In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 08-554V
Filed: July 22, 2015
For Publication

RICK LEHNER and SHELLEY LEHNER, as parents and natural guardians, on behalf of their minor daughter, C.L., Petitioners, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Influenza ["Flu"] Vaccination; Autism Spectrum Disorder ["ASD"]; Autoimmune Encephalopathy; Voltage Gated Potassium Channel ["VGKC"] Antibodies; Treating Physicians; Expert Qualifications; Causation; Motion to Exclude Expert as Duplicative.

Sheila A. Bjorklund, Esq., Lommen Abdo Law Firm, Minneapolis, MN, for petitioners.
Traci R. Patton, Esq., U.S. Department of Justice, Washington, DC, for respondent.

DECISION AND RULING[1]

Vowell, Chief Special Master:

On August 1, 2008, Rick and Shelley Lehner ["petitioners"] filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. §300aa-10, *et seq*.[2] [the "Vaccine Act" or "Program"], on behalf of their minor daughter, C.L.

[1] Because this decision contains a reasoned explanation for my action in this case, it will be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, 116 Stat. 2899, 2913 (Dec. 17, 2002). Each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the entire decision will be available to the public.

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

Petitioners initially claimed that thimerosal in C.L.'s childhood vaccines caused their daughter's autism spectrum disorder ["ASD"].[3] Petition, filed Aug. 1, 2008, at 2. In 2011, they amended their claim to allege that their daughter sustained an autoimmune encephalopathy as the result of an influenza vaccine received in November 2005. Petitioners' Amended Petition, filed Feb. 22, 2011, at 3.

In order to prevail under the Program, petitioners must prove either that C.L. sustained a "Table" injury[4] or that a vaccine listed on the Table was the actual cause of an injury (an "off-Table" injury). Because C.L.'s alleged injury is not a Table injury for the influenza vaccine, petitioners must produce preponderant evidence that the influenza vaccine was substantially responsible for C.L.'s injury. After considering the record as a whole,[5] I hold that petitioners have failed to establish their entitlement to compensation.

I. Procedural History.

A. Omnibus Autism Proceeding.

When petitioners filed their original petition, they requested to be included in the Omnibus Autism Proceeding ["OAP"].[6] Petition at 2. The OAP was created to resolve

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[3] "Autism Spectrum Disorder" or "ASD" is an umbrella term for certain developmental disorders, including autism (also referred to as autistic disorder), pervasive developmental disorder-not otherwise specified ["PDD-NOS"], and Asperger's Disorder. *See* R. Luyster, et al., *Language Assessment and Development in Toddlers with Autism Spectrum Disorders*, J. AUTISM DEV. DISORD., 38: 1426-38 (2008), filed as Res. Ex. DD [hereinafter "Luyster, Res. Ex. DD"], at 1426.

[4] A "Table" injury is an injury listed on the Vaccine Injury Table ["Table"], 42 C.F.R. § 100.3 (2011), corresponding to the vaccine received within the time frame specified.

[5] See § 13(a): "Compensation shall be awarded . . . if the special master or court finds on the record as a whole–(A) that the petitioner has demonstrated by a preponderance of the evidence the matters required in the petition by section 300aa-11(c)(1);" see also § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation).

[6] By opting into the OAP, petitioners alleged that:

> [a]s a direct result of one or more vaccinations covered under the National Vaccine Injury Compensation Program, the vaccinee in question has developed a neurodevelopmental disorder, consisting of an Autism Spectrum Disorder ["ASD"] or a similar disorder. This disorder was caused by a measles-mumps-rubella (MMR) vaccination; by the "thimerosal" ingredient in certain Diphtheria-Tetanus-Pertussis (DTP), Diphtheria-Tetanus-acellular Pertussis (DTaP), Hepatitis B, and H[a]emophilus Influenza[e] Type B (HIB) vaccinations; or by some combination of the two.

In re: Claims for Vaccine Injuries Resulting in Autism Spectrum Disorder or a Similar Neurodevelopmental Disorder, Various Petitioners v. Sec'y, HHS, Autism General Order #1, 2002 WL 31696785, at *2 (Fed. Cl. Spec. Mstr. July 3, 2002).

what ultimately totaled about 5,700 petitions alleging that vaccines or the thimerosal preservative contained in some vaccines caused autism spectrum disorders. In an omnibus proceeding, cases presenting similar theories of injury are grouped together in a manner similar to class action litigation. Test cases are selected in which to present the common question of vaccine causation, but unlike class action litigation, the parties, other than those in the test cases themselves, are not bound by the results. Instead, omnibus proceedings develop evidence on the issue of vaccine causation, and that evidence is available to resolve the remaining omnibus cases. In the OAP, the selection of test cases was made by the Petitioners' Steering Committee, a group of lawyers representing OAP petitioners. Three OAP test cases were selected for each of the two theories of vaccine causation advanced by the petitioners' bar. Hearings were conducted in 2007 and 2008 and decisions denying compensation issued in 2009 and 2010.[7] The decisions in the Theory 1 test cases (which advanced the theory that the MMR vaccine, either alone or in concert with thimerosal-containing vaccines, caused autism) were appealed; the decisions in the Theory 2 test cases (which advanced the theory that thimerosal-containing vaccines caused autism) were not appealed.[8]

C.L.'s case was filed after the hearings in the test cases began, but before the decisions were issued. Thus, unlike the early OAP petitioners, petitioners were required to produce medical records in order to position C.L.'s case for resolution after the special masters' decisions were issued in the test cases and appellate review concluded. Petitioners' Exhibits ["Pet. Exs."] 1 through 8 were filed on October 21, 2008.

When the final appellate decision in the OAP test cases was issued in August 2010,[9] the court began the process of notifying petitioners in the approximately 4,800 remaining OAP cases of the results and asking them how they intended to proceed.[10]

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[7] The Theory 1 test cases are *Cedillo v. Sec'y, HHS*, No. 98-916V, 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 89 Fed. Cl. 158 (2009), *aff'd*, 617 F.3d 1328 (Fed. Cir. 2010); *Hazlehurst v. Sec'y, HHS*, No. 03-654V, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 88 Fed. Cl. 473 (2009), *aff'd*, 604 F.3d 1343 (Fed. Cir. 2010); *Snyder v. Sec'y, HHS*, No. 01-162V, 2009 WL 332044 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), *aff'd*, 88 Fed. Cl. 706 (2009). Petitioners in *Snyder* did not appeal the decision of the U.S. Court of Federal Claims. The Theory 2 test cases are *Dwyer v. Sec'y, HHS*, No. 03-1202V, 2010 WL 892250 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); *King v. Sec'y, HHS*, No. 03-584V, 2010 WL 892296 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); *Mead v. Sec'y, HHS*, No. 03-215V, 2010 WL 892248 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). The petitioners in each of the three Theory 2 test cases chose not to appeal.

[8] A more detailed explanation of the creation of the OAP and the effects of opting into it can be found in *Dwyer*, No. 03-1202V, 2010 WL 892250, at *3.

[9] *Cedillo*, 617 F.3d 1328.

[10] The vast majority of these petitioners either voluntarily dismissed their cases or failed to respond, eventually resulting in dismissals for failure to prosecute. Petitioners' case is one of approximately 70 ASD cases currently proceeding to a decision on one of several alternative theories of causation.

B. Procedural History Post-Test Cases.

On February 22, 2011, petitioners asked that their petition be removed from the OAP,[11] and filed an amended petition alleging that the influenza vaccine that C.L. received on November 25, 2005, "substantially contributed to her development of clinically significant levels of VGKC-ABs [voltage-gated potassium channel antibodies[12]], leading to an autoimmune encephalopathy with resultant injury to brain cells and developmental regression." Amended Petition ["Am. Petition"] at 3. The amended petition was accompanied by an expert report from Dr. Richard Frye (Pet. Ex. 10) setting forth this new theory.

Between February 22, 2011, when petitioners filed their amended petition, and October 8, 2013, when I issued the pre-hearing order, petitioners filed both new and updated medical records. During the same time period, the parties filed multiple expert reports, as well as extensive medical literature.

Respondent initially filed an expert report from Dr. Mark Gorman in response to Dr. Frye's report. Respondent's Exhibit ["Res. Ex."] A, filed Apr. 26, 2011. Thereafter, on October 19, 2011, petitioners filed a status report informing the court that Dr. Frye would not be able to testify on petitioners' behalf.[13] On April 2, 2012, after being afforded additional time to locate a new expert, petitioners filed the report of Dr. Yuval Shafrir. Pet. Ex. 11. A supplemental report from Dr. Shafrir was filed on August 15,

[11] The special master initially assigned to this case granted petitioners' motion on February 25, 2011.

[12] Neurons in the central and peripheral nervous systems use proteins to communicate (signal) within and between cells. Voltage-gated potassium channels ["VGKC"] are cell membrane proteins that allow potassium ions to cross the cell membrane, generating electrical signals. The "gates" open and close based on changes in the cell membrane. In the central nervous system, these neuronal voltage-gated potassium channel proteins play an important role in axonal conduction and synaptic transmission. Autoantibodies, which were once thought to be targeted against the VGKC, have been reported to play a role in some types of neurological illnesses in children and adults. R. Dhamija, et al*., Neuronal Voltage-Gated Potassium Channel Complex Autoimmunity in Children,* PEDIATR. NEUROL., 44(4): 275-81 (2011), filed as Pet. Ex. 11c and as Res. Ex. N [hereinafter "Dhamija, Pet. Ex. 11c"]. "Autoantibodies against the voltage-gated potassium channel (VGKC) complex measured by radioimmunoprecipitation have been reported in a broad spectrum of immunotherapy-responsive neurological illnesses in children and adults." R. Patterson, et al., *Clinical relevance of positive voltage-gated potassium channel (VGKC)-complex antibodies: experience from a tertiary referral centre*, J. NEUROL. NEUROSURG. PSYCHIATRY, published online June 11, 2013, filed as Res. Ex. CC [hereinafter "Patterson, Res. Ex. CC"], at 1. Recently, "it has become clear that VGKC antibodies are not directed against the VGKC itself, but against other cell surface antigens that form part of the VGKC complex." *Id.* As one of C.L.'s treating physicians, Dr. Deborah Renaud, explained to C.L.'s family, "[i]t is presumed that the antibodies against the potassium channels caused them to malfunction and, therefore, the electrical current in the neurons which are the electrical cells of the brain [are] impaired." Pet. Ex. 9, p. 7

[13] Doctor Frye's inability to testify in Program cases was due to changed employment. *See* Order, issued Sept. 19, 2011.

2012. Pet. Ex. 16. Petitioners also filed a letter from Angela Vincent, Ph.D., to petitioners' counsel. Pet. Ex. 21.

Following the filing of Dr. Gorman's initial report, respondent filed two supplemental expert reports from Dr. Gorman (Res. Ex. I, filed July 16, 2012; Res. Ex. W, filed Jan. 2, 2013) and two expert reports from Dr. Joseph Dalmau (Res. Ex. J, filed Nov. 14, 2012; Res. Ex. AA, filed Aug. 23, 2013).

Prior to the two-day entitlement hearing on January 27-28, 2014, the parties filed pre-hearing briefs and a joint statement of facts not in dispute. Petitioners also filed a supplemental expert report from Dr. Shafrir (Pet. Ex. 23, filed Dec. 11, 2013), and shortly before the hearing, an affidavit from Mr. Lehner, and photographs and videos of C.L. Petitioners appeared at the hearing via video teleconference. The three expert witnesses appeared in person.

Post-hearing, petitioners filed supplemental medical records as well as additional video and photographs of C.L., pursuant to my order. Petitioners also filed a written motion to exclude Dr. Gorman's testimony, which supplemented and explained the oral motion to exclude that petitioners' counsel made during the hearing. Respondent filed a response to the motion to exclude on April 7, 2014, to which petitioners filed a reply on April 10, 2014.

This case presents diagnostic and causation issues, complicated by a change in the scientific and medical understanding of the role of voltage-gated potassium channel autoantibodies in autoimmune encephalitis that occurred around the time Dr. Frye authored his initial expert report in this case. The issues to be resolved include whether C.L. experienced encephalitis after her influenza vaccination, whether the vaccination played any role in her development of the antibodies found years later, and whether these antibodies played any role in her developmental regression. Ultimately, the issue is whether petitioners have demonstrated by preponderant evidence that the influenza vaccine caused the developmental regression which was diagnosed as an autism symptom by several treating specialists, and which was later characterized as autoimmune encephalitis or autoimmune encephalopathy by Dr. Frye and some of C.L.'s treating physicians.

II. Legal Standards Applying to Off-Table Causation Claims.

When petitioners allege an off-Table injury, eligibility for compensation is established when, by a preponderance of the evidence, petitioners demonstrate that the vaccinee received, in the United States, a vaccine appearing on the Table and sustained an illness, disability, injury, or condition caused by the vaccine or experienced a significant aggravation of a preexisting condition. They must also demonstrate that

the condition has persisted for more than six months.[14] Vaccine Act litigation rarely concerns whether the vaccine appears on the Table, the geographical location of administration, or whether the symptoms have persisted for the requisite time. Rather, in the very small minority of Vaccine Act cases that proceed to a hearing, the most common issue to be resolved by the special master is whether the injury alleged was caused by the vaccine.

