor or sensorimotor seizures, which may or may not generalize. *Id.* When the motor cortex is involved, patients may have clonic seizures which often alternate with episodes of epilepsia partialis continua. *Id.* These clonic seizures may propagate into tonic components or they may even immediately generalize leading to falls. *Id.* Finally, when FCD is more anterior, in the frontocentral regions, and involves the lateral premotor cortex or the supplementary sensorimotor area (SSMA), unilateral or bilateral tonic components occur from the start, occasionally mixed with head deviation and clonic facial features. *Id.*

C. Neuroimaging

Neuroimaging plays an important role in identifying possible areas of FCD. Palmini explained that for FCD, the cornerstone finding is disorganization of the cortical gray and subcortical white matter, which may vary from very subtle to gross abnormalities. Resp. Ex. II at 553. He elaborated:

> The imaging picture derives from a combination of abnormal intracortical neuronal distribution and positioning, occurrence of large-sized aberrant cell types and more or less discrete failures of the migration mechanisms with persistence of neurons in the juxta-cortical white matter. The lack of a columnar and laminar organization in the cortex (dyslamination) is often accompanied by an abnormally increased number of neurons in the deeper layers, invading the underlying white matter. Such disarranged neuropil interferes with afferent and efferent fibers and may lead to a number of MRI findings, including increased cortical thickness, abnormal gyration and sulcation and blurring of the gray-white transition… In addition, when dysplastic neurons are haphazardly included in abnormal neuropil and extend into the underlying white matter, increased cortical and subcortical MRI signal, at times extending until or from the ventricular wall, is often seen. The latter is usually denominated "transmantle dysplasia". Interestingly, the depths of the sulci are often involved[.]

Id. However, neuroimaging is often not completely sensitive or specific. Similar MRI patterns may be seen in different FCD subtypes or even other brain abnormalities. *Id.* In some patients, the structural abnormalities can be very subtle and defy even high-resolution MRI. *Id.*

In addition, neuroimaging is less useful in evaluating very young children for potential FCD. "In the immature and unmyelinated brain, increased T2 signal, localized or transmantle, is difficult to identify, as is the cortical white-matter junction blurring [which…] is a normal

finding during the postnatal stage of brain maturation. Incomplete myelination can also give the appearance of cortical thickening on T2 FLAIR and T1 weighted images, as partially myelinated white matter becomes transiently isointense to cortex." Resp. Ex. MM at 3-4. The expert neurologists concurred that neuroimaging often cannot detect FCD in the immature and unmyelinated brain, especially during the first year of life. Pet. Ex. 64 at 3; *see also* Resp. Ex. FF at 2. The use of high-resolution imaging modalities, such as 3T MRI scanners, can also improve the detection of FCD. Pet. Ex. 64 at 3; Resp. Ex. FF at 2; Tr. 264, 292-93.

In this case, A.A. was born in August 2012 and she had the onset of seizures at two months old. On the initial 1.5T MRIs (Pet. Ex. 5 at 35; Pet. Ex. 21 at 33), no abnormalities in the brain were seen. However, in October 2016, a 3T MRI (Pet. Ex. 56 at 86-88) identified potential FCD in the right high anterior parietal lobe within the depth of the sulcus. Heterotopic neurons were seen in the right high anterior parietal lobe within the depth of the sulcus. Heterotopic neurons were also seen in the subependymal layer adjacent to the right lateral ventricle. The right hemisphere, especially superiorly compared to the left hemisphere, had asymmetric sulcation. The right high anterior frontal lobe showed additional but questionable areas of cortical thickening. Both hemispheres had some scattered white matter T2 hyperintensities. *See* also Pet. Ex. 89 at 3-4. The hippocampal formations had slight asymmetry, with the right being slightly smaller than the left, but without significant signal abnormality or volume loss. *See* Pet. Ex. 56 at 86-88.

Respondent's expert pediatric neurologist Dr. Kohrman,opined – based on his experience interpreting MRIs, the first EEG findings of epileptic activity in the left front temporal region without any findings in the right hemisphere at that time, and the ultimate surgical confirmation of FCD on the right side – that these non-specific T2 hyperintensities represented additional areas of FCD. *See generally* Tr. 485-577 (citing Resp. Ex. UUUU (MRI images)); Resp. Ex. VVVV at 2-3 (citing Pet. Ex. 5 at 54 (initial EEG)).

Dr. Kohrman did not accept petitioner's expert neurologist Dr. Kinsbourne's opinion that A.A. instead had a single right-sided area of FCD that caused secondary epileptogenesis extending to the left side. Resp. Ex. VVVV at 2 (responding to Pet. Ex. 140 at 4-5). In rebutting this point, Dr. Kohrman emphasized Dr. Raymond's opinion that neocortical seizures do not cause tissue injury that results in further seizures. Resp. Ex. VVVV at 2-3 (citing Resp. Ex. HHHHH at 3-4). Dr. Kohrman also emphasized the clinical presentation in A.A.'s specific case: "It is not plausible to call [A.A.'s] left-sided seizure secondary to her right-sided [FCD] because the left-sided seizures were the initial presenting symptoms and no epileptic activity was initially noted over the right hemisphere. These are two independent seizure foci [which] are now reconfirmed by the 2018 PET scans in addition to the EEGs that have demonstrated seizure osnet independently in both hemispheres." Resp. Ex. YYYY at 7.

As noted above, I allowed Dr. Kohrman's testimony on this point over petitioners' objection, but afterwards, petitioners were permitted to retain their own expert neuroradiologist Dr. Kessler to review the case including the MRI films and the PET scans. Dr. Kessler agreed with the hospital radiologists that the scans done on December 17, 2012, and January 4, 2013, showed only mild benign infantile external hydrocephalus and were otherwise unremarkable. Pet. Ex. 136 at 1. Dr. Kessler also agreed with the Cleveland Clinic radiologist Dr. Hamidi's

reading that the September 29, 2014, films detailed interval appearance, since the previous study, of multiple focal areas of increased T2 signal in the subcortical and periventricular white matter. *Id.* at 1. Dr. Kessler noted that these were non-specific findings despite Dr. Kohrman's contention that in the context of this case, these white matter neurons represent heterotopic tissue that is in and of itself epileptogenic. *Id.*; Resp. Ex. RRRR at 4.

Dr. Kessler also opined that the MRI studies from October 13, 2016, forward demonstrated a small focus of subependymal cortical heterotopia along the superior aspect of the atrial region of the right lateral ventricle, an overlying region of cortical dysplasia restricted to the right parietal lobe with thickening of the cortex in this dysplastic area, mildly increased T2 signal and abnormal gyral formation as well as some increased T2 signal in the white matter below this area of cortical dysplasia. Pet. Ex. 136 at 2. Dr. Kessler concluded that these findings were consistent with a neuro-migrational abnormality which is restricted to the right cerebral hemisphere, particularly the right parietal lobe, the white matter under this abnormality in the right parietal lobe and a small area of cortical heterotopia situated beneath this abnormal portion of the right parietal lobe which borders the superior aspect of the atrial region of the right lateral ventricle. *Id.* at 2-3. Dr. Kessler agreed that such abnormalities can be an epileptogenic focus. *Id.* at 3.

Dr. Kessler did not see additional areas of FCD, but he did see multiple foci of increased T2 signal in the subcortical and periventricular white matter on the MRI studies from September 29, 2014 forward. Pet. Ex. 136 at 3. He opined that the latter were non-specific in appearance and could not be attributed to widespread migrational abnormalities even in the context of confirmed FCD on the right side. *Id.* Dr. Kessler emphasized the Cleveland Clinic radiologist Dr. Hamidi's characterization of these findings as "non-specific but can be seen in etiologies such as post-viral or post-vaccination ADEM, vasculitis, other inflammatory or infectious etiologies, or demyelinating processes." *See* Pet. Ex. 89 at 4. Dr. Kessler noted that several other treating radiologists did not form a conclusion on these findings. Pet. Ex. 139 (citing Pet. Ex. 56 at 86-88; Pet. Ex. 89 at 7-8; and Pet. Ex. 101 at 15-16); *see also* Pet. Ex. 156. However, Dr. Kohrman noted that these radiologists' reports were written before A.A.'s first surgery on June 23, 2017, which confirmed the presence of at least right-sided FCD. Resp. Ex. VVVV at 1.

In his final report, Dr. Kessler maintained that the MRI studies "demonstrated heterotopic grey matter adjacent to the superior aspect of the atrial region of the right lateral ventricle, increased T2 signal in the overlying white matter, and a gyral malformation in the overlying right superior parietal lobe – a focal cortical dysplasia [FCD] – indicative of a neuro-migrational abnormality in this region. In addition, there [were] hyperintense T2 weighted foci in the white matter of both cerebral hemispheres seen on the MRI scans of the brain done 9/29/2014 and studies performed thereafter." Pet. Ex. 156 at 1. Dr. Kessler continued to opine that the T2 hyperintensities were non-specific in appearance. *Id.* at 1-2. It is important to note that Dr. Kessler did not specifically disagree with the opinion that these hyperintense T2 weighted foci were evidence of migrational abnormalities even in the presence of a single (confirmed) FCD, but rather, Dr. Kessler did not think there was a sufficient level of confidence to reach that conclusion. *Id.* at 2.

Also of note, after the first surgery, A.A. underwent an FDG-PET scan which found "focal hypermetabolism in the inferior posterior aspect of the LEFT frontal lobe." Pet. Ex. 144 at 11-12. Dr. Kohrman opined that hypermetabolism is consistent with active seizure activity, *see* Tr. 463, and he opined that the left-sided findings were consistent with the location of her initial seizures, Resp. Ex. YYYY at 2.

Significantly, this FDG-PET scan also found "diffuse hypometabolism involving the entire RIGHT parietal, temporal, and a portion of the frontal lobe, without discrete focal abnormality." Pet. Ex. 144 at 11-12. Dr. Kohrman explained why a PET scan would show hypometabolism. Tr. 463. Namely, brain tissue that is chronically seizing becomes "tired out" and "doesn't' metabolize as well… because it's using up that glucose. Can't take it in, can't store it, and it doesn't stick around so it doesn't show up on the PET scan." Tr. 463-64. Dr. Kohrman opined that in A.A.'s case, the PET scan findings of diffuse hypometabolism reinforced the conclusion that her brain contained widespread epileptic tissue most likely representing FCD. Tr. 303-04.

In contrast, Dr. Kessler did not credit the widespread hypometabolism seen on the PET scan as supportive of more widespread FCD, because he opined that the PET scans are "not an accepted modality for the diagnosis of FCD." Pet. Ex. 156 at 3. However, this appears to be contradicted by the medical literature. For example, Palmini wrote that "a place for the coregistration of FDG-PET and subtraction ictal SPECT images with MRI has been increasingly recognized in patients with suspected FCD and normal or doubtful MRI… In particular, FDG-PET may point to very focal areas of hypometabolism that later prove to correspond to subtle regions of FCD in areas completely normal on MRI, the removal of which may be performed…" Resp. Ex. II at 8. Additionally, Lerner wrote that: "FDG-PET has been shown to be one of the more sensitive techniques in identifying areas of cortical dysplasia. Contemporary studies indicate that FDG-PET detected interictal hypometabolism localized to areas of cortical dysplasia in approximately 75% of patients. Many patients with cortical dysplasia and normal MRIs are reported to have positive FDG-PET scans." Resp. Ex. JJ at 13-14. Lerner further explained that in his study cohort, when FDG-PET images representing escalating levels of hypometabolism were overlaid onto structural MRIs, FCD was identified in 98% of patients. *Id.* at 14. "Hence, FDG-PET can be a very useful tool in detecting cortical dysplasia[.]" *Id.*

D. Surgical Findings

The "gold standard" to confirm FCD is surgery, which allows access to the actual brain tissue. Tr. 231-32, 259, 297. Because of the limitations of non-invasive methods such as scalp EEG and MRI, patients with suspected FCD who undergo surgery are often implanted with intracranial electrodes to localize areas of ictal onset in order to identify epileptic foci and facilitate surgical planning. Resp. Ex. JJ at 14. This procedure is called electrocorticography (ECoG). *Id.* at 14-15; *see also* Tr. 260, 298-300. After this procedure localizes the FCD, the FCD is resected, allowing for the histopathological examination which is key to the ILAE classification scheme referenced above.

The goal of surgery is to remove FCD and deliver seizure freedom to the patient. However, this requires *complete* resection. In a review of four past studies, 30 – 35% of patients with FCD have incomplete resection, with the most frequently cited reason being that areas of FCD, not visible on MRI, were located in cortical regions, the resection of which would lead to unacceptable motor, sensory, visual, or language deficits. Resp. Ex. JJ at 18. These patients had a 20% chance of becoming seizure-free, with seizure reoccurrence usually happening within six months of surgery. *Id.* In contrast, patients with "complete" resection had a 77% chance of becoming seizure-free. *Id.*

Petitioners and Dr. Kinsbourne submitted another relevant article,[53] by neurologist Elaine Wyllie, M.D. and colleagues at the Cleveland Clinic,[54] about results with a group of pediatric patients with epilepsy and MRI-identified brain lesions including FCD. Wyllie described the difficult pre-surgical considerations including that a visualized lesion, associated with generalized EEG findings, may simply represent "the tip of the iceberg" of a diffuse epileptic process. Pet. Ex. 142 at 7-8. After all non-surgical options for treating epilepsy are exhausted, surgery can be a final option that presents "low risk for new post-operative deficits in patients with pre-existing hemiparesis, limited language development, and functional reorganization and plasticity following pre- and peri-natal insults." *Id.* at 8. Wyllie wrote that "extensive surgeries, such as hemispherectomies and multi-lobal resections, with opportunity for complete resection of epileptogenic tissue" are sometimes necessary to achieve seizure freedom. *Id*.

To reiterate in this case, at the Cleveland Clinic in June 2017, A.A. underwent the first surgery which excised 4.5 by 2.6 by 1.2 centimeters of tissue from the right parietal lobe, which contained areas of FCD. Pet. Ex. 101 at 126-27. Pet. Ex. 100 at 1. The first surgery stopped short of additional FCD that extended to the central sulcus of the sensorimotor region, for fear of causing a left-sided hemiparesis. *See* Pet. Ex. 140 at 2-3; Tr. 519-20. Post-removal ECoG demonstrated continued spiking and epileptiform activity in the region directly ante to the resected site (right frontal parietal, central sulcus). Pet. Ex. 101 at 126-27, 134.

The first pathology report described FCD, nodular white matter heterotopia, hyaline protoplasmic astrocytopathy, focal perivascular white matter atrophy and focal perivascular chronic inflammation. There was focal cortical architectural disorganization associated with rare dysmorphic neurons. Heterotopic nodules of gray matter were focally situated within white matter areas. The gray-white junction displayed areas of possible blurring. Pet. Ex. 100 at 1-2.

Unfortunately, A.A. did not become seizure-free after the first surgery because it did not remove all of the FCD tissue. sEEG localized the focus of her continued seizures as being in the right fronto-insula region. At Beaumont Health in January 2019, A.A. underwent the second surgery which started at the cavity from the first surgery and excised an additional 14.8 by 6.3 by

[53] Wyllie et al., *Successful Surgery for Epilepsy due to Early Brain Lesions Despite Generalized EEG Findings*, 69 Neurology 389 (2007) [Pet. Ex. 142].

[54] As noted above, A.A. underwent her first surgical resection for FCD at the Cleveland Clinic in June 2017. Pet. Ex. 101 at 126-27. In March 2018, A.A. followed up at the Cleveland Clinic and was recommended for a further surgical resection, *see* Pet. Ex. 148 at 2, which occurred in January 2019 at Beaumont Hospital, *see* Pet. Ex. 175 at 1754-58

2.8 centimeters of tissue. The surgery removed tissue at the posterior margin of the previous surgery which was likely from the parietal lobe, as well as the entire frontal lobe, the cingulate gyrus, and the insula. Pet. Ex. 175 at 1754-58. The pathologist received certain excised tissue from this surgery, but he did not comment on all of the sections.

The pathologist commented: "Foci of probable cortical dysplasia are present. What is more prominent, however, is white matter heterotopia (white matter neurons) seen in multiple regions… Subacute gliotic changes, likely due to grid placement and removal, are present and do mask potential cortical dysplasia and tumor nodules, but white matter neurons are apparent even in the background of reactive changes. Areas of remote reactive changes, likely due to previous excision, are present. The white matter neurons are most apparent in the posterior aspect of the specimen but focal abnormalities are also seen in random sections of more anterior cortex." Pet. Ex. 176 at 2. The histopathology demonstrated numerous white matter neurons and mild cortical architectural distortion. *Id.* After this second surgery, A.A. remained on anti-seizure medications but she has had an abrupt, lasting cessation of seizures and she made gains in cognitive function. *See, e.g.*, Pet. Ex. 179 at 1-4.

At the hearing and in the post-hearing expert reports, there was extensive debate as to the extent of A.A.'s FCD, including the significance of diffuse white matter hyperintensities on MRI, with potential correlation on the PET-FDG scan, in both hemispheres. The pathologist reviewing the excised tissue from the second surgery did not expressly answer these questions, but he did write that "*foci* [plural] of probable cortical dysplasia are present." Pet. Ex. 175 at 2 (emphasis added). The pathologist also noted that the placement and removal of the sEEG had caused subacute changes which masked additional areas of "potential cortical dysplasia." *Id.*

The pathologist did not address the *significance* of "the abundant white matter heterotopia (white matter neurons) seen in multiple regions." Pet. Ex. 175 at 2. However, Dr. Kohrman emphasized in his very last report that "the white matter neurons represent heterotopic tissue that is in and itself epileptogenic." Resp. Ex. RRRRR at 4. Dr. Kinsbourne did not address this point, *see* Pet. Ex. 180 at 2 (opining that the second pathology report found "nothing out of the ordinary"). But Dr. Kohrman's opinion seems to be buttressed by the literature. For example as noted above, Lerner observed that 99% of FCD Type I cases also had excessive white matter heterotopia which was attributed to abnormal neuronal migration. Resp. Ex. JJ at 5.

The lack of detail in the second pathology report may have given rise to Dr. Kinsbourne's suggestion that "the extent of the resection was far greater than the area that turned out to be the source of the epileptogenesis." Pet. Ex. 180 at 2. However, it must also be remembered that the second surgery and pathological examination took place at a different institution, the sEEG demonstrated likely seizure foci throughout the frontal lobe, and the earliest seizure activity occurred in the left frontal lobe.

Although the treating radiologists did not characterize the diffuse white matter hyperintensities as FCD, the literature supports that MRI imaging is not definitive for identifying FCD. FDG/PET scan is more indicative and in this case, it detected widespread abnormalities throughout A.A.'s brain. While Dr. Kinsbourne opined that the confirmed FCD on the right side of the brain caused A.A.'s seizure activity in the left hemisphere, that opinion seems to be belied

by the fact that the left-sided seizure activity occurred first.

While the second surgery on the right side of A.A.'s brain led to an abrupt cessation in her seizures for at least a number of months, it is difficult to conclude that she had a single limited area of FCD that required a trigger for the onset of seizures when they in fact occurred. To the contrary, she underwent two surgeries which removed part of the right parietal lobe, part of the parietal cortex, the right frontal lobe, the cingulate gyrus, and the insula. In addition to the dysmorphic neurons in the right parietal lobe, there were foci (plural) of FCD as well as "prominent" white matter neurons in "multiple" regions. There is incomplete information from the second surgery because the insula was also implicated as being part of the epileptogenic region and was also removed, but the insula apparently was not examined by the pathologist. Based on the available information, the two surgeries combined removed an extensive area of FCD and other epileptogenic migrational abnormalities from A.A.'s brain. The pathologists and other treating physicians did not apply the Palmini/ ILAE classification scheme. However, the pathological findings, the imaging, and the evolution of A.A.'s seizures appeared consistent with either the early-onset epilepsy seen in some cases of FCD Type I or with FCD Type II which is also understood to be severe, even without a conclusive finding that there were additional areas of FCD elsewhere in A.A.'s brain.