To establish legal causation in an off-Table case, Vaccine Act petitioners must establish by preponderant evidence: (1) a reliable medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a proximate temporal relationship between vaccination and injury. *Althen v. Sec'y, HHS*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *see de Bazan v. Sec'y, HHS*, 539 F.3d 1347, 1351-52 (Fed. Cir. 2008); *Caves v. Sec'y, HHS*, 100 Fed. Cl. 119, 132 (2011), *aff'd per curiam*, 463 Fed. Appx. 932 (Fed. Cir. 2012) (specifying that each *Althen* factor must be established by preponderant evidence). The applicable level of proof is the "traditional tort standard of 'preponderant evidence.'" *Moberly v. Sec'y, HHS*, 592 F.3d 1315, 1322 (Fed. Cir. 2010) (citing *de Bazan,* 539 F.3d at 1351; *Pafford v. Sec'y, HHS*, 451 F.3d 1352, 1355 (Fed. Cir. 2006); *Capizzano v. Sec'y, HHS*, 440 F.3d 1317, 1320 (Fed. Cir. 2006); *Althen*, 418 F.3d at 1278). Although special masters are not bound by the formal rules of evidence generally applicable in federal courts, they are required to find evidence reliable before they may consider it. *Knudsen v. Sec'y*, *HHS,* 35 F.3d 543, 548-49 (Fed. Cir. 1994) (Petitioner has the burden to present a reliable and reputable medical theory, which must be "legally probable, not medically or scientifically certain."); *Daubert v. Merrell Dow Pharmaceuticals,* 509 U.S. 579, 590 (1993) (holding that scientific evidence and expert opinions must be reliable to be admissible). The preponderance standard "requires the trier of fact to believe that the existence of a fact is more probable than its nonexistence." *In re Winship*, 397 U.S. 358, 371 (1970) (Harlan, J., concurring) (internal quotation and citation omitted).

Another formulation of the causation requirement in off-Table cases is the "Can it cause?" and "Did it cause?" inquiries used in toxic tort litigation. These queries are also referred to as issues of general and specific causation. Prong 1 of *Althen* has been characterized as an alternative formulation of the "Can it cause?" or general causation query. Prong 2 of *Althen*, the requirement for a logical sequence of cause and effect between the vaccine and the injury, has been characterized as addressing the "Did it cause?" or specific causation query. *See Pafford v. Sec'y, HHS*, No. 01-165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004), *aff'd*, 64 Fed. Cl. 19 (2005), *aff'd*, 451 F.3d 1352 (2006). Prong 3 of *Althen*, the requirement that the injury sustained occur within a medically appropriate interval after vaccination, is subsumed into the

[14] Section 13(a)(1)(A). This section provides that petitioner must demonstrate "by a preponderance of the evidence the matters required in the petition by section 300aa–11(c)(1) . . . ." Section 11(c)(1) contains the factors listed above, along with others not relevant to this case.

other inquiries. Even if a particular vaccine has been causally associated with an injury, petitioner must still establish facts and circumstances that make it more likely than not that this vaccine caused the particular injury. Timing may be one of those circumstances.

Whether a case is analyzed under *Althen* or the "Can it cause?" formulation, petitioners are not required to establish identification and proof of specific biological mechanisms, as "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. Petitioners need not show that the vaccination was the sole cause, or even the predominant cause, of the injury or condition; showing that the vaccination was a "substantial factor"[15] in causing the condition, and was a "but for" cause, are sufficient for recovery. *Shyface v. Sec'y, HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999); *see also Pafford,* 451 F.3d at 1355 (petitioners must establish that a vaccination was a substantial factor and that harm would not have occurred in the absence of vaccination). Petitioners cannot be *required* to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect" (*Capizzano*, 440 F.3d at 1325), but the special master may certainly consider such evidence when filed. *Andreu v. Sec'y, HHS,* 569 F.3d 1367, 1379 (Fed. Cir. 2009) (Special masters may consider medical literature and epidemiological evidence, when it is submitted, in "reaching an informed judgment as to whether a particular vaccine likely caused a particular injury."). Causation is determined on a case by case basis, with "no hard and fast *per se* scientific or medical rules." *Knudsen,* 35 F.3d at 548 (Fed. Cir. 1994). Close calls regarding causation must be resolved in favor of petitioners. *Althen*, 418 F.3d at 1280; *but see Knudsen*, 35 F.3d at 550 (when evidence is in equipoise, the party with the burden of proof fails to meet that burden).

In Vaccine Act cases, special masters are frequently confronted by expert witnesses with diametrically opposing positions on causation. When experts disagree, many factors influence a fact-finder to accept some testimony and reject other contrary testimony. As the Federal Circuit noted, "[a]ssessments as to the reliability of expert testimony often turn on credibility determinations, particularly in cases . . . where there is little supporting evidence for the expert's opinion." *Moberly*, 592 F.3d at 1325-26. Objective factors, including the qualifications, training, and experience of the expert witnesses; the extent to which their proffered opinions are supported by reliable medical research and other testimony; and the factual basis for their opinions are all significant

[15] The Restatement (Third) of Torts has eliminated "substantial factor" in the factual cause analysis. § 26 cmt. j (2010). Because the Federal Circuit has held that the causation analysis in the Restatement (Second) of Torts applies to off-Table Vaccine Act cases (*see Walther v. Sec'y, HHS*, 485 F.3d 1146, 1151 (Fed. Cir. 2007); *Shyface*, 165 F.3d at 1352), this change does not affect the determination of legal cause in Vaccine Act cases: whether the vaccination is a "substantial factor" is still a consideration in determining whether it is the legal cause of an injury.

factors in determining what testimony to credit and what to reject. *Lalonde v. Sec'y, HHS,* 746 F.3d 1334, 1340 (Fed. Cir. 2014) (noting that "as the finder of fact, the special master was responsible for assessing the reliability of [the expert's] testimony by looking for reliable medical or scientific support" (citing *Moberly*, 592 F.3d at 1324-25)).

Congress contemplated that special masters would weigh and evaluate opposing expert opinions in determining whether petitioners have met their burden of proof. Congress clearly specified petitioners' burden of proof in off-Table cases as the preponderance of the evidence standard. It directed special masters to consider the evidence as a whole, but stated that special masters are not bound by any particular piece of evidence contained in the record.[16] In weighing and evaluating expert opinions in Vaccine Act cases, the same factors the Supreme Court has considered important in determining their admissibility provide the weights and counterweights. *See Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 149-50 (1999); *Terran v. Sec'y, HHS*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). As the Supreme Court has noted, a trial court is not required to accept the *ipse dixit* of any expert's medical or scientific opinion because the "court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

Although special masters are not bound by the formal rules of evidence generally applicable in federal courts, the Federal Rules of Evidence and cases interpreting them can guide special masters in their decisions. *Daubert*, which interpreted Rule 702 of the Federal Rules of Evidence, provides a useful framework for evaluating scientific evidence in Program cases. *Terran*, 195 F.3d at 1316 (concluding that it was reasonable for the special master to use *Daubert* to evaluate the reliability of an expert's testimony); *Cedillo v. Sec'y, HHS,* 617 F.3d 1328, 1339 (Fed. Cir. 2010) (noting that special masters are to consider all relevant and reliable evidence filed in a case and may use *Daubert* factors in their evaluation of expert testimony); *Davis v. Sec'y, HHS*, 94 Fed. Cl. 53, 67 (2010) (describing the *Daubert* factors as an "acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted . . . by special masters in vaccine cases"); *see also Snyder*, 88 Fed. Cl. at 718 (quoting *Ryman v. Sec'y, HHS*, 65 Fed. Cl. 35, 40-41 (2005) (special masters perform gatekeeping function when determining "whether a particular petitioner's expert medical testimony supporting biological probability may be admitted or credited or otherwise relied upon" and as a "trier-of-fact [a special master] may properly consider the credibility and applicability of medical theories")). The special master's use of the *Daubert* factors to evaluate the reliability of expert opinions in Vaccine Act cases has been cited with approval by the Federal Circuit more recently in *Andreu,* 569 F.3d at 1379 and *Moberly,*

[16] *See* § 13(a)(1)(A) (preponderance standard); § 13(a)(1) ("Compensation shall be awarded . . . if the special master or court finds on the record as a whole . . . ."); § 13(b)(1) (indicating that the court or special master shall consider the entire record in determining if petitioner is entitled to compensation and special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record).

592 F.3d at 1324. *See also Vaughan v. Sec'y, HHS,* 107 Fed. Cl. 212, 222 (2012) ("The Federal Circuit has repeatedly stated that the Special Master may refer to *Daubert* to assess reliability of expert testimony in vaccine cases."). Special masters decide questions of credibility, plausibility, probability, and reliability, and ultimately determine to which side the balance of the evidence is tipped. *See Pafford*, 451 F.3d at 1359.

Bearing all these legal standards in mind, I now turn to the evidence presented in this case.

III. Medical History.

Most of C.L.'s medical history is not in dispute.[17] Although C.L. experienced a loss of skills at some point between an early intervention evaluation in September 2005 and an evaluation by a neurologist in February 2006, more precise dating is difficult. Given the wide disparity in reports concerning when she began losing skills, it is unlikely that the loss of skills was sudden or abrupt. C.L.'s autism diagnosis is not seriously disputed; she met the diagnostic criteria on two different tests performed by different specialists in the spring and summer of 2006. Petitioners acknowledge the diagnosis, but claim that it is the result of an autoimmune encephalopathy as evidenced by the presence of voltage-gated potassium channel autoantibodies. Whether C.L. showed improvement in behavior and skills as the result of treatment for an autoimmune encephalopathy is a matter upon which the parties disagree. Petitioners contend that any improvement is evidence that the antibodies were responsible (or a marker) for autoimmune encephalitis and thus evidence that she had encephalitis, not autism *per se*. The ultimate basis for their claim for compensation is that the influenza vaccination triggered an autoimmune condition, a claim that respondent vigorously contests.

I set forth most of C.L.'s history prior to the vaccination in a summarized fashion while examining therapy records, contemporaneous medical records, and histories provided to specialists surrounding the regression/loss of skills in more detail. The records pertaining to her diagnosis and treatment for the VGKC antibodies are also set forth at greater length.

A. C.L.'s Early Medical History.

C.L. and her fraternal twin sister were born prematurely in late July 2003. There were initial concerns about C.L.'s oxygen levels after birth and her newborn metabolic screening test results, resulting in a week in a special care nursery on oxygen, tube

[17] The parties identified the following issues as disputed (1) "the extent of C.L.'s pre-existing developmental delay;" (2) "[t]he onset of C.L.'s neurological condition;" and (3) "[t]he cause of C.L.'s neurological condition." Joint Pre-hearing Submission Identifying Issues, filed Jan. 7, 2014, at 1.

feedings, and antibiotics before being discharged to home.[18] C.L. developed on the slower side of normal in her first 14 months of life. Pet. Exs. 7, p. 8; 4, p. 50; 13, p. 2; 3, p. 8; 9, p. 2. She experienced colic, gastroesophageal reflux ["GER"], formula intolerance, and bronchitis in her first three months of life. Pet. Ex. 3, pp. 10-13. However, petitioners testified that there were no concerns regarding C.L.'s development during her first year.[19] Transcript ["Tr."] at 10, 105.

Between October 2003 and October 2004, C.L. was seen for routine illnesses and received the standard childhood vaccinations, including an influenza vaccination in October 2004, without any apparent ill effects. Pet. Ex. 3, p. 2; *see generally* Pet. Ex. 3, pp. 14-31.

B. Concerns about Developmental Delay.

On October 27, 2004, C.L. was seen for her 15 month well child checkup. She was described as a "picky eater" and was still taking formula. Pet. Ex. 3, p. 32. The medical record reflected that problems or concerns about C.L.'s behavior were discussed, specifically noting a "? [question of] mild GM [Gross Motor] delay – just starting to walk beyond a few steps." *Id.* The examining physician noted a "[p]lan" to "watch [C.L.'s] GM closely." *Id.* Mrs. Lehner testified that "there was really no concern" at this time and the physician "just wanted to keep an eye on [C.L.] to make sure she kept progressing in her gross motor skills" and after that C.L. "started walking . . . and there were no issues at all." Tr. at 12. In an August 2008 letter to petitioners, C.L.'s pediatrician, Dr. Judith Snook, noted that C.L. was not using "mama" or "dada" specifically at this checkup. Pet. Ex. 8, p. 1.[20]

Behavior concerns were also raised at C.L.'s 18 month well child checkup on January 27, 2005. Pet. Exs. 3, p. 36; 8, p. 1. This time the pediatrician noted a few specific problems, including difficulty in getting C.L. to go to sleep and that she was a dramatic child prone to temper tantrums. *Id.* However, developmental issues were not specifically identified as a concern. *Id.* Her vocabulary contained at least three words, and the pediatrician and Mrs. Lehner estimated that C.L. had more than 10 words. *Id.* She scribbled and used a spoon. *Id.* Mrs. Lehner testified that C.L. was, and still is, a "very energetic, very strong-willed child" and that "there were no concerns as far as

[18] These facts are derived from histories in C.L.'s treatment records. Neither Mrs. Lehner's labor and delivery records nor C.L.'s medical records from her stay in the Special Care Unit following birth were filed by petitioner. *See* Res. Pre-hearing Br. at 2, n.1.