E. Petitioners' Proposition: "Seizures are Not Inevitable with FCD"[55]

Dr. Kinsbourne opined that the normal course is that an individual develops epilepsy, undergoes one or more MRIs of the brain which lead to a suspicion that FCD is present, but the presence of FCD "can only really be proven by direct examination of the brain" including ECoG, resection, and pathology of the tissue. Tr. 232. Dr. Kinsbourne said that the "normal" conclusion would be to say: "These people who have FCD develop epilepsy." *Id.* "How do we know? Because we cut their brains, their heads open. Of course, these are the most severe cases that come to that, but it gives an impression as if FCD has to be severe." *Id.* We are missing a population study, which would ask: "How many people with FCD in the general population do or don't have epilepsy?" *Id.*

Dr. Kinsbourne then opined that the information which is currently available suggests that the general population includes some proportion of individuals with FCD but without seizures or epilepsy. In support of this proposition, Dr. Kinsbourne opined that in a 1992 study, Meencke[56], found that on autopsy, approximately two percent (2%) of asymptomatic individuals had "gross cortical dysgenesis". Pet. Ex. 64 at 4, citing Pet. Ex. 78 at 1-2. However, Meencke did not suggest that this finding is usually benign. Rather, Meencke stated that previous studies "demonstrated the important significance of migrational disturbances for the pathogenesis of epilepsy." Pet. Ex. 78 at 1. In continuation of this research, in the 1992 study, Meencke compared approximately six hundred brains from subjects with epilepsy to approximately seven thousand controls without epilepsy, from autopsies conducted from the late 1950s to the late

[55] Pet. Post-Hearing Brief at 20.

[56] Meencke & Veith, *Chapter 3: Migration Disturbances in Epilepsy*, in *Molecular Neurobiology of Epilepsy (Epilepsy Res. Suppl. 9)* (Engel et al., eds., 1992) [Pet. Ex. 78].

1980s. Meencke stated that in the control group, "there was an average proportional group of 1.5% malformations," more specifically "dysraphic lesions in 2.6%, severe migrational disturbances in 1.7%, and disturbances from the maturation period in 0.4%". *Id.* at 1-2. "Slight migrational disturbances (microdysgenesis), histologically analyzed in only 150 control cases, were found in 6%." *Id.* at 2. Even if it were clear that any of these findings were consistent with the current classification for FCD, Meencke did not suggest that these are prevalent in the general population. Rather, Meencke discussed at great length the correlation of these findings with epilepsy. *Id.* at 2-8. Meencke concluded that "dysgenesis" is a "morphological factor that is closely correlated with the conditions responsible in a causal way for epilepsy." *Id.* at 8.

Dr. Kinsbourne also cited Kasper[57] for the proposition that on autopsy, subjects with epilepsy and subjects without epilepsy have "most" of the same variants of FCD. Pet. Ex. 102. On review, Kasper, in this study published in 1999, did not use the term FCD. They reported that "only four features out of the broad range of "microdysgenesis" reported previously are more common in TLE [temporal lobe epilepsy] brains as compared with control brains". Pet. Ex. 111 at 7. Kasper wrote that those four features are "correlated with epilepsy", irrespective of the exact relationship. *Id.* Kasper also wrote that this "data argues against the concept of a characteristic constellation of certain microscopical features constituting a histological syndrome of "microdysgenesis." *Id.* This article does not relate to the current understanding of FCD and its association with epilepsy because, as explained below, the term microdysgenesis usually refers to mild malformations of cortical development (mMCD) rather than FCD.

Dr. Kinsbourne also cited a case report by Tezer-Filik, published in 2010 in a Turkish medical journal[58] about a seventy-four (74) year old individual with no history of seizure activity. Pet. Ex. 77 at 1. After the individual experienced an episode of syncope, he underwent a cranial MRI which detected a tumoral mass lesion in the left frontal cortex. *Id.* at 1-2. Tezer-Filik suggested that this case represented asymptomatic FCD, which Tezer-Filik also referred to as "cortical dysgenesis", in the eighth decade of life. *Id.* at 1-2. Tezer-Filik suggested that the underdiagnosis of FCD "may result in a clinical spectrum that is too narrow to reflect the reality." *Id.* However, the individual at issue did not agree to surgical intervention, which would have allowed for more direct examination of the brain tissue (which the expert neurologists in this case agreed is the gold standard for confirming FCD, *see* Tr. 231-32, 259, 297). Tezer-Filik admitted that they were "unable to show that there might really be… pathological involvement of focal cortical dysplasia [FCD]" in this individual. *Id.* at 2.

Dr. Kinsbourne, following the approach in the articles cited above, used interchangeably the terms "dysplasia" and "dysgenesis." *See, e.g.*, Pet. Ex. 64 at 3 ("A brain MRI… located a previously not apparent cortical dysgenesis"); *id.* at 4 ("Is cortical dysgenesis alone a sufficient explanation for the epilepsy that ensued so early in [A.A.'s case?"); *id.* ("the mere presence of

[57] Kasper et al., *Temporal Lobe Microdysgenesis in Epilepsy Versus Control Brains*, 58 J. Neuropathol. Exp. Neurology 22 (1999) [Pet. Ex. 111].

[58] Tezer-Filik, et al., *A Case with an Asymptomatic Malformation of Cortical Development Diagnosed in Eighth Decade of Life*, 111 Bratisl Lek Listy 167-68 (2010) [Pet. Ex. 77].

even gross cortical dysgenesis by no means necessarily indicates that the patient will have epilepsy" according to Dr. Kinsbourne.).

Respondent's expert neurologist Dr. Raymond responded that "dysgenesis" reflects "an older definition of cortical abnormality without the diagnostic definitions presently used for FCD." Resp. Ex. FF at 2. Dr. Raymond's assertion is supported by the literature. For example, in 2004, Palmini . wrote that Meencke originally introduced the term microdysgenesis "to describe minimal, subtle abnormalities of intracortical architecture". Ct. Ex. 1 at 2. However, that terminology has "been the focus of significant confusion" and "should be abandoned". *Id.* In his critical review and invited commentary on FCD published in the journal Epilepsia in 2009, Lerner wrote: "Another category, termed mMCD or microdysgenesis, also referred to as mild malformations of cortical development, consists of normal cortical organization with an excess of neurons in the subcortical white matter or molecular later. Without cortical disorganization and dyslamination, it is controversial whether mMCD represents a 'true' form of cortical dysplasia." Resp. Ex. JJ at 3. Similarly in 2010, Spreafico and Blumcke[59] mention that Meencke . introduced the term "microdysgenesis" to describe "minimal subtle abnormalities", but that term has since been considered misleading and avoided in later classification schemes for FCD. Pet. Ex. 133 at 3. Finally, in 2011, upon presenting the current classification scheme for FCD, Palmini and the other ILAE members offered a glossary of terminology. Resp. Ex. MM at 14. They wrote that there was previously confusion created by various usages of descriptive and diagnostic terms: "Dysplasia (synonymous with Dysgenesis and Malformation): this is a general term referring to any tissue that is imperfectly developed in embryonic or fetal life. However, Dysplasia, is a diagnostic term used here to identify specific malformations of the cortex, the so-called Focal Cortical Dysplasias…" *Id.* Thus, the more recent literature regards microdysgenesis as a confusing term and one likely to be associated with mild malformations of cortical development (mMCD), rather than FCD which is the most prevalent etiology for difficult-to-treat epilepsy in children.

Dr. Kinsbourne also cited a 2017 article by Maynard[60], who hypothesized that because most healthy individuals do not undergo a brain MRI, the prevalence of FCD is unknown. Pet. Ex. 73 at 2. Maynard acknowledged that large studies performing brain MRIs on healthy individuals have not identified FCD as a common finding. *Id.* Nevertheless, Maynard cited Tezer-Filik's case report and two others for the hypothesis that the "'atypical clinical presentation' of FCD without epilepsy is not rare, just rarely reported." *Id.* To test this hypothesis, Maynard reviewed a large pediatric medical center's database, which included records from ninety-seven (97) pediatric patients who underwent brain MRIs that were suggestive of FCD. *Id.* at 3. Sixty-seven (67) of the patients (71%) had epilepsy, which was the most common indication for undergoing the MRIs. *Id.* at 6. The remaining twenty-eight (28) patients (29%) did not have epilepsy; their indications for MRIs included limited seizure activity, developmental delay, headaches or migraines, or head trauma. *Id.* Dr. Kinsbourne opined that

[59] *See also* Spreafico & Blumcke, *Focal Cortical Dysplasias: Clinical Implication of Neuropathological Classification Systems*, 120 Acta Neuropathologica 359 (2010) [Pet. Ex. 133] at 3.

[60] Maynard et al., *Epilepsy Prevalence and Severity Predictors in MRI-Identified Focal Cortical Dysplasia*, 132 Epilepsy Research 41-49 (2017) [Pet. Ex. 73].

Maynard's findings supported that FCD can be present without epilepsy. He opined that their study was of children who had some kind of indication for MRI so they were not a "strictly normal" population. *Id.* at 235. Dr. Kinsbourne opined that in the "general population of children" who did not undergo MRI, the incidence of FCD is "much higher than 29 percent". *Id.*

On the other hand, respondent's expert neurologist Dr. Raymond questioned Maynard's interpretation that the non-epileptic patients had FCD absent surgical confirmation. Resp. Ex. FF at 5. Dr. Raymond and Dr. Kinsbourne agreed that surgical evaluation is the gold standard for confirming FCD. *See* Tr. 231-32, 259, 297. It is important to note that surgery did not appear to be clinically indicated or ethically possible for the non-epileptic patients.

However, the Maynard article is of limited weight for other reasons. Even if I accepted *arguendo* Maynard's theory that many non-epileptic patients may indeed have FCD, despite the lack of surgical confirmation, Maynard found that only 29% (less than one-third) of the patients with MRI findings suggestive of FCD *did not* develop epilepsy. Pet. Ex. 73 at 3. Dr. Kinsbourne agreed that the corollary conclusion was that 71% (a solid majority, over two-thirds) of the subjects *did* develop epilepsy. Tr. 274. Thus, respondent contends, it is more likely than not that FCD will be associated with epilepsy. Resp. Post-Hearing Response at 17.

Moreover, Maynard admitted to several limits to her study, including "the retrospective study population and a relatively short follow-up period." Pet. Ex. 73 at 6. Maynard then recommended future studies, including a follow-up study of their cohort or a study of an adult population with MRI-identified FCD. *Id.* And contrary to Dr. Kinsbourne's opinion that Maynard.'s subjects all had some indication for MRI, rendering them less than a "normal population" and a normal population would likely have more undiagnosed FCD *see* Tr. 235, Maynard wrote that "large studies performing brain MRIs on healthy individuals *have not* identified FCD as a common finding." Pet. Ex. 73 at 2 (emphasis added). Thus, Maynard acknowledged that she could not find any other support for her hypothesis.

Most importantly, the literature from Palmini, Lerner, and others supports a strong association between FCD and epilepsy. And as seen in this case, A.A. was born with either FCD type II or the early onset subtype of FCD type I, with abnormalities extending through the parietal and frontal cortex, the central sulcus, and other areas in the frontal lobe, which were seen in conjunction with severe epilepsy and multiple seizure types occurring frequently over her first six years of life. A.A.'s extensive pathology and her clinical presentation can hardly be compared to cases of either mMCD or more limited FCD.

F. Petitioners' Proposition: "An Individual with FCD is not Predestined to Develop Seizure Activity at a Particular Time… FCD May Need an Additional Insult (Second Hit) to Become Epileptic in Some Cases."[61]

Dr. Kinsbourne acknowledged that FCD is associated with epilepsy but that there is an "enormous[ly]" wide range of onset. Pet. Ex. 64 at 4. He opined that: "an additional hit seems to be necessary before the first seizure occurs." *Id.*

[61] Pet. Post-Hearing Brief at 20.

In support for this proposition, Dr. Kinsbourne cited a study by Kral[62] of 53 patients with surgically confirmed FCD. Dr. Kinsbourne emphasized that in Kral's study, "the mean age of seizure onset was 12.4 years, the enormous range was 0.4 – 36 years." Pet. Ex. 64 at 4, citing Pet. Ex. 72. While Dr. Kinsbourne's characterization is accurate, Kral did not discuss the significance of the onset range or the specific histopathological findings that the study found. Kral's objective was to describe the outcome of surgery. Pet. Ex. 72 at 1.

Dr. Kinsbourne cited another study by Fauser[63] of one hundred and twenty (120) subjects with surgically confirmed FCD and epilepsy. Dr. Kinsbourne emphasized that for the entire cohort, the onset was from less than one year to sixty (60) years of age. Pet. Ex. 69 at 1. Dr. Kinsbourne also quoted Fauser.'s statement that FCD "can exist for prolonged periods of time without giving rise to clinically manifest seizures". Pet. Ex. 64 at 4, citing Pet. Ex. 69 at 7. Upon review, in that quote, Fauser was addressing the single individual who was 60 years old when he developed epilepsy. Pet. Ex. 69 at 7. Fauser also noted that in that individual, resection of the FCD did not resolve his seizures, which raised the possibilities that he had further subtle FCD or a completely different pathology. *Id.* Apart from that one individual, in a few other subjects, epilepsy started between 12 and 31 years of age. *Id.* However, "the vast majority" of the subjects with surgically confirmed FCD had the onset of epilepsy "in the first 11 years of life". *Id.* Indeed, the largest concentrations of seizure onset occurred in the first and second years of life. See Table of age distribution. Fauser also proposed an explanation for the range of seizure onset in the subjects. Fauser observed that FCD involving only heterotopic cells and no architectural abnormalities have more homogenously distributed onset over the first two decades of life. *Id.* In contrast, FCD with both architectural abnormalities and abnormal cells [dysmorphic neurons in type IIa, plus balloon cells in type IIb] "are associated with an earlier age at seizure onset". *Id.* Fauser proposed that these abnormal cells "have a high epileptogenic potential and may thus contribute to an earlier manifestation of clinically manifest seizures". *Id.*

Dr. Kinsbourne also cited a study by Widdess-Walsh[64] of one hundred and forty-five (145) subjects with surgically confirmed FCD and epilepsy. Dr. Kinsbourne emphasized that, for the entire cohort, the "median age of onset of seizures [was] 7.5 years, with the enormous range of 3 months to 47 years." *See* Pet. Ex. 64 at 4. Widdess-Walsh actually divided the patients based on the histopathological findings. Pet. Ex. 83 at 2. Seventy-six (76) patients had FCD type Ia – defined by architectural abnormalities, but no dysmorphic neurons or balloon cells – which correlated with later onset: the median was 11.6 years old, with a range of 0.25 to 47 years old. *Id.* at 2. In contrast, FCD types Ib, IIa, and IIb correlated with earlier onset – with median ages of about 3 years old and with differing ranges, but as early as 0.003 years and as late as 24 years old. *Id.* FCD types IIa and IIb were also associated with more clinically severe drug-resistant epilepsy. *Id.* at 7. Widdess-Walsh also wrote: "Clinically important differences

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[62] Kral et al., *Outcome of Epilepsy Surgery in Focal Cortical Dysplasia*, 74 J. Neurology, Neurosurgery & Psychiatry 183 (2003) [Pet. Ex. 72].

[63] Fauser et al., *Clinical Characteristics in Focal Cortical Dysplasia: A Retrospective Evaluation in a Series of 120 Patients*, 129 Brain 1907 (2006) [Pet. Ex. 69].

[64] Widdess-Walsh, Najm et al., *Electroclinical and Imaging Characteristics of Focal Cortical Dysplasia*, 67 Epilepsy Research 25 (2005) [Pet. Ex. 83]

exist between the pathological subtypes of FCD, which may assist in their management, and provide further insight into their underlying pathophysiology." *Id.* at 1.

Dr. Kinsbourne quoted Widdess-Walsh as stating that: "a 'second hit' to an already dysplastic area may facilitate eventual epileptogenesis." Pet. Ex. 64 at 4, citing Pet. Ex. 83 at 7. Upon review, Widdess-Walsh did not propose that all cases of FCD require a "second hit", rather: "…A trend towards a higher incidence of *perinatal adverse events* in the type IIb group may suggest the occurrence of a *birth-related environmental insult*. Although most cortical neurons have undergone migration at this point, a 'second hit' to an already dysplastic area may facilitate eventual epileptogenesis." Pet. Ex. 83 at 7. Widdess-Walsh also noted an association between head trauma and seizures with FCD type Ia and Ib, and an association between febrile seizures and seizures with type Ia. *Id.* at 1, 4. However, Widdess-Walsh did not explain why these events represent risk factors and Widdess-Walsh did not mention vaccines.

Dr. Kinsbourne cited another article in which Najm (who was a coauthor on the Widdess-Walsh study)[65] wrote that, according to past studies, subjects with FCD develop epilepsy at various ages. Pet. Ex. 74 at 6. Some subjects "do not express epilepsy till later in life and if they do, epilepsy appears after some type of trigger". *Id.* at 9. Najm asked: "(1) Is there a need for a 'second hit' before the transformation of a preexisting 'dormant' lesion into an active/ epileptogenic focus?, and (2) what are the mechanisms that underlie the transformation of these dormant lesions into active/ epileptic foci?" *Id.* at 6. Although Najm raised these questions, his paper is a review on the current understanding of the pathophysiological mechanisms for FCD. He reviewed the existing data but he did not perform any new studies. He recommended improvements to conventional MRI technology, studies using ECoG, and animal models. *Id.* at 8-9. As Dr. Raymond correctly noted: "So while these authors [Najm et al.] speculate about a second hit in the human condition, they do not have evidence that one is necessary." Resp. Ex. FF at 5.

It should also be noted that Widdess-Walsh's article was published in 2005 and Najm's article was published in 2007, during a period in which the growth of understanding of this condition was growing substantially. Dr. Palmini, who has consistently been one of the leaders in this field, provided more solid data on the role of FCD in seizure generation, as synthesized in his 2013 book chapter (Resp. Ex. II) introduced above.

In contrast to Dr. Kinsbourne, respondent's experts opined that FCD is intrinsically epileptogenic and it does not need a trigger for the development of seizures and epilepsy. *See,*

[65] Najm et al., *Pathophysiological Mechanisms of Focal Cortical Dysplasia: A Critical Review of Human Tissue Studies and Animal Models*, 48 Epilepsia 21 (2007) [Pet. Ex. 74].

e.g., Resp. Ex. FF at 2.[66] Dr. Raymond cited Palmini's 2013 book chapter[67] for a summary of this research. Specifically, electrographic recordings (such as EEG and ECoG) display exquisitely epileptogenic potentials, namely: "(1) continuous, rhythmic, or semi-rhythmic spikes; (2) paroxysmal bursts of high-frequency spikes; or (3) recurrent electrographic seizures." *Id.* at 7-8. These recordings demonstrate that FCD itself was hyperexcitable and generating epileptiform potentials. *Id.* at 8. When the analysis is restricted to subjects with type II FCD, more than 80% have one or more of these highly excitable electrographic patterns. *Id.* Palmini characterized these as the "the electrophysiological signature of the underlying pathology." *Id.* Respondent's second expert neurologist Dr. Kohrman agreed that FCD is sufficient in and of itself to cause infantile spasms. Resp. Ex. BBBB at 1, citing Resp. Ex. DDDD.[68]

Respondent's expert neurologists offered several reasons for the possible range of seizure onset in FCD, which are supported by my review of the literature authored by Palmini and others as discussed above. First, the histopathological findings matter. Compared to FCD with only cytoarchitectural abnormalities, FCD with dyslamination and abnormal cells may be correlated with an earlier onset and a more severe epilepsy. *See, e.g.*, Resp. Ex. FF at 4-5; Resp. Ex. MM at 5-6; *accord* Widdess-Walsh [Pet. Ex. 83] at 2; Fauser [Pet. Ex. 69] at 7.

Second, the *extent* of FCD can also correlate with onset and severity. *See, e.g.*, Resp. Ex. FF at 4-5; Tr. 477, 527, 541-42, 563. Dr. Kohrman opined that you need a certain volume of abnormal brain tissue, about five square centimeters of cortex, for the epileptic discharge to spread and result in a clinically observable seizure. Tr. 524. He opined that a small, single FCD will also fire neurons abnormally, and that can be measured "if we were to put a wire in them", but it will not implicate enough brain tissue to cause seizures. Tr. 524-25. The literature also supports this proposition. For example, the ILAE task force provides that "the extent of the lesion" influences the age of seizure onset, epilepsy duration, and seizure frequency. Resp. Ex. MM at 8.