[19] As C.L.'s primary caretaker, Mrs. Lehner provided testimony that was much more detailed than Mr. Lehner's. Accordingly, as petitioners testified consistently with one another, I have focused on Mrs. Lehner's testimony.

[20] This letter was dated August 4, 2008, three days after the original petition was filed in this case. The first line of the letter indicated that the letter was intended as a summary of how concerns with C.L.'s development became apparent, and was prepared at petitioners' request. Pet. Ex. 8, p. 1.

behavior issues" at C.L.'s 18 month well child checkup. Tr. at 13. She was seen again in February 2005 for an upper respiratory infection ["URI"]. Pet. Ex. 3, p. 37.

C.L. was evaluated again about a month later, this time specifically for "behavioral concerns," including temper tantrums that lasted more than one hour, excessive crying, extreme clinginess, insensitivity "to temperature, sound, touch," and restricted food choices. Pet. Ex. 3, p. 38. She was described as an "emotional child." *Id.* Although she slept "ok" and usually took a one hour nap, she was not well-rested. *Id.* Appropriate responses to these behaviors were discussed, including recommended reading about the "strong willed child." *Id.* This visit is not mentioned in Dr. Snook's August 2008 letter. Pet. Ex. 8, p. 1. Mrs. Lehner testified that the causes of these behavioral concerns were the URIs that C.L. suffered between October 2004 and February 2005.[21] Tr. at 14. However, no illnesses (other than a pustule on C.L.'s heel) were listed as concerns on this visit. Pet. Ex. 3, p. 38. Mrs. Lehner testified to her belief that the physician simply thought C.L. was "a very strong-willed child", and that "there were no concerns about her behavior." Tr. at 14.

At her two year well child checkup on August 9, 2005, C.L. was diagnosed with a mild language delay. Pet. Ex. 3, p. 41. Doctor Snook, the same physician who saw C.L. at her 18 month well child visit and who had evaluated the behavioral concerns in February 2005, again noted behavioral concerns, including occasional temper tantrums. *Id.*; Pet. Ex. 8, p.1. She noted that C.L. had less than 20 words, spoke no sentences, and babble[d]"a lot." *Id.* C.L. could not name pictures. Pet. Ex. 8, p. 1. Doctor Snook also recorded that C.L. had mild constipation and was a picky eater. Pet. Exs. 3, p. 41; 8, p. 1. She referred C.L. for a speech and language evaluation. *Id.*

Mrs. Lehner testified that when C.L. was two years old, she spoke about 20 words, was walking and running, had no eating concerns, and was a very social child who used eye contact, words, and gestures to communicate. Tr. at 15-17. Mrs. Lehner recalled that Dr. Snook had some concerns at this visit because C.L. "was not yet making full sentences" and suggested that she be evaluated through the school system where C.L.'s twin sister was receiving speech and physical therapy.[22] Tr. at 17-18. Mr. Lehner testified that he had no concerns about C.L.'s language development at this time, noting she was clearly "outpacing" her twin sister. Tr. at 107.

[21] C.L.'s pediatric records document three visits during this time period for URI symptoms. Pet. Ex. 3, pp. 31, 33, 37.

[22] Mrs. Lehner reported that C.L.'s twin had developmental delay as well, and received early intervention services due to motor and speech delays. Pet. Ex. 9, p. 233. C.L.'s twin sister had a history of significant delays earlier than C.L. and had features of pervasive developmental disorder ["PDD."]. Pet. Ex. 7, p. 8.

C. Initial Developmental Evaluation.

C.L.'s speech and language evaluation was conducted by the Shakopee Public Schools in September 2005, with a written report issued on October 12, 2005. Pet. Ex. 5, p. 2. During the evaluation, Mrs. Lehner stated that the reason for the referral was concern by C.L.'s pediatrician that she was not putting two words together. *Id*.

C.L. was evaluated using several diagnostic tests, including the Bayley Scales of Infant Development ["BSID"] and three types of language tests. Pet. Ex. 5, pp. 2-4. She was classified as "mildly delayed" in cognitive development (*id.*, p. 2), but was significantly delayed in language *(id.*, p. 4).[23] During the in-home evaluation, C.L. laughed and vocalized, but did not spontaneously use words during play. *Id.*, p. 3. The only recognizable words uttered during the visit were "mommy" and "bye." *Id.* These observations contrasted somewhat with C.L.'s scores on the Preschool Language Scale, which showed her expressive and receptive language to be in the low average range. *Id*. The most concerning language delay was observed in the evaluation of her spontaneous language sample. C.L. made 20 "utterances," only 10 of which were understood as words; the other 10 were scored as babbling. A child of C.L.'s age should have been able to make 50 utterances. The only items C.L. could name during one test were "dog," "boat," "apple," and "eye." The evaluator commented that C.L.'s expressive vocabulary was "significantly delayed." *Id*., p. 4.

Mrs. Lehner's impression of C.L.'s performance during this evaluation was that she was found to be "right on track" in her mental abilities, to have "normal" gross motor skills ("running, jumping, climbing") (something not formally evaluated during this testing), and a "mild language delay." Tr. at 19-20. She testified that at the time of this evaluation, C.L. was "using words constantly," "cleaning up [her] articulation," and pairing words "with eye contact, gesturing, [and] pointing." *Id.* at 20. This testimony contrasts with what Mrs. Lehner reported at the time of the evaluation, which was that C.L. had "about 20 words, and [was] not saying two or more words together in a phrase." Pet. Ex. 5, p. 2. Additionally, on a form completed by Ms. Lehner prior to the evaluation that asked her to list any concerns she had about C.L., Mrs. Lehner wrote that C.L. "tries to communicate but babbles instead of using words." *Id*., p. 9.

C.L. was found eligible for special education services as a child with a language disorder. Pet. Ex. 5, p. 5. She received a weekly home visit and was eligible to attend a weekly toddler group and a parent and child group. *Id*., p. 12. Records of individual

[23] During testimony, Dr. Shafrir asserted that C.L.'s language delay was "mild." Tr. at 143, 145, 208-13. Although C .L. scored in the low average range on the Preschool Language Scale-4 test, she qualified for speech and language services because her expressive vocabulary was 2.6 standard deviations below the norm, and her spontaneous language was 3.0 deviations below the norm. Pet. Ex. 5, p. 5. On the expressive vocabulary test, she scored below the first percentile. *Id*., p. 4. Taken together, the language tests establish that C.L.'s expressive language was significantly delayed.

therapy sessions were not filed, but C.L.'s six-month review by the school district was filed and is discussed in more detail in Part D. 2, below.

D. Allegedly Causal Vaccination and Subsequent Development.

1. Vaccination.

C.L. received an influenza vaccination on November 25, 2005. Pet. Ex. 3, p. 2. Since no office visit notes were prepared for this visit, it is likely that C.L. was not otherwise examined or treated that day. Mrs. Lehner testified that C.L. had an immediate reaction to this vaccination,[24] developing a low grade fever and becoming cranky and irritable. Tr. at 23. Mrs. Lehner indicated that she had been warned that this type of reaction was a normal side effect of vaccination and she treated C.L. with Advil for several days, as instructed at her vaccination appointment. Tr. at 23-24. No subsequent contemporaneous medical record reported any reaction.

2. Post Vaccination Development.

Petitioners claim that C.L. experienced a dramatic developmental regression after her influenza vaccination. Tr. at 24. However, the formal assessments of her development during that period do not reflect a sudden regression, but rather a gradual loss of skills and abilities. Indeed, it was not until February 13-14, 2006, that her parents became concerned enough about the loss of vocabulary and other symptoms to request an urgent neurology consultation. Although it is clear that C.L. experienced a plateau (if not a regression) in her language skills and a significant loss of social and cognitive abilities between September 2005 and December 2006 (*compare* Pet. Ex. 5, pp. 2-5 (initial evaluation) *with* pp. 22-35 (reevaluation)), the contemporaneous medical and therapy records do not show a sudden regression on the heels of—or even within a month of—her influenza vaccination.

Mrs. Lehner testified that over the course of the month following her influenza vaccination, C.L.'s behavior became much worse, she became withdrawn, and she began "the rocking, the humming, . . .finger-flicking . . . she kind of went into her own world." Tr. at 24.

However, on December 19, 2005, during a speech and language pathology evaluation at St. Francis Capable Kids ["St. Francis"], C.L.'s parents recounted that they had become concerned about her speech and language development six months earlier when she was not gaining new words, was unable to combine words, and most of her

[24] In responding to a question from her attorney that contained an incorrect date for this vaccination, Mrs. Lehner implied that the vaccination occurred on November 21, 2005. Tr. at 23. C..L. received her vaccination on November 25, 2005.

sounds came out as "da-da." Pet. Ex. 14, p. 2.[25] At this evaluation, Mrs. Lehner reported that C.L. was currently in good physical health, but "has difficulty with her sleep and has feeding issues." *Id.* The background information reflected that C.L.'s "developmental pattern consists of an overall delay." *Id.* Mrs. Lehner also reported that C.L. communicated largely through gestures and that she and her husband were able to understand her speech only about 10% of the time. *Id.* C.L. was frustrated when she was not understood. *Id.* None of these concerns were noted as sudden or recent.

The evaluation included the Rosetti Infant-Toddler Language Scale, which included an assessment of preverbal and verbal areas of communication and interaction, based on direct observation or elicitation of a behavior or caregiver report. Pet. Ex. 14, p. 3. C.L.'s pragmatic language skills evaluation reflected that she did not vocalize to call others, respond to other children's vocalizations, or attend to her name. *Id*. Overall, C.L. showed mastery of language skills primarily at the level of a six to nine month infant (except for gestures, in which she scored at the 12-15 month level), with scattered skill mastery from the 15-27 month level. *Id.* The evaluator concluded that C.L. had significant delays in expressive and receptive language, and delays in pragmatic and play skills. *Id.* Cognitive development was not evaluated. *Id*., p. 5.

There were no references in the several pages of observations to C.L. rocking, humming, finger-flicking, or being disengaged from others. The evaluation apparently included some assessments of her interaction with other children, but it is unclear whether these were observations by the speech and language pathologist or based on parental report. Pet. Ex. 14, pp. 3-5. The therapist noted that her play was appropriate and that C.L. initiated eye contact. *Id*., p. 6.

C.L. saw Dr. Snook again on December 22, 2005, for concerns about "sleep problems" and "feeding issues," some of the same concerns raised at the St. Francis evaluation three days earlier. Pet. Ex. 3, p. 42. No reactions to or concerns about the influenza vaccination were reported. This pediatric record reflected that C.L. was receiving Pediasure to supplement her diet and that she refused many solids. *Id.* It noted that she put her hands in her mouth "a lot." *Id.* A referral to St. Francis for feeding issues was discussed at this visit. *Id.*; Pet. Ex. 8, p. 2. She slept about 10-11 hours per night but would not nap. *Id.*[26] When placed in her crib to nap, she cried and jumped but refused to sleep. *Id.* In the evening, she would cry for a minute and then fall asleep. *Id.* In her August 2008 letter, Dr. Snook interpreted the next part of the note as stating that C.L. was awakening "3-4 times at night." Pet. Ex. 8, p. 2. She would then cry for 30-90 minutes before returning to sleep. Pet. Ex. 3, p. 42. Neither the

[25] Mrs. Lehner testified that the statement that their concerns arose "six months ago [June 2005]" is inaccurate and that the evaluator must have "rounded up" because the first time she became concerned about C.L.'s speech was at her two year well child check with Dr. Snook in August of 2005. Tr. at 26-27.

[26] In the August 2008 letter, Dr. Snook phrased this as C.L. "stay[ed] in bed for 10 to 11 hours at night, but was not sleeping very well." Pet. Ex. 8, p. 2.

sleep nor the eating issues were precisely new; both had been reported at various times during sick and well child visits. *See, e.g.*, Pet. Ex. 3, pp. 32, 36, 38. However, Dr. Snook thought the sleep problems were a significant departure from C.L.'s previous sleep patterns (Pet. Ex. 8, p. 2), a point echoed by Mrs. Lehner in her testimony. Tr. at 25.

C.L. had her first speech therapy session at St. Francis on January 4, 2006. Pet. Ex. 14, p. 7. She put her fingers in her mouth upon entering the session, a mannerism C.L. reportedly employed when unsure of her environment. *Id.* She warmed to the therapist quickly and imitated the words "up," "baba" for bubbles, and called her mother by name to get her attention. *Id.* Eye contact was sporadic but purposeful. *Id*. No concerns regarding recent regression or loss of words were noted.

At the next therapy session on January 18, C.L. vocalized two syllables for "cracker" and "bubbles" and made eye contact with the therapist about 20% of the time. Pet. Ex. 14, p. 1. She was frequently frustrated, however, with attempts to relate pictures to the actual item. *Id.*

On January 20, 2006, Dr. Snook saw C.L. for a URI and her ongoing feeding problems and referred her to a gastroenterologist. Pet. Exs. 3, p. 43; 8, p. 2. Again, no concerns regarding regression were noted in the record.