Dr. Raymond also highlighted Palmini's description of a particular subgroup of "early onset severe childhood epilepsies" caused by FCD type I. Resp. Ex. HHHH at 2, citing Resp. Ex. II at 3. In this subgroup, seizure onset is usually within the first year of life. Resp. Ex. II at 3. MRIs show subtle regional or hemispheric hypoplasia, with subtle increased signal on T2-

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[66] Citing Palmini et al., *Intrinsic Epileptogenicity of Human Dysplastic Cortex as suggested by Corticography and Surgical Results*, 37 Ann. Neurol. 476 (1995) [Resp. Ex. QQ]; Dubeau, Palmini, Spreafico et al., *The Significance of Electrocorticographic Findings in Focal Cortical Dysplasia: A Review of their Clinical, Electrophysiological and Neurochemical Characteristics*, 48 Electroencephalogr. Clin. Neurophysiol. Suppl. 77 (1998) [Resp. Ex. RR]; *see also* Morioka et al., *Intrinsic Epileptogenicity of Focal Cortical Dysplasia as Revealed by Magnetoencephalography and Electrocorticography*, 33 Epilepsy Res. 177 (1999) [Resp. Ex. SS].

[67] Palmini & Holthausen, *Chapter 58: Focal Malformations of Cortical Development: A Most Relevant Etiology of Epilepsy in Children*, in Handbook of Clinical Neurology, Vol. III – Pediatric Neurology Part I (2013 Dulac et al., eds.) [Resp. Ex. II].

[68] Citing *Chapter 10: PET: Pediatric Epilepsy, Excerpt on Epileptic Spasms* in *Neuroimaging in Epilepsy* (Chugani, ed., 2011) [Resp. Ex. DDDD] at 4 (adding that ictal FDG PET scans have unique findings "suggesting that the spasms are initiated by a primary cortical epileptic focus that interacts with subcortical and brainstem structures," beginning during a "critical stage of brain development", at about 3 months old).

weighted cuts and on FLAIR. *Id.* The subjects have no neurological deficits or very mild hemiparesis only, but a high risk of severe mental retardation. *Id.* They display all kinds of focal seizures, but the seizures are very often "generalized". *Id.* EEGs can display both epileptiform and non-epileptiform discharges. *Id.* The response to medication is poor. *Id.* Resection of one or multiple lobes, excluding the motor strip, is associated with a less favorable seizure outcome. In contrast, hemispherectomy is associated with better outcomes. *Id.*

I asked Dr. Raymond, if FCD is locked in place by 22-23 weeks of gestation, why does it not become clinically epileptic until some later time, for example, "four months, ten months, ten years…". Tr. 313. Dr. Raymond answered: "that probably has to do with development of associated circuits as well as connections being made." Tr. 313. In some instances, the FCD is "in a location… and there's connections" that allow for the onset of seizures "in a one-day-old". *Id.* He continued:

> The other thing that you have to understand, though, it that there's a shifting of certain channels that naturally occurs, and so there may be a falling out of certain inhibitory circuits as the rest of the brain is trying to remodel, because that's what it does, and so this – these are potential mechanisms for why the specific area and specific time we see these things come forward.
>
> Certain shifting of neurochemical channels or neurochemical receptors, as well as shifting of other types of receptors, as well as myelination occurs, now allowing parts of the brain that might have been in isolation to now communicate more easily, which is what it's supposed to do, and that's why we talk and we walk, and that's why a newborn doesn't but now that's working against that individual.

Tr. 312-13. Petitioners had the opportunity to rebut the above testimony, but they did not do so. I found Dr. Raymond's testimony on this point to be credible and *supplementing* the reasons provided in the literature by Palmini and others.

G. Conclusion Regarding FCD

Overall, a preponderance of the available evidence submitted by both parties supports that there is a range for the onset of epilepsy associated with FCD. Dr. Kinsbourne cited some authors who hypothesized that later-onset epilepsies may involve a trigger and they hypothesized potential triggers such as head trauma but without specific correlating evidence. It is tempting to theorize that the onset of seizures with FCD requires a second hit and perhaps it does in some of the outlier cases, such as the 60-year-old man described by Fauser. However, in the majority of cases described, even in petitioners' literature, the strongest concentrations of seizure onset occurred in the first three years of life.[69]

[69] Petitioners cited one other article for the proposition that vaccinations can cause an earlier onset of seizures not specifically in individuals with FCD, but with other susceptibilities towards epilepsy. *See* Pet. Post-Hearing Brief at 17 and Pet. Post-Hearing Reply at 4-5, both citing McIntosh et al., *Effects of Vaccination on Onset and Outcome of Dravet Syndrome: A Retrospective Study*, *9* Lancet Neurol. 592 (2010) [Resp. Ex. U]. In this article, Mcintosh reported on children with identified mutations in the SCN1A gene, which is strongly associated with the seizure disorder Dravet syndrome. The onset of seizures tended to be at an earlier age, when the onset had a close temporal association (0 – 1 days) after the DTaP and other vaccines routinely given at two months, four months, and six

To the contrary, the evidence supports that FCD is the most prevalent etiology for difficult-to-treat epilepsy in children. Leading researchers including Palmini have provided significant detail about the advances in understanding of FCD which strongly suggest that FCD, particularly when large and/or when involving heterotopic or dysmorphic cells in addition to the laminar disorganization, is physiologically epileptogenic and becomes symptomatic without the need for a trigger. The extent and specific histopathological findings most likely dictate the age at onset, as well as the severity of the seizures and resulting developmental delay.

Here, A.A.'s evolving seizures were consistent with FCD-caused epilepsy as described in the literature. The initial MRIs did not visualize any abnormal findings which is explained by the fact that she was under one year old and her brain was still in the process of myelination. However, multiple potential lesions were visualized on subsequent higher-resolution MRIs and the lesions were correlated on PET, SPECT, ECoG, and sEEG, before A.A. finally underwent surgical resection. In particular, the surgeries and post-surgical pathology on the resected right parietal lobe, frontal lobe, and cingulate gyrus identified significant FCD characterized by cortical disorganization as well as dysmorphic neurons, extensive white matter heterotopia which can be epileptogenic in and of itself, thickening of the cortex, and an area of gyral malformation. The insula was also suspected to be part of the epileptogenic region but that tissue was not examined by the pathologist. It is apparent that these findings were more than enough to cause the severe epileptic condition that A.A. experienced without implicating her four-month vaccines as a trigger or second hit. For these reasons in particular, petitioners have not established causation in fact specifically under *Althen* prongs one and two. However, I will review certain additional arguments raised in the case for the sake of completeness.

H. Comparison to *Reilly*

In *Reilly*, another special master accepted Dr. Kinsbourne's opinion that FCD can be asymptomatic, that a trigger is needed for the onset of seizures, and that early childhood vaccines can serve as that trigger. *Reilly*, 2016 WL 3456844. Dr. Kinsbourne offered a similar opinion and similar if not identical literature as he did in this case.

However, in *Reilly*, the special master did not discuss "the classification of FCDs according to their severity and structural features and how prone they are to cause epilepsy," because there was insufficient information available to classify that child's FCD. *Reilly* at *3 and n. 20. The child's diagnosis was based on MRI findings. Then, in 2010, the child

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months. Resp. Ex. M at 4-5. However, McIntosh reported that earlier onset of seizures was not associated with worse clinical outcome. *Id.* at 4-5. McIntosh concluded that "there is not rational basis for withholding [DTaP] vaccinations… for fear of causing Dravet syndrome." *Id.* at 5. Respondent correctly noted that the Vaccine Program has adjudicated multiple petitioners' claims that the routine childhood vaccinations can cause or significantly aggravate the course of Dravet syndrome. Those petitioners consistently referenced the above study by McIntosh et al. Those claims have been uniformly denied. *See* Resp. Post-Hearing Brief at 12-13 (internal citations omitted). Moreover, the literature filed in this case provides that each form of epilepsy has unique etiology and causal mechanisms. Petitioners have not established why an article about vaccinations in the context of SCN1A gene mutations and Dravet syndrome can predict anything about vaccinations in the context of FCD and infantile spasms.

underwent a "right temporal craniotomy and temporal lobectomy[70] via cauterization[71] which preserved little tissue for pathological examination. *Reilly*, 2016 WL 3456844, at *3. Therefore, the special master did not discuss the type and extent of FCD in her analysis of *Althen* prongs one and two. *Id.* at n. 20.

In contrast here, respondent's expert neurologists were persuasive in describing FCD as a heterogeneous condition, in which the tissue is intrinsically epileptogenic, and that the specific histopathological findings and particularly the extent of the FCD are the primary determinants of the severity of epilepsy. This view is also reflected in some of Dr. Kinsbourne's key articles.

Also unlike in *Reilly*, here in the case of A.A., there is thorough documentation including MRIs, ECoG, sEEG, and post-surgical pathologic examination which reflect the extent of her FCD, which I have concluded to be the sole cause of her seizures. Overall, the record before me supports that FCD is inherently epileptogenic without need for a trigger particularly as it presented in this child.

I. Petitioners' Proposition: In General, the Vaccines at Issue Can Induce "Seizures and Epilepsy."[72]

Under *Althen* prong one, petitioners' theory was premised on propositions that are not novel within the Vaccine Program. Petitioners averred that vaccines, particularly DTaP, can cause seizures and epilepsy, especially in an at-risk host. *See, e.g.*, Pet. Post-Hearing Brief at 17. Petitioners' expert neurologist Dr. Kinsbourne was the first to raise this proposition. *See* Pet. Ex. 32 at 7-8. In their post-hearing brief, petitioners relied on Dr. Kinsbourne's reports and three main articles.

First, Dr. Kinsbourne cited a CDC information statement[73] which provided that the risks from DTaP vaccine include: "Seizure (jerking and staring) (about 1 child out of 14,000)." Pet. Ex. 106 at 2. The statement also referenced reports of DTaP vaccine followed by "long-term seizures", however, the statement added: "These are so rare it is hard to tell if they are caused by the vaccine." *Id.*

Dr. Kinsbourne also opined that: "It is widely acknowledged in the Vaccine Injury Compensation Program and elsewhere that when DTaP causes a seizure, epilepsy not uncommonly results." Pet. Ex. 64 at 1. He cited two articles in support of this proposition.