On January 24, 2006, C.L. returned to St. Francis for an occupational therapy ("OT") evaluation regarding her feeding issues. Pet. Ex. 14, pp. 9-15. She reportedly responded "fairly well to all activities presented, but . . . did become agitated at times" and kept her blanket close throughout most of the session as a self-soothing mechanism. *Id.*, p. 11. Mrs. Lehner reported that C.L. had a sinus infection and was on antibiotics, but indicated that C.L.'s behavior during the evaluation was typical of what she saw at home. *Id.* Mrs. Lehner shared that she was concerned about the "significant limitations" in what food C.L. was willing to eat and the poor volume of food she consumed. *Id.* The evaluator, occupational therapist Margaret Taylor, found that C.L. displayed "emerging imitation skills, comprehension of simple one-step directions, and positive response to routine." *Id.,* p. 12. However, she also found that C.L. had "substantial delays in sensory processing skills, oral[-]motor strength and coordination and decreased muscle tone," which impacted "her nutritional well-being and overall health." *Id.*

Ms. Taylor concluded that "these delays can, in part, be attributed to [C.L.'s] birth history and her developmental delays following a period of reportedly normal development until 2 years of age." Pet. Ex. 14, p. 12. Doctor Snook's concern about C.L.'s gross motor development at 15 months of age was not mentioned. Mrs. Lehner reported that C.L. "met most of her developmental milestones late" and exhibited "signs of regression in terms of her communication development at the same time she started having feeding difficulties around two years of age." *Id.*, p. 13. Individual feeding

therapy was recommended on a weekly basis, as were changes to home feeding routines. *Id.*, pp. 14-15.

At C.L.'s February 1, 2006 speech session at St. Francis, she did not make eye contact with her mom, but did hand her bubbles upon request. Pet. Ex. 14, p. 16. She used the word "no" twice, but did not say "hi" or "bye," words she had previously used. *Id*. She was still having trouble using the picture exchange system (abbreviated as "PECS" in the therapy records). *Id.*; *see also* Pet. Ex. 4, p. 69 (explaining PECS).

At the February 8, 2006 speech session, Mrs. Lehner reported that C.L. was "doing more lining up of items at home." Pet. Ex. 14, p. 17. C.L. smiled at and made eye contact with the therapist during a game, and used the words "bubble" and "quack." *Id.* During her feeding therapy session, which she tolerated for only about 15 minutes, she made poor eye contact. *Id*., p. 18. Her response to bath time had reportedly improved, but she had decreased tolerance for changes in her routine. *Id*.

Mrs. Lehner's testimony about the period between the Christmas holiday of 2005 and February 2006 was that C.L. became "a completely different child." Tr. at 30. The changes included a loss of previously acquired words, episodes of staring into space, and repetitive behaviors, such as rocking, humming, and finger flicking. Tr. at 30. Mrs. Lehner testified that she was troubled by these changes and contacted Dr. Snook in February 2006 for a consultation. Tr. at 31-32. There is no record reflecting an office visit, but the telephone records for the pediatric practice reflect that Mrs. Lehner communicated with the pediatric practice on February 13 and 14, 2006, to voice concern about C.L.'s "loss of milestones, loss of words." Pet. Ex. 3, p. 109; *see also* Pet. Ex. 8, p. 2 (noting that "therapists had similar concerns" about loss of words, not talking much, waving or pointing). C.L. was referred to a specific neurologist, Dr. Steve Janousek, at petitioners' request for a "sooner appointment." *Id*.; Pet. Ex. 7, p. 2. Apparently, petitioners were already familiar with Dr. Janousek, possibly because C.L.'s twin had seen him. *See* Pet. Ex. 7, p. 2.

C.L. demonstrated the use of two signs in lieu of words at the speech therapy session on February 15, 2006. Pet. Ex. 17, p. 20. She paid attention to the therapist during the feeding session, and imitated gestures. *Id*. She vocalized during feeding, but without any apparent meaning. *Id*. She used "mommy" once. She would not imitate new words. *Id*. She made eye contact during a game, and said "hi" three times. *Id*. The therapist noted that C.L.'s attention was better at this session, but reported that she had staring episodes that were unaffected by calling her name or moving into her space. Pet. Ex. 17, p. 20. The therapy note indicated that C.L. was going to have a neurological checkup, as recommended by her physician. *Id*.

On February 22, 2006, C.L. saw Dr. Janousek for developmental delay and "a new regression of skills." Pet. Ex. 7, pp. 2, 8. Petitioners completed a checklist at the time of the appointment, which included a developmental history. Pet. Ex. 7, pp. 3-6.

They reported that C.L. said her first word with meaning and without prompting between 12-16 months of age, but was still not putting two words together. Pet. Ex. 7, p. 4. She "sometimes" had problems making or maintaining eye contact, difficulty with change or transitions, and "school problems." Pet. Ex. 7, p. 4. Presumably the latter reference was to the speech or occupational therapy C.L. was receiving. They also noted that C.L. had "always" had problems with outbursts in response to frustration and tended to be isolated in play. *Id*. Additionally, they indicated that there had been a worsening of motor or intellectual skill. *Id*.

The chart notes from this visit reflected that C.L." has had a concerning degree of developmental regression." *Id*., p. 8. By history, she had "mild delays" in her development, but otherwise was doing well. *Id*. The primary focus had been on C.L.'s twin sister, who reportedly had significant delays and "some PDD [pervasive developmental disorder] features." *Id*. Doctor Janousek recorded that "[o]ver the last several months, [C.L.] stopped talking," developed poor eye contact, exhibited outbursts, and became more isolated in her play, whereas she was previously reported to be very social." *Id.* No significant decline in motor function was noted. *Id.*

In comparing Dr. Janousek's notes to those of the speech therapist at St. Francis, the reference to C.L. having stopped talking was not completely accurate, as the therapy records did reflect the use of words. The few words recorded in the January-February 2006 therapy sessions did not add up to the 20 words C.L. had (as reported by Mrs. Lehner) during the September 2005 school system evaluation, indicating a possible loss of language. C.L.'s eye contact was diminished as compared to the September evaluation as well. The temper tantrums, reported as "outbursts" in Dr. Janousek's records, were not new; they had been a subject of concern since C.L.'s 15 month checkup. And, C.L.'s parents had reported the day of Dr. Janousek's evaluation that C.L. had "always" engaged in isolated play. The only new symptom reported to Dr. Janousek was the staring spells, and those were first noted by the therapist two days after the requested referral to a neurologist.

On neurological examination, C.L. was described as alert, avoidant of eye contact, exhibiting "significant tactile defensiveness," and nonverbal. Pet. Ex. 7, p. 8. Her motor examination and reflexes were normal and she was not ataxic. *Id.* Doctor Janousek diagnosed regression, and ordered an MRI,[27] EEG,[28] genetic testing, blood tests for lactate, pyruvate, and ammonia, and urine amino and organic acid testing, tests typically performed to assess the possibility of a mitochondrial disorder. *Id*., pp. 9-12. The EEG was performed the same day as the initial visit to Dr. Janousek and,

[27] Magnetic resonance imaging (MRI) is "a method of visualizing soft tissues of the body." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (31st ed. 2007) ["DORLAND'S"] at 928.

[28] An electroencephalogram (EEG) records the electrical activity of brain cells and is typically performed "to identify and evaluate patients with seizures." K. Pagona & T. Pagona, MOSBY'S MANUAL OF DIAGNOSTIC AND LABORATORY TESTS (4th ed. 2009) ["MOSBY'S LABS"] at 573.

although the testing was terminated early, the results were read as normal. *Id*., p. 10. Serum lactate and pyruvate levels were normal and the ammonia level was very slightly below the reference range. *Id*., pp. 13-14. Urine amino acids were assessed as essentially normal, as were the urine organic acids. Genetic testing ruled out Fragile X and Rett syndromes.[29] *Id*., p. 24. The MRI was normal as well. *Id.*, p. 27. Doctor Janousek diagnosed C.L. with "encephalopathy, other." *Id*., p. 23.

According to Mrs. Lehner's testimony, Dr. Janousek "agreed that [C.L.] exhibited autistic features," but he "could not officially diagnose her."[30] Tr. at 33. Mrs. Lehner further testified that Dr. Janousek felt C.L.'s regression was more pronounced than was typical and that she exhibited developmental delay.[31] *Id.*

On April 11, 2006, C.L. was reevaluated by the Shakopee Public Schools to determine her progress in achieving the goals set in October 2005 after the September evaluation. Since C.L. failed to meet any of the goals set to improve her speech and language, these goals were adjusted downward. Pet. Ex. 5, p. 20. In view of her problems with social interaction, goals regarding joint activities were set, to include increasing eye contact, verbalizing and gesturing greetings, and engaging in joint activity with another person for short periods of time. *Id*., p. 18. C.L.'s vocabulary continued to be limited to about 20 words—the same level reflected in the October 2005 report.[32] *Id.*, p. 20.

C.L. was seen by her pediatrician, Dr. Snook, on April 25, 2006, to clear her for anesthesia for the MRI. Doctor Snook noted that C.L. was experiencing a regression of skills to include social skills, language, and eye contact. Pet. Ex. 3, p. 45. She also

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[29] The test interpretation contained a note that reflected an "understanding that this individual has clinical features that are consistent with a diagnosis of Rett syndrome" and that the "negative results neither confirm nor rule out the diagnosis of Rett syndrome." Pet. Ex. 4, p. 15. Rett syndrome is an autism spectrum disorder that has a known genetic cause. *Snyder,* 2009 WL 332044, *31, 36, 48. Symptoms include loss of language and motor skills, as well as some characteristic stereotypic movements (handwringing). *Id.* at *36, 42. Other than the complete or near complete lack of language, C.L. did not present with symptoms indicative of Rett syndrome. Thus, this disclaimer on the laboratory report may have been standard language and not specific to C.L.'s case.

[30] In August 2006, Mrs. Lehner also reported to a developmental pediatrician that Dr. Janousek told her that C.L. exhibited "autistic features." Pet. Ex. 9, p. 232.

[31] Doctor Janousek's records did indicate that C.L.'s regression was more pronounced than would be expected in a typical autism case, but this was at a follow-up visit in May 2006, not at the initial visit. *See* Pet. Ex. 7, p. 29.

[32] The record indicates "October 2006." Clearly this was an error, given that Pet. Ex. 5, p. 2 reflects that the initial evaluation took place in September 2005 and the report was dated in October 2005. Based on the many concerns about loss of language reflected in other reports and the few words reported by C.L.'s teachers at St. Francis and in the school system evaluation, it is unlikely that C.L. still had the 20 word vocabulary reported here.

indicated that C.L. had no intelligible words and repetitively placed her hand in front of her face. *Id.*

Doctor Janousek evaluated C.L. again on May 30, 2006, and noted that despite "[e]xtensive evaluation . . . no definable reason for [C.L.'s] developmental regression" had been found. *Id.*, p. 29. Doctor Janousek described C.L. as having "typical features of autism" but "a more pronounced developmental regression than one would expect, given an autism spectrum diagnosis."[33] *Id.*, p. 29. Doctor Janousek also indicated that C.L. had experienced no further regression in her developmental skills, was alert during her examination, exhibited some tactile defensiveness, and made some eye contact, although no language was heard. *Id.*

3. Formal Autism Diagnosis.

In June of 2006, a psychological evaluation was conducted at Children's Hospitals and Clinics of Minnesota. The evaluation was at the request of Drs. Snook and Janousek "due to concerns regarding the possibility of an autism spectrum disorder." Pet. Ex. 4, p. 50. C.L.'s parents reported that their concerns regarding her language began when she turned two and was not yet putting two words together. *Id.* They reported that C.L. began to lose skills (particularly social skills) at two and one-half years of age (which would have been in late January 2006), and developed feeding problems in January 2006. *Id.* Her social functioning had "greatly decreased" as well. *Id.* She had difficulty getting to sleep and would often scream for over an hour when put to bed. *Id.* Newer symptoms included a loss of interest in others, often seeming to be in her own world, not acknowledging the presence of others, and the emergence of repetitive, self-stimulatory behaviors. Pet. Ex. 4, p. 50. C.L. no longer allowed others to read to her and appeared to resent others imposing themselves on her. *Id.* She was described as seldom happy and typically irritable. She reportedly laughed for no reason. *Id.*

During testing, C.L. wandered around the room, calmed herself by lying on the floor with a blanket over her head, made minimal eye contact, banged toys just to hear a repetitive noise, displayed minimal pointing, and used some single words mixed with

[33] Three articles filed by respondent suggest that C.L.'s "pronounced developmental regression" was not unusual for a child with an autism diagnosis. *See* S. Rogers, *Developmental Regression in Autism Spectrum Disorders*, MENTAL RETARDATION & DEVELOP. DISAB. RESEARCH REV, 10: 139-43 (2004), filed as Res. Ex. S [hereinafter "Rogers, Res. Ex. S"], at 140 (reporting that a clear developmental loss of previously acquired skills is well-documented as one of the patterns of regression in ASD); C. Lord, et al., *Regression and word loss in autistic spectrum disorders,* J. CHILD PSYCH. & PSYCHIAT., 45(5): 936-55 (2004), filed as Res. Ex. R [hereinafter "Lord, Res. Ex. R"], at 946 (reviewing literature on loss of words and noting that almost all children who experienced a loss of words also experienced a loss of social skills); R. Landa, *Diagnosis of autism spectrum disorders in the first 3 years of life*, NATURE CLINICAL PRACTICE NEUROL., 4(3): 138-47 (2008), filed as Res. Ex. EE ["Landa, Res. Ex. EE"], at 141 (observing that retrospective reviews found regression in 10-50% of those with an ASD diagnosis).

gibberish. Pet. Ex. 4, p. 51. She also engaged in visual stimulation by waving her hand in front of her eyes. *Id*. Mrs. Lehner testified that C.L.'s abilities at the time of this testing "were pretty much the same as they were right after she regressed." Tr. at 36. C.L. spoke a few words but most vocalizations were just sounds. *Id*.

Her cognitive skills had improved since the initial administration of the BSID; she was now functioning at the developmental age of 23 months, but the improvement had not kept pace with her age. Pet. Ex. 4, p. 51. Because she was older (35 months of age), her cognitive score dropped from 80 to 52.[34] *Id.* Her score of 41 on the Childhood Autism Rating Scale ["CARS"] fell within the autistic range. *Id.*, p. 52.

After a thorough evaluation,[35] Dr. (Ph.D.) Mary Zielinksi diagnosed C.L. with significantly delayed cognitive skills, scattered skill development, and significantly delayed adaptive skills, particularly in language, social functioning, and interaction. These difficulties resulted in a diagnosis of "pervasive developmental disorder (a.k.a. autism spectrum disorder)." Pet. Ex. 4, pp. 52, 63.

4. Subsequent Evaluations.

Robert Voight, M.D., performed a developmental pediatric assessment of C.L. at the Mayo Clinic on August 10, 2006. Pet. Ex. 9, p. 231. By report, C.L. began waving "bye-bye" at just over one year of age, but then stopped and currently used the gesture only with prompting.[36] *Id*. She began using "mama" and "dada" at 12-18 months of age specifically to refer to her parents and had never lost this skill.[37] *Id*. By two years of age, she used between 20-25 words, but at the time of the assessment, she used only two or three words spontaneously. *Id*. Her pediatrician first became concerned about

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[34] Doctor Shafrir described this decline in the cognitive score on the BSID when compared to C.L.'s score on the first administration of the BSID as a "profound regression" adding that "you can't have a better example of regression." Tr. at 150. Rather than showing a loss of skills—the usual definition of regression in the context of ASD—the test components showed that C.L. had acquired skills as she aged, but not at the rate expected for a typically developing child. Doctor Shafrir did not comment on the third administration of the BSID in which C.L.'s cognitive abilities were scored as 90, within the normal range. Pet. Exs. 9, p. 232; 5, p. 24. In a re-evaluation by Shakopee Public Schools on December 5, 2006, the evaluator commented on these discrepant scores by noting that C.L.'s symptoms could be highly variable. Pet. Ex. 5, p. 24. Doctor Renaud, who first treated C.L. for the VGKC antibodies discovered in 2008 commented that C.L. had good days and bad days as well. Pet. Ex. 9, p. 3.

[35] The evaluation included interviews with petitioners, C.L.'s speech pathologist, the evaluations for speech and occupational therapy performed by St. Francis staff and the school district (all discussed *supra*), and the test results from these evaluations as well as administration of additional tests, including the CARS. Pet. Ex. 4, p. 51.

[36] Mrs. Lehner did not indicate when C.L. lost this skill.

[37] Doctor Snook's letter suggests that C.L. began using these words with specificity between 15-18 months of age. Pet. Ex. 8, p. 1.

her development when she was two years old but not yet combining words. *Id.,* p. 232. C.L. learned to indicate body parts before the age of two and never lost this skill. *Id.*, p. 231. She was able to follow single-step commands without gestures, but had never mastered two-step commands. *Id*. Her language acquisition stopped between the ages of 24 and 30 months of age. Mrs. Lehner indicated that she first became concerned about C.L.'s social and behavioral interactions when C.L. was around the age of two and one-half.[38] *Id*., pp. 231-32. Sometime thereafter, C.L began engaging in stereotypic behavior and repetitive running in circles. *Id*., p. 232.

Prior to Dr. Voigt's assessment, C.L. was tested on August 4, 2006, by a child psychologist at the Mayo Clinic. Pet. Ex. 9, p. 232. One of the tests performed was the BSID, the same test performed by the school system in September 2005, and by Dr. Zielinksi at Children's Hospitals and Clinics of Minnesota in June 2006. C.L.'s cognitive function score on the September 2005 test was 80 (with 100 being average and a standard deviation of 15). *See* Pet. Ex. 5, p. 2. Her score in June 2006 was 52. *See* Pet. Ex. 4, p. 51. In the August testing, her cognitive functioning score had risen to 90, placing her within the average range, but she scored well below the norm in social-emotional and adaptive functioning. Pet. Ex. 9, p. 232. Testing specific for ASD was performed using the Autism Diagnostic Observation Schedule ["ADOS"]. C.L.'s communication score was 5, exceeding the autism cutoff of 4, and her ADOS social interaction score was 14, exceeding the cutoff of 7. *Id.* Her overall score of 19 significantly exceeded the autism cutoff of 12. *Id.*

At this visit, Dr. Voigt diagnosed C.L. with autism. Pet. Ex. 9, pp. 234-36. He noted concerns about regression in speech and language development at two years of age, with "persistent discrepant and disproportionate delays in her speech and language development relative to her nonverbal, visual problem solving and gross motor development over time." *Id.*, p. 234. He also diagnosed her with developmental dysphasia/communication disorder. *Id*., pp. 236-37.

She was seen again at the developmental pediatric clinic at Children's Hospitals and Clinics of Minnesota on August 15, 2006 "to discuss medical and development[al] issues related to autism." Pet. Ex. 4, p. 60. By history, C.L. was colicky and irritable as an infant, in contrast with her twin sister, who was described as "laid back." *Id*. C.L. had early problems with reflux, and was reported to be a "high need" infant who had tantrums with little provocation. *Id*. Mrs. Lehner reported that C.L. walked at 15 months of age, began combining words at two years of age,[39] and had adequate social skills. *Id*. Mrs. Lehner indicated that she and her husband began to be concerned in December (referring to December 2005). *Id.* C.L.'s language was described as "mainly

[38] C.L. would have been two and one-half years old in late December 2005.

[39] Once again, Mrs. Lehner's recall was imprecise, as, at two years of age, C.L. was referred to early intervention services precisely because she was not combining words.

gibberish and squeals." *Id.* She had a couple of words and would say "no." *Id.* She was reported to understand what was said to her. *Id.* Mrs. Lehner also described repetitive behaviors, including running in clockwise circles and putting her hand over her right eye. *Id.* Additionally, C.L. occasionally walked on tiptoes, enjoyed tactile simulation,[40] and had difficulty with sitting and having a book read to her. *Id.*

On examination, C.L.'s height and weight were both reported as greater than the 50th percentile, and she was observed to have coarse facial features and mildly flattened affect. Pet. Ex. 4, p. 61. She did not seek assistance, but engaged in self-directed activities. *Id.* She spun a puzzle, ran back and forth, put her right hand to her face at times, and had some high pitched vocalizations. *Id.* Although she had a stable walk, she could not jump on command or throw or catch a ball. *Id.* She was able to point at pictures in a book and stack six blocks, but could not identify colors or count. *Id.* Mrs. Lehner asked for and received information about supplements and other supports.[41] *Id.; see also id.,* p. 83.

Prior to this appointment, C.L.'s early childhood special education teacher completed a questionnaire about C.L.'s abilities and performance to be used during the August 15 evaluation. Pet. Ex. 4, p. 68. She identified C.L.'s ability to pick up on ideas presented and to follow a schedule as strengths, but found her cognitive, communication, and social skills, along with her sleep and feeding problems, to be areas of concern. *Id*., p. 69. She described C.L. as withdrawing from other children and adults. *Id*., p. 70. Goals for C.L.'s new IEP were to include increasing her communication (through pictures, words, or signs), social interaction, and problem solving (cognitive) skills, as well as working on sensory integration. *Id.* In response to a question about progress, she noted that C.L. had begun using PECS. *Id*. Also, C.L. was sharing eye contact and laughter when she enjoyed an activity. *Id*. The teacher wrote that beginning in April, she had begun thinking that C.L. needed much more time in therapy as well as more peer involvement time. *Id*. She noted that she had suspected for some time that C.L. might have ASD, as C.L. exhibited many ASD characteristics. *Id*., p. 71.

The parent questionnaire completed for this evaluation reflected that C.L.'s parents first became concerned about her lack of verbal and social skills, lack of eye contact, and poor eating and sleeping when C.L. was about 27 months of age. Pet. Ex. 4, p. 72. C.L. was 27 months of age in October 2006, around the same time the school system completed C.L.'s initial evaluation. On the form, C.L.'s parents noted a loss of

[40] Based on reports of tactile defensiveness, this likely referred to C.L.'s desire to touch different textured items, such as books with a tactile focus, rather than a desire to be touched, tickled, or otherwise stimulated by the touch of others. Pet. Ex. 5, p 26 (Shakopee Public Schools' Evaluation of December 5, 2006, showed C.L. to be seeking books with tactile themes).

[41] Doctor Voigt had cautioned against the use of alternative treatments for autism, including dietary supplements. *See* Pet. Ex. 9, p. 236.

verbal and social skills, and described her as withdrawn, easily frustrated, and prone to temper tantrums. *Id*., pp. 76-77. They reported that the regression had occurred about six to seven months prior to this visit. *Id*., p. 77. This would place the onset of regression in the January-February 2006 time frame (assuming the form, which is undated, was completed in late July or early August in preparation for the August 15 appointment).

Doctor Snook saw C.L. for her three year well child visit on August 18, 2006, and reported that she had been diagnosed with autism, but was "sleeping better, [had] fewer tantrums, [and] less extreme behavior." Pet. Ex. 3, p. 47.

C.L.'s occupational therapist at St. Francis reported on October 18, 2006, that C.L. demonstrated "increased participation, cooperati[on], tolerance, and independence with activities," as well as "increased eye contact." Pet. Ex. 14, p. 115.

A reevaluation of C.L. by the Shakopee school system took place on December 5, 2006. Her special education teacher reported that she had limited vocabulary, with three words used spontaneously, but not consistently or frequently. Pet. Ex. 5, p. 22. She was beginning to use the picture exchange system, but was not imitating words. *Id*. Any eye contact was fleeting. *Id*., p. 23. She played by herself in the classroom and did not show any awareness of her twin sister there. *Id*. She did not use toys functionally and did not demonstrate any pretend play. *Id*. Mrs. Lehner shared that C.L. "appeared to regress in her skills approximately around December of 2005." *Id*., p. 23. She and Mr. Lehner noted the loss of social and verbal skills. *Id*.

Prior to this evaluation, C.L. was retested with many of the same testing instruments used in September 2005. Although the school system did not re-administer the BSID, the evaluators compared C.L.'s initial September 2005 score with the June 2006 test performed by Minneapolis Children's Hospital (scored as 52) and the August 2006 test performed at the Mayo Clinic (scored as 90). Pet. Ex. 5, p. 24. The evaluation team noted the "great variability or inconsistency" in these test scores. *Id*. Her teacher commented that it was difficult to assess C.L.'s cognitive skills because of her communication delays. *Id*. She was unable to perform most tasks on the Hawaii Early Learning Profile at the 36 month level. *Id*. Her receptive vocabulary was scored at 80, with 100 being the mean score and a standard deviation of 15, placing her in the 9th percentile. *Id*., p. 25. Her expressive vocabulary was not scored, as she did not identify any pictures. *Id*. In summarizing C.L.'s speech and language, the evaluators noted that she had decreased eye contact, no verbal communication in the classroom setting, was avoidant of physical proximity to other children and adults, and had difficulty initiating or responding to joint attention and reciprocal social communication. *Id*., p. 26.

C.L. was observed by an ASD consultant for the school district as part of the evaluation. Pet. Ex. 5, pp. 31-33. The observations were scored against a school

system checklist for ASD eligibility, and C.L. was found eligible for special education services as a student with ASD and also required occupational and speech therapy. *Id*., p. 33.

Doctor Janousek evaluated C.L. again on January 23, 2007 and found that she had "made slow gains in development" since her last appointment in May 2006, including "some gains in eye contact and language development." Pet. Ex. 7, p. 36. Mrs. Lehner testified that C.L. began to receive ABA therapy in January 2007, after an extended time on the Minnesota Autism Center's waiting list. Tr. at 37-38. The therapy was recommended by Dr. Janousek. Tr. at 35.