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[70] Temporal lobectomy is defined as "an excision of part or all of a temporal lobe in the treatment of temporal lobe epilepsy." *Dorland's*.

[71] Cauterization is defined as "destruction of tissue with a hot or cold instrument, electric current, caustic substance, or other agent." *Dorland's*.

[72] Pet. Post-Hearing Brief at 17-18.

[73] CDC, *DTaP Vaccine Information Statement*, May 17, 2007 [Pet. Ex. 106].

However, they are not helpful. First, Von Spiczak[74] described a retrospective analysis of Germany's national database of reported post-vaccine adverse events mentioning seizures and epilepsies in children aged 0 – 6 years. Pet. Ex. 76 at 2. Dr. Kinsbourne highlighted that there were reports of epilepsy following acellular pertussis vaccine. Pet. Ex. 32 at 1, citing Pet. Ex. 76 at 13 – Supplementary Table 4. Dr. Kinsbourne also highlighted that of the reported fifty-eight (58) cases of post-vaccine onset of epilepsy, thirty-two (32) cases involved onset of seizures within three days post-vaccination. Pet. Ex. 32 at 1, citing Pet. Ex. 76 at 14 – Supplementary Table 5a. However, von Spiczak wrote that these reports might be explained by coincidence in light of the childhood immunization schedule coinciding with the typical age at onset of certain severe childhood epilepsies. Pet. Ex. 76 at 13. Von Spiczak also stated specifically that the specific diagnosis of infantile spasms required "particular attention with respect to the diagnosis of *possible underlying etiologies such as* genetic causes or *cortical malformations* and *an assumption that a proximate vaccination is causative should not be made.*" *Id.* at 10 (emphasis added). Here of course, there is objective evidence of a cortical malformation, specifically FCD, which is viewed as a leading etiology for difficult to treat epilepsies in children.

Second, Dr. Kinsbourne opined that an article by Verbeek[75] "clearly demonstrated that vaccine-triggered and specifically DTaP-triggered seizures can lead to epilepsy (even using the strict criterion of onset within no more than one day after vaccination", adding, "Unsurprisingly, like [A.A.], many of the children had susceptibility factors." Pet. Ex. 65 at 2. Upon review, Verbeek compiled reports of post-vaccination seizures in 990 pediatric subjects in the Netherlands. Pet. Ex. 80 at 1. Contrary to Dr. Kinsbourne's statements, Verbeek did not conclude that vaccines can cause seizures or that the vaccines did so in their subjects. Rather, Verbeek considered whether seizure onset with a "temporal relation to vaccination" was potentially "vaccination related." *Id.* at 2, 5 at Fig. 1. Then Verbeek evaluated for a known etiology. Verbeek went on to identify "underlying causes of the epilepsy syndromes" in two-thirds of the subjects and suspected that there were underlying causes in the remaining one-third. *Id.* at 5-6. Verbeek wrote: "In the past, the absence of a detectable underlying cause in children with vaccination-related seizure onset led to the assumption that the vaccination itself was the cause of the subsequent neurologic deterioration in some. However, the large variability in electroclinical syndromes and corresponding cognitive outcomes in our study further support the hypothesis that predisposing factors within the child, and not the vaccination, cause the observed neurologic deterioration." *Id.* at 6. Verbeek recommended further research in hopes of supporting public faith in vaccination programs. *Id.*

Contrary to Dr. Kinsbourne's opinion, the above articles do not support that vaccines can cause epilepsy in general. Rather, they provide that epilepsy onset may have a temporal association with vaccines, but there are different types of epilepsy with different etiologies that are being identified and better understood over time (such as seizures caused by FCD, as discussed above). Here, I conclude that A.A.'s FCD and related heterotopic and dysmorphic cells are much more likely to be the sole cause for her seizure condition.

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[74] Von Spiczak et al., *A Retrospective Population-Based Study on Seizures Related to Childhood Vaccination*, 52 Epilepsia 1506 (2011) [Pet. Ex. 76].

[75] Verbeek et al., *Etiologies for Seizures Around the Time of Vaccination*, 134 Pediatrics 1-19 (2014) [Pet. Ex. 80].

Respondent's expert neurologists also disclaimed an association between vaccines and epilepsy. Dr. Kohrman opined that there was no such evidence. Resp. Ex. BBBB at 3. Dr. Raymond opined that there were no definitive studies. Resp. Ex. A at 10. At the hearing, Dr. Raymond conceded that vaccines "may result in an increase in fever and result in a febrile seizure." Tr. 319. However, in this case, petitioners' theory did not implicate fever and there is no evidence that A.A. developed a post-vaccinal fever. This one concession from one of respondent's experts on cross-examination did not support *Althen* prong one or two.[76]

J. Petitioners' Proposed Mechanism: Vaccines Can Cause the Release of Pro-Inflammatory Cytokines, Which Can Interact with FCD in the Brain, to Cause the Onset of Seizure Activity.[77, 78]

Also relating to *Althen* prong one, Dr. Gershwin opined that from the outset, FCD tissue is a "vulnerable target tissue" in a "pro-inflammatory state," which is evidenced by FCD containing a high expression of pro-inflammatory cytokines, particularly interleukin 1 beta (IL-1β). *See, e.g.*, Pet. Ex. 157 at 3.[79] Dr. Gershwin essentially opined that upregulation of the

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[76] The Federal Circuit recently reinstated entitlement in favor of petitioners who relied on Dr. Kinsbourne's opinion that DTaP can and did cause a four-month-old child with an *unspecified* susceptibility to suffer the onset of infantile spasms, in the absence of fever, within less than a week. The Circuit held that a special master was not arbitrary or capricious upon accepting Dr. Kinsbourne's opinion that two studies supported an association between DTP and infantile spasms, which were also relevant in that claim concerning DTaP. *See Kottenstette v. Sec'y of Health & Human Servs.*, -- Fed. Appx. --, 2021 WL 2434329 (Fed. Cir. 2021).

The present case initially resembled *Kottenstette*. A.A. initially developed myoclonic seizures, hypsarrhythymia, and developmental delays and she was initially diagnosed with infantile spasms. Dr. Kinsbourne's opinion started from that basis. In his first report, he noted that the initial neuroimaging "failed to detect any structural lesions that could have been causal." Pet. Ex. 32 at 6. Dr. Kinsbourne also filed an article by Riviello which divided infantile spasms into three forms: "[1] Symptomatic refers to IS secondary to a known neurological insult; [2] cryptogenic refers to a suspected, but not definitely identified neurological insult; [3] idiopathic is used when no specific insult has been identified. The prognosis is worse if the spasms are either symptomatic or cryptogenic." Riviello J., *EEG Pediatric Abnormalities*, in *The Clinical Neurophysiology Primer* (2007) (Blum & Rutcove, eds.) [Pet. Ex. 40] at 15. Riviello also wrote that for infantile spasms, the known neurological insults included tumor, stroke, and most commonly FCD. *Id.*

Thus, the medical evolution of this case, as described in detail above, distinguishes it from *Kottenstette.* While at the time of Dr. Kinsbourne's first report, A.A.'s condition resembled the child's condition in *Kottenstette*, over time, A.A.'s condition became more clearly defined. It is apparent that this case centers on a "known neurological insult" – FCD – which is understood to be epileptogenic without need for a trigger.

[77] *See* Pet. Post-Hearing Brief at 17-18, 20.

[78] Dr. Kinsbourne was the first of petitioners' experts to suggest this mechanism, but he then deferred to Dr. Gershwin to elaborate on the mechanism which was more within the latter's area of specialty, immunology. *See* Pet. Ex. 102 at 7.

[79] Citing Srivastava et al., *Comparative Analysis of Cytokine-Chemokine Regulatory Networks in Patients with Hippocampal Sclerosis (HS) and Focal Cortical Dysplasia (FCD)*, 7 Scientific Reports 15904 (2017) [Pet. Ex. 123] at 2 (finding that compared to non-epileptic subjects undergoing surgery to remove brain tumors, epileptic subjects with HS and FCD have significant upregulation of pro-inflammatory cytokines including IL-1β) and IL-6); *see also* Ravizza and Boer, *The IL-1β System in Epilepsy-Associated Malformations of Cortical Development*, 24

inflammatory pathway, including the release of those cytokines, initiates seizure activity in FCD tissue. *Id.*[80] He further opined that once seizure activity begins in FCD, these cytokines help to perpetuate a "vicious cycle." *Id.*[81] In contrast, Dr. McCusker opined that seizure activity causes the upregulation of the inflammatory pathway, which causes the release of cytokines. Resp. Ex. IIII at 4. But as Dr. Gershwin noted, *see, e.g.*, Pet. Ex. 90 at 2, this is a "chicken or the egg" dilemma. It is unknown what is present first – upregulated cytokines or seizure activity – in the human brain. The answer would likely require invasive studies on the brain prior to the onset of seizure activity which is not feasible.

Dr. Gershwin also opined that FCD tissue features high expression of the downstream effector or signaling protein CCR5. Pet. Ex. 157 at 1.[82] Dr. Gershwin opined that CCR5 helps to direct immune cells to sites of inflammation. *Id.*[83] He also noted literature supporting that seizure activity in general (not specifically in FCD tissue) causes enhanced permeability of the blood brain barrier ("BBB"). *Id.* at 4.[84]

Dr. Gershwin cited an article by Srivastava[85] who observed that compared to hippocampal sclerosis (HS)[86], in FCD, there is not only inflammation arising within the brain, but a more significant contribution from peripheral immune cells. Tr. 137-39; Pet. Ex. 138 at 3.

Neurobiology of Disease 128 (2006) [Pet. Ex. 114] at 19 (finding that compared to non-epileptic subjects on autopsy, epileptic subjects with FCD, there was "strong neuronal expression" of IL-1β and its receptor).

[80] Zhang et al., *Upregulation of HMGB1-TLR4 Inflammatory Pathway in Focal Cortical Dysplasia Type II*, 15 J. Neuroinflammation 1 (2018) [Pet. Ex. 162].

[81] Citing, *e.g.*, Gatti, Vezzani et al., *Chapter 12: Mechanisms of Fever and Febrile Seizures: Putative Role of the Interleukin-1* System, in *Febrile Seizures* (Baram and Shinnar, eds. 2002) [Resp. Ex. TTTT]; Vezzani & Baram, *New Roles for Interleukin-1 Beta in the Mechanisms of Epilepsy*, 7 Epilepsy Currents 45 (2007) [Pet. Ex. 81]; Vezzani et al., *The Role of Cytokines in the Pathophysiology of Epilepsy*, 22 Brain, Behavior & Immunity 797 (2008) [Pet. Ex. 161]; Li et al. (2011) [Pet. Ex. 38].

[82] Citing Srivastava et al. [Pet. Ex. 123] at 2.

[83] Citing Srivastava et al. [Pet. Ex. 123] at 2 (providing that CCR5 "may relate to increased glial glutamate release and disruption of the BBB); Louboutin et al., *Relationship Between the Chemokine Receptor CCR5 and Microglia in Neurological Disorders: Consequences of Targeting CCR5 on Neuroinflammation, Neuronal Death and Regeneration in a Model of Epilepsy*, 12 CNS & Neurological Disorders – Drug Targets 815 (2013) [Pet. Ex. 158] at 5 (reporting on studies which "suggest that CCR5 plays a role in the synergistic interactions between leukocyte adhesion, endothelial activation, BBB leakage, and seizure activity").

[84] Li et al., *Cytokines and Epilepsy*, 20 Seizure 249 (2011) [Pet. Ex. 38] at 5.

[85] Citing Srivastava et al. [Pet. Ex. 123] at 2.

[86] Srivastava et al. wrote that FCD and hippocampal sclerosis (HS) are "the two most frequent drug-resistant epilepsy (DRE) pathologies" leading to surgery and that both conditions "involve alterations in several cellular processes and multiple cell signaling pathways." Pet. Ex. 123 at 1. HS is defined as "loss of neurons in the hippocampal region with gliosis." *Dorland's*.

Drs. Gershwin and McCusker agreed that vaccines can activate the innate immune system which includes the release of cytokines in the periphery. These vaccine-induced cytokines promote inflammation. This is a normal response which usually does not cause harm in the general population. *See, e.g.*, Resp. Ex. GG at 4-5; Pet. Ex. 90 at 1.[87]

Dr. Gershwin opined that this same response to vaccines can cause harm in a susceptible individual: "In other words, the levels of cytokines required to produce neuropathology in an otherwise healthy individual, will not be the same as those who have pre-existing neuropathology". Pet. Ex. 90 at 1-2. Specific to this case, he opined that vaccine-induced cytokines can contribute to the "vicious cycle" of seizure activity in an individual with FCD.

Specifically, as introduced above, Dr. Gershwin opined that FCD already has a high expression of cytokines which maybe induces seizure activity, but at the very least furthers seizure activity once it begins. FCD makes the BBB more permeable. Then, when vaccines induce the same cytokines in the periphery, the cytokines cross the BBB, reach the FCD, and enhance the existing "vicious cycle" of seizure activity. Pet. Ex. 157 at 6.

Dr. McCusker disagreed with Dr. Gershwin that FCD increases the potential for vaccine-induced cytokine damage leading to epilepsy. *See, e.g.*, Resp. Ex. IIII at 3. She disputed various points. For example, she opined that within the brain, microglial cells release cytokines including IL-1β under baseline conditions. Resp. Ex. GG at 5; Tr. 350-51, 355-56. More cytokines are released in response to stressors including psychological stressors, acute brain injury, neurodegeneration, trauma, CNS infection, and seizures. Resp. Ex. GG at 5-6. She opined that in the acute period following the onset of seizures, cytokines may be neuroprotective. Resp. Ex. IIII at 3; *see also* Tr. 354-55, 376, 384-85. Dr. McCusker opined that there was no evidence that cytokines can initiate *afebrile* seizure activity generally or in FCD in particular. Resp. Ex. GG at 5-6; Tr. 404.[88]

Dr. McCusker allowed that there is evidence that cytokines may play a role in chronic epilepsy. Resp. Ex. GG at 5-6. Dr. McCusker emphasized that there is no research on whether FCD tissue prior to the onset of seizures contains cytokines. Tr. 343. The only research has involved subjects who had chronic intractable seizures, which prompted surgery accessing the

[87] Petitioners also emphasized Dr. Gershwin's opinion that "fever produces cytokines and that such peripheral cytokines themselves can cause seizures." Pet. Post-Hearing Response at 18, citing Pet. Ex. 157 (Dr. Gershwin's report) at 3. This statement is not particularly clear. However, in other cases, I have seen petitioners present that theory that cytokines, namely IL-1β, that are released in the periphery can cross the blood-brain barrier, where they stimulate the hypothalamus to cause fever, which then can cause seizures. If an individual is observed to have a fever following vaccination, that may lend support to the proposition that the vaccine-activated cytokines have reached the brain. *See, e.g.*, *Morales v. Sec'y of Health & Human Servs.*, No. 14-1186V, 2019 WL 4047626, at *10, 12, 21-22 (Fed. Cl. Spec. Mstr. July 30, 2019). Dr. Gershwin may have intended to present similar reasoning in this case. However, there are important distinctions. First, in the present case, there is no allegation that A.A. developed even a mild fever, which might support that the peripheral cytokines crossed the blood-brain barrier. Second, the present case does not involve peripheral cytokines causing seizures in the hypothalamus, but instead, in the cerebral cortex.

[88] Dr. McCusker drew the distinction that: "It is very clear that vaccines are associated with the development of fever and fever can lead to febrile seizures in children." Tr. 435.

FCD tissue. Tr. 359-60; Resp. Ex. WWWW at 2. Dr. Gershwin noted that, of course, it would be impossible to evaluate cytokine levels in subjects with FCD prior to the onset of seizure activity because the presence of FCD is unknown prior to the onset of seizures. Brain pathology in asymptomatic people would not be studied. *See, e.g.*, Pet. Ex. 90 at 2.

Dr. McCusker agreed that after the onset of seizure activity, increased CCL3/ CCL4 signaling via CCR5 can lead to disruption of the BBB. She opined that this could also recruit *some* peripheral immune cells, namely T cells, to the areas of FCD. Resp. Ex. WWWW at 3; Resp. Ex. AAAAA at 4. However, she disagreed that peripheral cytokines would be recruited. Resp. Ex. WWWW at 3.

Dr. McCusker opined that while vaccines can induce the release of cytokines, the level of cytokines are low and do not remain for long. Resp. Ex. GG at 4-5; Resp. Ex. IIII at 4-5; Tr. 406-07, 413; Resp. Ex. WWWW at 3. She opined that cytokines induced by vaccines or other stimuli *can* impact the brain either through "peripheral nerve stimulation" or by themselves crossing the BBB. Tr. 393-95. These cytokines can reach areas such as the hypothalamus, which generates fever and other sickness behaviors. Tr. 393-95. However, Dr. McCusker did not find "any evidence that the pathways involved in the cytokine signaling in the CNS lead to the cortex." Tr. 400; *see also* Resp. Ex. WWWW at 3. Dr. McCusker also argued that, even if vaccine-induced cytokines can cross the BBB and those cytokines are pro-inflammatory within the brain, whether they would be in a sufficient amount to cause seizure activity seemed unlikely in her opinion. Tr. 402, 439-40. However, this ignored Dr. Gershwin's opinion that the vaccine-induced cytokines would *add* to an existing process.

I have devoted considerable time reviewing the expert immunologists' lengthy testimony, multiple reports, and considerable literature in support of their respective positions. Many of Dr. McCusker's arguments concern the normal immune response to vaccines including the amount of cytokines generated, how long they remain, and whether they interact with the brain. It would take additional time to review and form a conclusion as to whether the submitted evidence supports Dr. Gershwin or Dr. McCusker's position on these issues.

There are gaps in the available evidence, such as the cytokine profile in FCD in the human brain prior to the onset of seizures. However, it is most likely impossible to design a study on this subject that would receive ethical approval. Dr. Gershwin therefore drew the reasonable interpretation that once seizure activity begins in FCD, these cytokines at least help to perpetuate a "vicious cycle". Dr. Gershwin also opined that FCD's inherent properties – the seizure activity and the high expression of CCR5 – cause breakdown of the BBB, rendering it more vulnerable to external insults. Dr. Gershwin did not address the degree of cytokines that would be generated in response to the vaccines.

Needless to say, while there may be no pathology studies to examine the passage of cytokines into various areas of the brain such as the cortex, prior to seizures, there is essentially no evidence going either way as to whether the immune response to a peripheral stimulus such as a vaccine causes cytokines to migrate to vulnerable tissue in the brain causing seizures or whether the seizures lead to the upregulation of cytokines in the brain. There is some logic to the proposition that cytokines generated peripherally may be drawn to susceptible tissue in the brain

prior to seizure activity, but the only existing evidence is that cytokines are present afterwards. However, in this case, because of the substantial evidence favoring the causal role of A.A.'s extensive FCD, it is unlikely that the peripherally generated immune response played a significant, if any, role in the generation of her seizures.

And significantly, Dr. Gershwin deferred to the expert neurologists to address whether FCD on its own is sufficient to cause a seizure disorder and what the "natural history" would be absent vaccines. *See* Tr. 163. Thus, even if the vaccine-induced cytokines do cross the BBB and join the existing cytokines in the FCD tissue, they are not likely to be a substantial cause of seizure activity at least as presented in this case, particularly in light of the opinions and the literature about the inherent epileptogenicity of FCD.

K. Evidence of A.A.'s Immune Response

Relevant to *Althen* prong two, Congress has tasked special masters to evaluate the preponderance of evidence available in a particular case, which can include "circumstantial evidence" of the vaccinee's immune response. *Althen*, 418 F.3d at 1280.

Here, Dr. Gershwin opined that A.A.'s December 10, 2012 vaccinations caused an innate immune response including the release of pro-inflammatory cytokines which interacted with the brain, specifically the area of FCD, to cause the clinical manifestation of seizures. Pet. Post-Hearing Brief at 21-22, citing Pet. Exs. 90, 138. 157.