C.L. continued to be seen by Metropolitan Pediatric Specialists throughout 2007 and 2008 for various routine illnesses, including URIs, chronic cough, rhinitis, constipation, and thrush. *See generally* Pet. Ex. 3, pp. 53-70. She was also seen at the University of Minnesota Children's Hospital-Fairview in 2007-08 for a variety of testing and treatment, mostly related to potential allergies. *See generally*, Pet. Ex. 6, pp. 1-87.

Doctor Janousek examined C.L. on September 26, 2008 and found that, while she "has received ABA therapy and is making some progress, . . . she continues to have profound neurodevelopmental deficiency." Pet. Ex. 7, p 51. Doctor Janousek found that C.L. "continued to exhibit autistic features," had experienced a "pronounced neurodevelopmental regression at one point," and "has a twin who also has autistic features, but is higher functioning." *Id.* He referred C.L. for an evaluation with Dr. Renaud at the Mayo Clinic, as Mrs. Lehner sought further evaluation into the cause of C.L.'s developmental regression. *Id.* Precisely why he selected Dr. Renaud was not clearly stated in the record of his referral but, as discussed below in Part E, Dr. Renaud was engaged in research into voltage-gated potassium channels and autoimmune encephalopathy, and Dr. Janousek may have been aware of this research.

E. Voltage-Gated Potassium Channel Antibodies: Testing and Treatment.

1. Background Information.

According to respondent's expert, Dr. Dalmau, autoimmune encephalitis—C.L.'s appropriate diagnosis, according to petitioners—was discovered in 2005-07. Tr. at 297; *see also* J. Dalmau, et al., *Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis*, LANCET NEUROL. 10: 63-74 (2011), filed as Pet. Ex. 16b [hereinafter "Dalmau, Pet. Ex. 16b"] (explaining how various forms of autoimmune encephalitis came to be recognized as diagnostic entities); M. Gable, et al., *The Frequency of Autoimmune* N-*Methyl-D-Aspartate Receptor Encephalitis Surpasses That of Individual Viral Etiologies in Young Individuals Enrolled in the California Encephalitis Project*, CLINICAL INFECTIOUS DISEASES, 54(7): 899-904 (2012), filed as Pet. Ex. 16a [hereinafter "Gable, Pet. Ex. 16a"], at 899 (discussing a novel form of autoimmune

encephalitis first reported in 2007 (anti-NDMAR encephalitis)).[42] In another article, Dr. Dalmau was credited with being the first to describe limbic encephalitis associated with anti-NMDAR antibodies. *See* T. Hung, et al., *Anti*-N-*Methyl-D-Aspartate Receptor Encephalitis*, PEDIATR. AND NEONATOL., 52: 361-64 (2011), filed as Pet. Ex. 16c [hereinafter "Hung, Pet. Ex. 16c"], at 361.

The discovery that some previously idiopathic forms of encephalitis were attributable to autoantibodies produced as the result of tumors (paraneoplastic syndromes) or from unknown causes generated considerable research.[43] Doctor Angela Vincent's laboratory in England, the Mayo Clinic in Minnesota, and Dr. Dalmau were major contributors to the growing body of information filed as exhibits in this case.[44] The idea that autoantibodies could be responsible for otherwise idiopathic forms of encephalitis began to encompass other newly identified antibodies in the absence of tumors. According to Dr. Dalmau, voltage-gated potassium channel antibodies were so named in a study performed about 16 years prior to the hearing. Tr. at 301. They eventually became suspects as causal of some forms of encephalitis, based in part on work done at the Mayo Clinic.[45]

In 2001-07, the Mayo Clinic's Neuroimmunology Laboratory began widespread autoantibody screening of patients suspected of having an autoimmune neurological disorder, as a part of a prospective clinical study. *See* Tan, et al., *Clinical spectrum of voltage-gated potassium channel autoimmunity*, NEUROL., 70(20): 1883-90 (2008), filed as Pet. Ex. 10i [hereinafter "Tan, Pet. Ex. 10i], at 2.[46] Out of more than 130,000 serum

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[42] Doctor Dalmau was a co-author of this study, which reported findings of the California Encephalitis Project, an entity established to study encephalitis and its causes. Anti-NDMAR encephalitis was first reported in 2007 and later discovered to be "a significant cause of encephalitis in certain age groups." Gable, Pet. Ex. 16a at 899-900.

[43] Doctor Gorman's testimony reflected that body of research has continued to grow. He testified that since July 16, 2012, around the time he authored his second report in this case, about 50 new journal articles on voltage-gated potassium channel antibody encephalitis had been published. Tr. at 469.

[44] Of the medical journal articles filed as exhibits, Dr. Vincent was a contributor or senior researcher on at least nine articles; Drs. Renaud and McKeon (both of whom treated C.L.) on at least three articles, and Dr. Dalmau a contributor to or senior researcher on at least eight articles. Doctor Vincent is not a practicing physician. However, she is a well-known researcher in the field of autoimmune neuroimmunology who has published with Dr. Dalmau. Tr. at 382, 448.

[45] As discussed in more detail later in this decision, Dr. Dalmau testified at some length that only certain subtypes of the so-called VGKC antibodies, with antibodies against specific proteins, are pathogenic or disease-causing, and that limbic encephalitis, which had been attributed to VGKC antibodies was actually caused by other autoantigens. *See generally*, Tr. 300-20; Pet. Ex. J at 7-9 (Dr. Dalmau's expert report); Dalmau, Pet. Ex. 16b, at 63 (noting that leucine-rich, glioma-inactivated 1 (LGI1) is a synaptic antibody "which is the main autoantigen of limbic encephalitis previously attributed to voltage-gated potassium channels").

[46] Ordinarily, I cite to the page numbers of the article itself, rather than the page numbers assigned by the party filing the medical journal article, in order to allow those reading the decision who do not have access

samples, 80 patients (with a median age of 65) were found to have VGKC autoantibodies. Additional information for 72 of the 80 patients was obtained. Sixty of the patients had diagnoses which included inflammatory or neurodegenerative disorders, Creutzfeldt-Jakob disease ["CJD"],[47] recurrent transient amnesia, and several other psychiatric disorders. *Id*., p. 5. Cognitive impairment was the most common neurological complaint. *Id*., p. 6.

Doctors Renaud and McKeon, two of C.L.'s treaters, were co-authors of an article discussing documentation of VGKC antibodies in children. C.L. was one of the 12 children discussed in the article as positive for the VGKC antibodies. C.L. was Patient No. 11 in the report. Tr. at 398-99; Dhamija, Pet. Ex. 11c. This article is discussed in more detail in Section V.B.1.b.(2)(b), below.

2. Referral to Mayo Clinic Child and Adolescent Neurology.

Mrs. Lehner testified that Dr. Janousek referred C.L. to Dr. Renaud at the Mayo Clinic because her regression was "more pronounced than a typical autistic regression." Tr. at 40. Doctor Renaud, a pediatric neurologist, examined C.L. on October 20, 2008. She found C.L. to be "a 5-year-old girl with a history of normal early development and subsequent regression with a diagnosis of autism." Pet. Ex. 9, p. 4. Doctor Renaud noted that Mrs. Lehner "feels that the regression followed an influenza vaccine." *Id.* Doctor Renaud ordered a number of laboratory tests as part of her evaluation. *Id.*, pp. 4-5. She diagnosed C.L. with "[d]evelopmental regression with autistic features" and "[p]ossible coarsening of the features, rule out storage disorder." *Id*., p. 1.

The history of onset of C.L.'s regression reported at this visit was somewhat different from the histories appearing in more contemporaneous records and histories provided by Mrs. Lehner at around the time of the autism diagnosis. Mrs. Lehner reported that after the influenza vaccination in November 2005, C.L. developed self-stimulatory behaviors in December, including rocking her body and humming—reported behaviors that do not appear in any of the therapy or medical records from December 2005 or January 2006. Pet. Ex. 9, p. 2. Decreased eye contact and flicking her fingers in front of her eyes were also reported as occurring prior to the loss of words. *Id.* At the December 2005 St. Francis evaluation, the therapist noted that C.L. initiated eye contact, but one can infer some loss of eye contact from contemporaneous therapy records from January and February 2006. Pet. Ex. 14, pp. 1, 6-7, 16. The finger flicking was not reported during this time. Some stereotypic behaviors were reported, including placing her hand in front of her face (April 2006) (Pet. Ex. 3, p. 45) and putting

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to the exhibits to follow the citations. The copy of the article filed does not contain page numbers integral to the article. Therefore, for this exhibit, citations are made to the exhibit page numbers assigned by petitioners, which are found at the bottom of each page.

[47] A variant of CJD is caused by the same agent that causes bovine spongiform encephalopathy or "mad cow disease." DORLAND'S at 538, 622.

her hands in her mouth (December 2005) (Pet. Ex. 3, p. 42). Mrs. Lehner indicated at the St. Francis evaluation that C.L. put her hands in her mouth when she was unsure of her environment, suggesting that this mannerism was not of recent origin. Pet. Ex. 14, p. 7. Waving her hand or fingers in front of her eyes was not reported until June 2006. Pet. Ex. 4, p. 51. Although Mrs. Lehner did not provide Dr. Renaud a specific time period for when the loss of social skills and affectionate behavior were first observed, the contemporaneous records indicate that a regression of C.L.'s social skills was first reported in February 2006. Pet. Ex. 7, p. 8.

Mrs. Lehner also reported at Dr. Renaud's evaluation that C.L. then had approximately 50 words or approximations of words, but rarely combined two words. Pet. Ex. 9, p. 3. She could follow simple one-step commands. *Id.* C.L. had bad and good days, but had no new regressions. *Id.* She learned slowly and made gains, but the gap between C.L. and her peers was widening. *Id.* Intelligence testing in January 2008 had placed her IQ at 70. Pet. Ex. 9, p. 3.

Other reported symptoms included flicking her hands,[48] humming, galloping, and teeth grinding. Pet. Ex. 9, p. 3. She reportedly had "hypotonia since the regression," fell asleep well, was rested in the morning, and did not nap. *Id.* The number of nighttime awakenings had improved in the past six months. *Id.*

On examination, C.L. was noted to be "mildly coarse-appearing," with acne, bilateral ear pits, slightly coarse facial features, bushy eyebrows, coarse thin hair, mild hypotonia with good strength and symmetric deep tendon reflexes. Pet. Ex. 9, p. 4. Doctor Renaud noted that Mrs. Lehner "felt that the regression occurred following a flu vaccination" and had brought with her to the appointment "a number of items from the internet" regarding autism and developmental regression, which Dr. Renaud reviewed with the family. *Id.*

Doctor Renaud proposed a battery of tests. Because C.L.'s regression was described as "sudden," a "paraneoplastic antibody panel" was ordered "to ensure that there are no antibodies against the brain which could represent a treatable autoimmune disorder." Pet. Ex. 9, p. 5. This panel encompassed the testing for VGKC antibodies to determine if C.L. had experienced autoimmune encephalitis.[49]

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[48] This appears to be the first report of C.L. "flicking" her hands, but this does not seem to be materially different from the "finger flicking" previously reported. Such stereotypic mannerisms are common in children diagnosed with ASD. *See* Landa, Res. Ex. EE at 138, 141 (discussing stereotypical behavior in ASD).

[49] The test results appear at Pet. Ex. 9, pp. 9-16. As Dr. Renaud did not comment on any of the results other than the VGKC antibodies, presumably none of the testing raised any diagnostic concerns.

3. Diagnosis of VGKC Antibodies and Possible Autoimmune Encephalitis.

On November 17, 2008, Dr. Renaud saw C.L. for a follow-up visit after C.L.'s laboratory tests indicated in October 2008 that C.L. had an abnormal level of "antibodies to neuronal voltage-gaited potassium channels." Pet. Ex. 9, p. 7. Prior to this visit, C.L. had been placed on prednisolone to suppress any ongoing immune response. Pet. Ex. 9, p. 7. Increased appetite and thirst along with flushed cheeks were reported. *Id.* There had been no dramatic changes in C.L.'s behavior while on this steroid, but C.L. may have had an increase in eye contact, both as reported by C.L.'s parents and as observed by Dr. Renaud. *Id.*

During the visit, Dr. Renaud "discussed the function of potassium channels" in detail with petitioners. Pet. Ex. 9, p 7. She noted that "it is unclear at this time whether this is the cause of her developmental regression and autism," but as the antibodies are "a potentially treatable cause of deterioration, we will treat this as an autoimmune disorder." *Id.* Although no significant change in C.L. was seen with the 18 days of prednisolone treatment, Dr. Renaud indicated that, in view of the three years since C.L.'s deterioration, a response to treatment might not be seen for "several months." *Id*. Her plan was to continue with prednisolone[50] to suppress "the ongoing immune response" and intravenous immunoglobulin ["IVIG"] to "hopefully remove the antibodies." *Id.*, pp. 7-8. She revised her diagnosis of C.L. to include neuronal voltage-gated potassium channel antibodies with possible autoimmune encephalopathy, in addition to the global developmental delay and autistic features in her earlier diagnosis.[51] *Id*., p. 8

4. Treatment for VGKC Antibodies and Response.

a. Petitioners' Assertions.

From October 2008 through the time of the hearing, C.L. was treated, more or less continuously, for presumed autoimmune encephalopathy or encephalitis, based on the presence of high levels of VGKC antibodies.[52] Mrs. Lehner testified that C.L.