Respondent averred that there was no evidence that this theory applied to A.A.'s case. Resp. Post-Hearing Brief at 26. Specifically, there was no evidence to suggest that in response to the vaccination, A.A. mounted an immune response involving pro-inflammatory cytokines, in either the periphery or in the brain. *Id.* Dr. McCusker noted the absence of symptoms such as inflammation at the site of administration or fever. *See, e.g.*, Resp. Ex. GG at 4.

Dr. Gershwin responded that vaccine-induced cytokines would disproportionately impact FCD, which would represent a more vulnerable target tissue with a lowered seizure threshold. *See* Pet. Ex. 90 at 1-2; Tr. 140; Pet. Ex. 138 at 1-2. Dr. Gershwin opined that even a normal child's immune response to vaccination can include fever. Tr. 140. He opined that the presence of fever is indicative that IL-1 beta is crossing the blood-brain barrier and entering the brain, where it stimulates the hypothalamus to generate fever. *Id.* However, Dr. Gershwin would not require a showing of fever to conclude that peripherally generated cytokines or other immune cells can indeed cross the blood-brain barrier and potentially cause an inflammatory or other autoimmune response in the brain. *Id.* In this case, A.A. did not develop fever, but that is not significant to my analysis.

Petitioners are certainly not required to present circumstantial evidence that A.A. mounted an immune response including the release of pro-inflammatory cytokines. Indeed, such a response would be expected on some level. However, the absence of evidence that A.A. developed a fever or any other signs of an inflammatory response that would be consistent with cytokine activity generated in the periphery) makes it more difficult to demonstrate that her immune response to the vaccinations was associated with the onset of seizure activity. Without

any such specific evidence, little remains but a temporal connection particularly when the preponderant evidence favors FCD as the likely cause.

L. A.A.'s Treaters' Opinions

Also relevant to *Althen* prong two, here, when A.A. was first brought to the emergency room at Beaumont Hospital in December 2012, a registered nurse and an attending physician recorded a temporal association between her four-month vaccines and her first observed seizures. Pet. Ex. 19 at 9, 10. A.A.'s primary care provider also recorded the temporal association. Pet. Ex. 15 at 39. She also recorded that due to *the parents'* concerns, A.A. would be delayed from receiving further vaccines. *Id.* However, the primary care provider recorded: "I don't think this [the onset of seizures] is vaccine related." *Id.*

In March 2013, a geneticist at Beaumont Children's Hospital recorded that "[A.A.]'s seizure disorder is very unlikely to have been caused by vaccination but that it is possible that [A.A.] may (or may not) have had a pre-existing pre-disposition to epilepsy made manifest following vaccination." Pet. Ex. 2 at 49. The geneticist was considering specific gene mutations associated with seizure disorders, including SCN1A. *Id.* In December 2013, a different geneticist at the Cleveland Clinic recorded that the temporal association between the four-month vaccinations and the onset of seizures "raise[d] the concern of a sodium channelopathy", such as those associated with mutations in the SCN1A gene. Pet. Ex. 27 at 9.[89] However, the geneticist recorded that this was not consistent with A.A.'s clinical picture of infantile spasms. *Id.* Subsequent testing ruled out the genetic disorders that these treaters suggested were made "manifest" by the vaccinations. Thus, these records do not support vaccine causation.

Perhaps the most important treating provider is the neurologist Dr. Arndt. In his first evaluation, Dr. Arndt recorded that A.A. received her four-month vaccinations on December 10, 2012, she had "no associated febrile reaction or vaccine encephalopathy (outside of postictal agitation/ lethargy)", and then she had the onset of seizures the next day. Pet. Ex. 19 at 305. Dr. Arndt "suspect[ed] developmental/ structural etiology – likely focal cortical dysplasia (current imaging not definitive)" although a genetic etiology was also possible. *Id*. at 312. These records reflect that Dr. Arndt recognized a potential causal connection between vaccines and encephalopathy, but that A.A.'s clinical picture did not resemble encephalopathy. Rather, Dr. Arndt was looking for other causes for A.A.'s seizures, most likely a structural cause – FCD – which was subsequently confirmed. Thus, A.A.'s treaters did not support that the four-month vaccinations caused or contributed to her seizures.

[89] *See, e.g.*, Resp. Ex. U at 1 (providing that "de novo mutations of the sodium channel gene SCN1A" are highly correlated with Dravet syndrome); Chockalingam et al., *Fever-Induced Life-Threatening Arrhythmias in Children Harboring an SCN5A Mutation*, 127 Pediatrics e239 (2011) [Pet. Ex. 47] (providing that mutations in another gene, SCN5A, can impact sodium channel function and cause "cardiac channelopathies").

M. Timing

Under *Althen* prong three, here, A.A. received the scheduled four-month DTaP, Hep B, IPV, pneumococcal, Hib, and rotavirus vaccines on Monday, December 10, 2012. She had the onset of seizures on either Wednesday, December 12, or Thursday, December 13, 2012, which was within approximately seventy-two (72) hours post-vaccination. On Saturday, December 15, 2012, she had seizure activity which prompted the parents to bring her for medical attention that same day. Pet. Ex. 19 at 9-12.

In support of the temporal relationship, petitioners cited a CDC report published in 1997[90] which stated that "convulsions with or without fever, occurring within 3 days" after DTaP contraindicate further administrations of DTaP. Pet. Post-Hearing Brief at 24, citing Pet. Ex. 113 at 18. Petitioners argued that this CDC report represents "respondent's public health stance," which made respondent's "litigative defense that the risk for seizures is not increased within three days following DTaP vaccination less credible." Pet. Post-Hearing Brief at 25.

Petitioners also cited Dr. Kinsbourne's opinion that the overall risk for seizures is increased within three days following DTaP vaccination. Pet. Ex. 32 at 7; *see also* Pet. Exs. 76, 80. However, Dr. McCusker correctly observed that these articles stated that in some children, the onset of epilepsy may occur following DTaP vaccination, but that by itself does not support vaccine causation or establish an acceptable temporal association. Resp. Ex. GG at 7.

Respondent also argued that in the event that petitioners fail to establish *Althen* prongs one and two – which I have concluded above – it is unnecessary to reach a conclusion as to *Althen* prong three. Resp. Post-Hearing Response at 30-31, citing *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992) (holding that "temporal association is not sufficient… to establish causation in fact"). Although some evidence may suggest that in a more appropriate case, a petitioner may be able to establish an appropriate temporal association between certain vaccination(s) and the onset of seizures in the setting of FCD so as to satisfy *Althen* prong three, in this case, the evidence of extensive known FCD with demonstrated dysmorphic and heterotopic cells makes the temporal relationship appear to be more coincidental than causal. Thus, such a finding would not change the outcome here.

N. Significant Aggravation

Petitioners' briefing addressed only causation-in-fact. However, they preserved the alternative allegation that the vaccines "aggravated" A.A.'s condition. *See* Petition (ECF No. 1) at Preamble. If petitioners had styled their claim following the significant aggravation legal standard, the outcome would be essentially the same. Under *Loving* prongs one through three, I would conclude that petitioners demonstrated that A.A.'s onset of intractable seizures shortly after the vaccinations constituted a "significant aggravation" as defined in the Vaccine Act. *See* However, as stated above, I have concluded that this child's extensive, underlying FCD with

[90] Centers for Disease Control and Prevention, *Pertussis Vaccination: Use of Acellular Pertussis Vaccinations Among Infants and Young Children Recommendations of the Advisory Committee on Immunization Practices (ACIP)*, 46 MMWR 1 (March 28, 1997) [Pet. Ex. 113].

dysmorphic and heterotopic cells was sufficient in and of itself to cause her severe seizure disorder. I would also conclude that petitioners did not establish *Loving* prongs four and five, which correspond to *Althen* prongs one and two, for the reasons set forth above. *See* 42 U.S.C. § 300aa-33(4); *Loving v. Sec'y of Health & Human Servs.*, 86 Fed. Cl. 135, 144 (2009); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (adopting this as the proper legal standard for significant aggravation claims brought under the Vaccine Act). This is the approach that I have followed in prior significant aggravation cases. *See, e.g.*, *Pavan v. Sec'y of Health & Human Servs.*, No. 14-60V, 2020 WL 5351332 (Fed. Cl. Spec. Mstr. July 28, 2020).

IV. Conclusion

From all outward appearances, A.A. was in good health when she received the scheduled four-month vaccines on December 10, 2012, and until she developed the onset of seizures within three days thereafter. A.A.'s family displayed great dedication in seeking treatment and an explanation for her condition. It is understandable that they noted the temporal association with the vaccines. Early in her presentation, A.A.'s treating neurologist Dr. Arndt suspected that she had FCD, which is a malformation of cortical development which arises well before birth, by 22- or 23-weeks' gestation. The initial MRIs utilized less powerful 1.5T scanners and A.A.'s brain was still in the process of myelination. Both factors make it more difficult to visualize the FCD. However, the subsequent medical history, including more powerful MRI scanning when A.A. was older, confirmed Dr. Arndt's early suspicion that A.A. had FCD. The expert opinions and literature submitted in this case demonstrate that FCD is highly correlated with epilepsy without need for a trigger. The specific histopathology and the extent of lesions impacts the severity. Here, as the litigation progressed and indeed well after the entitlement hearing in the case, A.A.'s physicians, the parties, their experts, and I gained additional information about the nature and the extent of A.A.'s FCD. In particular, the second surgery confirmed that A.A. had multiple foci of cortical dysplasia in the right hemisphere. Resection of that tissue has delivered to A.A. seizure freedom and some improvements in cognition. Hopefully A.A.'s condition will remain stable.

I again want to extend my sympathy to the family and say that I appreciate the stress and trauma that they have endured while contending with A.A.'s condition. I extend my best wishes to them. However, for the reasons set forth above, I must conclude that petitioners have not established that A.A.'s vaccines caused or substantially contributed to her seizure disorder. They have not carried their burden of establishing causation in fact and therefore they are not entitled to compensation. Their claim must be and is hereby **DISMISSED.** In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of the Court is directed to enter judgment forthwith.[91]

IT IS SO ORDERED.

s/ Thomas L. Gowen
Thomas L. Gowen
Special Master

[91] Entry of judgment is expedited by each party's filing notice renouncing the right to seek review. Vaccine Rule 11(a).