[50] The text of Dr. Renaud's notes in the Impression/Report/Plan section indicated in one sentence that C.L. was taking prednisolone, and in a later sentence that she was taking prednisone. The "Current Medications" section indicated that she was taking prednisolone. Pet. Ex. 9, p.7. A telephone message from Mrs. Lehner to Dr. Renaud on November 25, 2008, reflected that C.L. had been on prednisone for a month or so, and was reporting side effects. However, her medication listing referred to prednisolone.

[51] In February 2009, Dr. Renaud changed C.L.'s diagnosis from possible to probable autoimmune encephalopathy, with the global developmental delay and "autistic features" diagnoses unchanged. Pet. Ex. 9, p. 26

[52] It does not appear that C.L. received any treatment for her VGKC antibodies between April 2010 and November 2011. Pet. Exs. 6, p.128 (noting last rituximab treatment in April 2010); 9, pp. 118-19 (resuming treatment in late November 2011).

exhibited "gains" while on treatment, but suffered some side effects. Tr. at 43-44. By 2010, C.L. was making "slow and steady gains," but was still globally developmentally delayed. Tr. at 46. Mrs. Lehner testified that in the fall of 2011 she began to see improvement in C.L.'s "attending" (i.e., ability to pay attention and observe her environment and imitate others) after C.L. resumed treatment with Dr. Renaud (which occurred in September 2011, Pet. Ex. 9, p. 81) and started a higher dose of the steroid prednisolone. Tr. at 48. C.L. made further improvements in her behavior after the dosage was increased in March 2012. Tr. at 48-49. Mrs. Lehner testified that at the time of the hearing [January 28, 2014], C.L. was able to make requests with eye contact, label things, seek out affection without prompting, read words, write letters, and respond to two step commands. Tr. at 53-55. She conceded that C.L. was still not able to read sentences and that her articulation needed to be "clean[ed] up." Tr. at 54. Mrs. Lehner testified that C.L. received special services in an autism classroom and ABA therapy at home on a part-time basis during the school year and full-time during the summer. Tr. at 54-56. A more objective assessment of C.L.'s level of performance is found in C.L.'s school records during 2009-11 and December 2012-March 2013, *see generally* Pet. Ex. 5, pp. 45-266, portions of which are discussed in subsections b and f, below.

b. Initial Treatment at Mayo Clinic and Response.

C.L.'s initial treatment, from October 2008 through June 2009, was provided by Dr. Renaud. C.L. was treated with a steroid (prednisolone) and an immune suppressant drug (CellCept)[53] to suppress production of the VGKC antibodies, and with intravenous immunoglobulin ["IVIG"] therapy to remove the antibodies from her system. Steroid therapy began in late October 2008, but due to side effects reported by her parents,[54] she was weaned off prednisolone beginning in January 2009. *See* Pet. Ex. 9, pp. 7 (beginning treatment), 22 (discussion about discontinuation of prednisolone due to side effects and lack of any significant improvement). In February 2009, CellCept was substituted, initially at a low dose (*id.*, p. 26), but when the dose was substantially increased in April 2009 (*id.*, p. 36), severe side effects ensued[55] and she was abruptly

[53] "Mycophenolate (CellCept) is used with other medications to help prevent transplant organ rejection (attack of the transplanted organ by the immune system of the person receiving the organ) in people who have received kidney, heart, and liver transplants. . . . It works by weakening the body's immune system so it will not attack and reject the transplanted organ." U.S. National Library of Medicine, MedlinePlus, http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601081.html (last visited July 9, 2015).

[54] Mrs. Lehner reported that C.L. experienced sleep disturbances, became very clingy, and made a new noise when crying or shouting. Pet. Ex. 9, p. 19. She was advised that prednisolone is known to often cause behavioral disturbances and restless sleep, but IVIG was unlikely to cause such side effects. A reduction in the dose of prednisolone was suggested. *Id.* The family temporarily reduced the dose, but observed no changes in her behaviors. *Id.*, p. 20.

[55] *See* Pet. Ex. 9, pp. 39, 41-43 (telephone calls and office visits reporting significant side effects, including incontinence and a facial rash from CellCept). Doctor Renaud consulted a rheumatologist who recommended stopping the treatment, as incontinence was a recognized side effect of CellCept. *Id.*, p.

taken off the drug (*id*., pp. 39, 41-43). IVIG therapy began in November 2009, initially on a monthly basis, but when therapy with CellCept ended, the IVIG schedule was increased to every two weeks beginning in April 2009. *Id*., pp. 35-36.

In mid-April 2009, C.L.'s parents indicated that they were not sure if they wanted to continue with the treatment for the VGKC antibodies, including IVIG and medications. Pet. Ex. 9, p. 42. However, at a visit near the end of April 2009, they agreed to try three more IVIG infusions at two week intervals. *Id*., p. 46. On July 2, 2009, C.L.'s parents notified Dr. Renaud that they were stopping IVIG therapy. *Id*., p. 61.[56]

During her treatment, C.L.'s blood was drawn regularly to measure the levels of VGKC antibodies in her system. Antibody levels fluctuated over the course of treatment, but remained persistently abnormal. Pet. Ex. 9, p. 106.

Doctor Renaud's treatment records, including parental reports and her own observations, reflect overall improvement in C.L.'s behavior and symptoms; however, the improvements did not appear to correspond to the varying antibody levels measured throughout her treatment.[57] Although parental reports at most of the appointments

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42. The incontinence improved when CellCept was stopped, but some problems persisted as of April 29, 2009. *Id*., p. 45.

[56] C.L.'s parents thought the IVIG treatment might be causing some side effects as well. In February 2009, Mrs. Lehner called Dr. Renaud's office to report that C.L. was being very clingy and more irritable. Pet. Ex. 9, p. 27. This behavior persisted through March 5, 2009. *Id*., pp. 29, 32 (telephone calls concerning behaviors they thought might be related to IVIG treatment). However, it appears that the lack of any real improvement may have contributed to this decision. *See id*., pp. 58-59 (Mr. Lehner's assessment of C.L.'s progress after being out of the country for a period of time).

[57] A normal potassium channel antibody level is less than 0.02 according to the Mayo Clinic's laboratory reports. *See*, *e.g.*, Pet. Ex. 9, p. 106. C.L.'s antibody levels fluctuated over time, as did her behavior and skills; however, there was no consistent correlation between low antibody levels and improved behavior or, conversely, between high antibody levels and poor behavior or loss of skills. On January 8, 2009 C.L.'s antibodies had dropped to 0.78 (down from 1.69 on November 18, 2008), but there was no significant change in her behavior reported at her January 7, 2009 doctor visit. Pet. Ex. 9, pp. 22-23,106. Improvement was reported at the February 18 visit, although C.L.'s antibodies had risen to 0.94 as measured on February 19, 2009. Pet. Ex. 9, pp. 26, 106. On April 15, 2009, C.L.'s antibodies were 1.74 and Mrs. Lehner reported that she thought C.L. was regressing (although this regression was attributed to C.L.'s use of CellCept). Pet. Ex. 9, pp. 39-42, 106. On May 14, 2009, C.L.'s antibodies measured 1.18 and she was reported to be doing well and talking more. Pet. Ex. 9, pp. 50, 106. On August 26, 2009, C.L.'s VGKC antibody level was up to 1.82 after not having IVIG for two months and she was reported to have greater understanding and to be more focused. Pet. Ex. 9, pp. 63,106. On February 18, 2012, C.L.'s VGKC antibodies measured 0.92, up from 0.31 on January 21, 2012, and C.L. was reported to have experienced some gains at her March 7, 2012 doctor's visit. Pet. Ex. 9, pp. 127-28. On July 26, 2012, C.L.'s antibodies were measured at 0.56, slightly up from 0.44 on May 17, 2012, and she was reported to be "having some tantrums and aggressive behavior" although her "skills, language, and cognitive abilities" remained stable. Pet. Ex. 9, pp. 183, 141.

included some area in which C.L. had improved,[58] other evidence suggests that the improvements may not have been as substantial as reported. At the end of June 2009, just prior to the July 2, 2009 decision to stop IVIG treatment, Mr. Lehner was out of the country for a period of time, which was variously reported as three weeks and three months. Upon his return, he commented that he thought C.L. was vocalizing more, but had not noticed any other specific changes. Pet. Ex. 9, p. 58. Her eye contact with family members was described as "reasonable." *Id.*

In March 2009, C.L. received an assessment of her progress by a psychologist. *See* Pet. Ex. 5, p. 78. Her scores on the Vineland Adaptive Behavior Scale were largely in the 1st percentile or below, and her score on the ADOS was again in the autistic range. *Id*.

Additionally, C.L.'s school records from the period of March through November 2009 (including a classroom observation and two IEP reviews) do not reflect the increased vocabulary and significantly improved eye contact reported at the monthly visits to Dr. Renaud. *See* Pet. Ex. 5, pp. 45-49 (classroom observations in March 2009 noting C.L.'s use of two-word phrases only when motivated and prompted; C.L.'s need for prompting to produce 20 different two-word requests within three hours; her making eye contact only with a familiar person; her non-responsiveness to questions; and her need for an assistive device to make "I want" requests); pp. 55, 57 (observations on her April 2009 IEP which noted that she was not spontaneously putting words together in a sentence); pp. 57-59 (observations for IEP progress in June and November 2009); p. 61 (noting at April 2009 meeting to develop IEP for the following school year that C.L.'s

[58] C.L. was reported in February 2009 as improving in vocabulary, using two-word phrases, and having slightly improved eye contact; however, when frustrated she ground her teeth, gagged herself, and banged her head. Pet. Ex. 9, p. 25. Shortly after the February IVIG treatment, Mrs. Lehner reported her as very clingy and more irritable. *Id*., p. 27. In March 2009, she was reported as acquiring a few new words and having reasonable eye contact, but continued to have behavioral problems. *Id*., pp. 30-31. In early April 2009, Mrs. Lehner reported that C.L. was combining words, making requests, and interacting more, but continued to have stereotypical behavior and had begun gagging herself. At a visit on April 15, 2009, though, Mrs. Lehner reported that C.L.'s behaviors had "not improved at all" and she felt that "in general she was regressing." *Id*., p. 39. She was concerned that the school would not permit C.L. to return the following school year, due to her behavior problems. She reported that C.L.'s vocabulary had remained stable while off the prednisolone. Doctor Renaud commented that C.L. did not use any words during this visit. *Id*., p. 41. At a visit on April 29, 2009 (when C.L. was off prednisolone and CellCept, and had not received IVIG since April 1, 2009 (*see* Pet. Ex. 9, pp. 94,101)), she was reported to be using two- to three-word phrases, seeking out more social interaction, and was more content at school. *Id*., p. 45. In mid-May 2009, C.L.'s family thought her communication and interaction had improved since the last IVIG dose. Doctor Renaud noted that C.L. greeted her and answered a few questions with single words. *Id*., p. 53. She assessed C.L. with incremental improvements after each IVIG infusion on the two-week interval schedule. At the end of June 2009, C.L. was reported to be calmer, with improved understanding, but still galloping and humming. *Id*., p. 58. At the end of August 2009, two months after the last IVIG treatment, C.L. was described as more focused, with better understanding. A recent EEG was described as normal, and C.L. had not had any regressions since stopping treatment. *Id*., pp. 63-64, 67 (phone call reflecting that C.L. had an EEG, not an MRI as reported at the August 26 visit).

progress had been "limited" and that she had struggled with irritability and behavioral problems in the past few months); p. 63 (evaluation from summer session reflecting that she could say familiar words in a song, would say her own name when asked, followed one-step directions, and played alongside peers without interaction); p. 65 (October 2009 IEP report reflecting that she could use one-word phrases, needed frequent prompting, and was using PECS at home to make "I want" requests).

C.L. was retested to confirm her continued need for special education services in December 2009 (a state-mandated requirement). While she had gained skills since the initial testing in September 2005 (performed by the school system) and June 2006 (testing outside the school system), she again scored as severely impaired—frequently in the 1st percentile ranking or below. Pet. Ex. 5, pp. 70-72. Her parents reported their primary concerns were her autism diagnosis and her lack of communication and peer interactions. *Id*., p. 70. C.L. was also retested for an autism spectrum disorder. The cut-off score for an autism diagnosis was 85 or higher; C.L. was scored over 100 in separate evaluations by her parents, kindergarten teacher, and special education teacher. *Id*., p. 74.

During the same time frame when C.L. received VGKC antibody treatments from Dr. Renaud, she was also receiving ABA therapy at the Lovaas Institute and speech and occupational therapy through the school system. Pet. Ex. 17, pp. 22-23 (Lovaas history of services received by C.L. from 2005-10). Consequently, it is difficult to attribute C.L.'s improvement, if any, to the specific therapies prescribed by Dr. Renaud. What is clear is that there was not a dramatic or significant improvement in C.L.'s functioning. This is especially evident when considering that her April 2009 IEP goals were continued at the June and November 2009 progress reviews, rather than marked as achieved. *See* Pet. Ex 5, pp. 56-60.

c. Switch in Therapies and Providers.

On August 26, 2009, C.L. saw Dr. Renaud again. She had received her last IVIG treatment on June 24, 2009. Pet. Ex. 9, pp. 63-64. She was reported to be more vocal and having better understanding since the June visit. Off therapy, her antibody level as measured on this visit had risen to 1.82. *Id*., p. 66. In a sample taken in October 2009, C.L.'s antibody level again rose, this time to 2.17. *Id*., pp. 67-68.

C.L. saw Dr. Renaud and Dr. Ann Reed, a rheumatologist, on November 3, 2009. C.L. had been ill about a month earlier and had eye surgery about two weeks prior to the visit. Pet. Ex. 9, p. 72. Her parents reported regression in C.L.'s communication and behavior over the prior four to six weeks. *Id.* Doctor Reed recorded that since July, C.L. had more aggressive behavior, screaming, and bedwetting. *Id.*, p. 69. I note that this appears to contradict the reports of her behavior at the August visit to Dr. Renaud. On examination by Dr. Reed, C.L. was interactive but distractible. *Id*., p. 70. The side

effects and potential benefits of rituximab[59] were discussed. *Id.* In discussions with Dr. Renaud, the family expressed concern about her deterioration, and Dr. Renaud attributed it to withdrawal of treatment. *Id.*, p. 73.

In December 2009, Mrs. Lehner requested that C.L.'s treatment records from Mayo be sent to the University of Minnesota, Fairview. Pet. Ex. 9, p. 75. In February 2010, C.L. had her first appointment at the pediatric rheumatology clinic there. The reason for the appointment was described as to obtain a second opinion regarding C.L.'s VGKC autoantibodies. Pet. Ex. 6, p. 89. Doctor Binstadt reviewed C.L.'s records with petitioners, noting that her "primary symptoms are developmental delay on the autism spectrum." *Id.* C.L.'s parents reported to Dr. Binstadt that C.L. had been "doing well" until she was found to have speech delay in October of 2005. *Id.* They described a loss of words and the onset of self-stimulatory behaviors as beginning two weeks after her November 2005 influenza vaccination. *Id.*

Doctor Binstadt referenced the Tan article, Pet. Ex. 10i, for the work done by the Mayo group on VGKC antibodies, the link of such antibodies to neurological disorders in adults, and the success in treating patients by immunosuppressive therapy. Pet. Ex. 6, p. 89. He summarized C.L.'s treatment by Dr. Renaud. *Id.*

After discussion of the risks and potential benefits, Dr. Binstadt and petitioners elected to treat C.L. with rituximab. Pet. Ex. 6, pp. 90-91, 96-97, 119. No evidence of improvement in C.L.'s condition was observed after she received two rituximab treatments and treatment was discontinued in April 2010, notwithstanding Dr. Binstadt's view that it was likely too early to see a benefit. *Id.*, p.128. Her VGKC antibodies, which were measured at 1.68 prior to receiving the first treatment (*id*., p. 98), rose between the first and second treatments to 1.89 (*id*., p. 119); and were 2.69 after the second treatment (*id*., p. 130). Doctor Binstadt did not know what clinical significance the increase in VGKC antibodies might have. *Id*. ("Whether there is any clinically significant difference between these two values is not known, to my understanding.").

d. Involvement with Dr. Vincent.

Petitioners' Ex. 20 contains a series of email messages from Dr. Vincent to Mrs. Lehner, C.L.'s maternal grandfather, or to Dr. Binstadt. Although the exhibit does not contain their messages to Dr. Vincent, the one-sided messages give a fairly clear

[59] Rituximab (trade name Rituxan) was described by Dr. Bryce Binstadt, a physician who later prescribed it as a treatment, as a monoclonal antibody that acted as a B-cell depletion therapy. Pet. Ex. 6, p. 90. He explained that it "works by depleting the CD20-expressing B cells, the precursor cells to antibody-producing plasma cells" and is "well tolerated and leads to improvement in patients with autoantibody mediated disorders." *Id.*

picture of what transpired in their correspondence between March 2011 and December 2012.[60]

C.L.'s grandfather, who attended many of C.L.'s appointments with Dr. Renaud, somehow learned of Dr. Vincent's work on VGKC antibodies. He wrote Dr. Vincent about C.L.'s history and treatment. On March 22, 2011, Dr. Vincent responded, commenting on several aspects of C.L.'s recent treatment and testing. Pet. Ex. 20, pp. 2-3. She stated that it was not unusual for antibody levels to vary and speculated that the variations could be due to the possible presence of two specific proteins, LGI1 and CASPR2.[61] *Id.*, p. 3. She offered to test a sample of C.L.'s serum for these specific antibodies and the "proteins they are against – eg. caspr2 or lgi1 [sic]." *Id.* She indicated that what had been reported to her about C.L.'s clinical course was "difficult to understand well," but that "rituximab may take some time to work." *Id.*

Throughout the correspondence, Dr. Vincent expressed excitement at finding a possible connection between VGKC antibodies and autism. She mentioned an unpublished study she had conducted looking for CASPR 2 antibodies in children with autism but the wording suggested that she had been unable to find the antibodies. Pet. Ex. 20, p. 3. She also mentioned her research into maternal antibodies and autism. *Id*.

Doctor Vincent's email messages to Dr. Binstadt concerned the testing of C.L.'s serum for antibodies. Pet. Ex. 20, pp. 4-5. When C.L.'s serum sample was finally obtained, shipped and tested in May 2011, she tested negative for CASPR2 and LGI1 antibodies, but positive (at a level of 0.91) for VGKC antibodies. Pet. Ex. 20, pp. 14-17. Doctor Vincent then suggested she continue to study C.L.'s "serum to try to determine the exact target of her antibodies." *Id.*, p. 19. She suggested testing C.L.'s serum on cultured brain cells to see where there might be binding of the antibodies present. *Id.*, pp. 19-21, 23. The email messages do not indicate whether this testing was ever performed.

Doctor Vincent's opinions on the significance of the antibodies present in C.L. are discussed in Section V.B.1.b.(1)(c), below.

e. Return to Treatment at Mayo.

C.L. resumed treatment with Dr. Renaud in September 2011. Pet. Ex. 9, p. 81. Doctor Renaud noted that C.L.'s VGKC antibody level increased during her treatment by Dr. Binstadt, but that the level had declined to 1.30 in November 2010, some four

[60] One additional message, which is undated, appears at Pet. Ex. 20, p. 24, after the last dated message from December 31, 2012. *Id*., p. 23.

[61] These are the two antibodies found in the VGKC complex that have specific pathogenic associations. *See, e.g.*, Tr. at 416-17; Pet. Ex. 21, p. 1.

months after rituximab treatment ended.[62] Pet. Ex. 9, p. 81. She also noted that there had been no obvious regression of skills. *Id.* Although C.L. was not communicating much verbally, she was using single words to label things, was beginning to use an iPad as an assistive communication device, seemed to understand more than she could say, followed two step commands, and had occasional two word combinations. *Id.* Her words, however, were "often approximations." *Id.* Additionally, she noted that C.L.'s eye contact had improved "over time despite not receiving ABA therapy since September 2010." *Id.* The foregoing suggests that the reports provided of C.L.'s functioning during Dr. Renaud's earlier treatment were either somewhat inflated or C.L. had indeed lost some skills. Given that this description of C.L.'s level of functioning was more consistent with what was recorded in her school records, the "improvements" noted earlier may not have been accurate. *Compare id*. *with* descriptions in n.58, *supra*. Although Dr. Renaud assessed C.L. as not having regressed since her last evaluation in November 2009, C.L.'s family felt that she had "not made two years of progress" in that time. Pet. Ex. 9, p. 82.

Doctor Renaud recommended intermittent pulse IV methylprednisolone, rather than the oral prednisolone C.L. had received in 2008. Pet. Ex. 9, p. 82. She also suggested pairing this therapy with another drug, Imuran.[63] Interestingly, Dr. Renaud recorded C.L.'s diagnoses as global developmental delay with autistic features and neuronal voltage-gated potassium channel antibodies, but, in contrast to her earlier diagnoses, did not record either a possible or probable autoimmune encephalopathy as a diagnosis. *Id*.

The family apparently agreed with the recommendation to treat C.L. with IV steroids monthly, as she received her first infusion in late November 2011. Pet. Ex. 9, pp. 118-19. Her antibody level was measured at 1.0 prior to beginning the infusion, which was slightly higher than the level in September 2011, when she returned to Dr. Renaud's practice. *Id*., p. 119. No side effects were reported. Doctor Renaud also noted that ABA therapy had resumed full-time in September. *Id*. Her antibody levels declined to 0.69 on December 5, 2011. *Id.*, p. 121. The antibody levels were even lower at the time of the second infusion on December 23, 2011, down to 0.42, and lower still, to 0.31, after a subsequent infusion. *Id*., pp. 124-25.

At a February 2012 visit with Dr. Renaud, Mrs. Lehner reported that C.L. had experienced gains since resuming steroid therapy, including improvement in eye contact, responsiveness to her name, imitation of vocalizations, and spontaneous vocalizations. Pet. Ex. 9, p. 127. Although it was not a huge gain, she indicated that there had been some benefit and none of the sleep problems and aggression seen during the earlier oral steroid therapy. *Id.* On examination, Dr. Renaud observed good

[62] The level had further declined as of the date of this appointment. The sample drawn on September 14, 2011, was reported as 0.83. Pet. Ex. 9, p. 90.

[63] It does not appear that this additional medication was ever added to C.L.'s treatment regimen.

eye contact, the use of some single words, and that C.L. was calmer than on previous visits. *Id*. C.L.'s most recent antibody level showed some rebound, going up to 0.92, but the increase in antibodies was not accompanied by any clinical deterioration. *Id*., p. 128. Doctor Renaud opted to increase the dose of oral steroid and to infuse every two weeks for five infusions. *Id.*

C. L.'s antibody level was down to 0.48 in the April 2012 blood draw. Pet. Ex. 9, p. 151. C.L. was next seen by Dr. Renaud on May 24, 2012. *Id.*, p. 154. C.L. was reported as agitated for about a day after the infusion of the increased dose. *Id.* The skills reported were similar to those at previous visits, but C.L. was saying things when prompted, rather than initiating the use of words. *Id.* Mrs. Lehner described C.L. as "less settled" over the past week and reported that she was having trouble falling asleep. *Id.* C.L.'s grandfather raised questions about the effectiveness of plasma exchange as a possible treatment; Dr. Renaud reviewed the papers he had found and noted that this treatment had been used in limbic encephalitis, a more acute illness than C.L. demonstrated.[64] *Id*., p. 155.

Behavioral concerns resurfaced at the July 2012 visit to Dr. Renaud. C.L.'s skills, language and cognitive abilities were described as stable, and she had not received any steroid infusions since May 2012. Pet. Ex. 9, p. 183. However, she was having tantrums and aggressive behavior, was scratching, and was described as "quite emotional." Pet. Ex. 9, p. 183. She was gagging herself to the point of vomiting, had stopped eating solid food, and was taking more than two hours to fall asleep, after which she would awaken during the night and not return to sleep. *Id.* After a review of past and proposed treatments, Dr. Renaud suggested that C.L. see one of the clinic's neuroimmunologists. The family agreed, and Dr. Renaud arranged an appointment on July 31. *Id*., pp. 183-84.

The reports of gains from the IV steroid treatment were undercut by other evaluations of C.L.'s condition. A May 30, 2012 reassessment by the Minnesota Autism Center indicated that C.L.'s "Full Scale IQ" score was 40, which was in the "mentally deficient range," and was certainly not improved over prior scores. Pet. Ex. 13, p. 31. Additionally, C.L.'s CARS score remained in the "severely autistic" category." Pet. Ex. 13, p. 33.

f. Evaluation at the Autoimmune Neurology Clinic.

[64] Doctor Vincent had mentioned plasma exchange as a possible treatment in July 2011. Pet. Ex. 20, p. 20.

C.L. saw Drs. Andrew McKeon[65] and Stacey Clardy in the Autoimmune Neurology Clinic on July 31, 2012. Doctor Clardy reviewed the medical history provided by C.L.'s mother and grandfather, which repeated the claim that C.L. lost milestones and had a complete change in personality and behavior within a few weeks of her influenza vaccination. Pet. Ex. 9, p. 189. They reported that her language had stayed stable with about 50 words or word approximations, that she could follow some simple two-step commands, and that she had no major regressions or dramatic improvements since 2005, but was gaining skills at school. *Id*. Doctor Clardy characterized the oral steroid treatment as producing "questionable minor improvement in language use, but with intolerable behavioral side-effects." *Id*., p. 190. She saw no "appreciable benefit" from IVIG; no apparent benefit and some side effects from CellCept; and no significant improvement but no side effects from the IV steroid treatment. *Id*. She described C.L. as a "unique case." *Id.*, p. 191. She noted that the "phenotype of VGKC-antibodies in the pediatric population is not fully characterized," and that the few case reports available described many manifestations.[66] *Id*. Doctor Clardy indicated that, at this point, it was impossible to know if C.L. had experienced autoimmune encephalitis when she was two, whether some of her symptoms represented sequelae of that condition, or whether the VGKC antibodies were related to her autism. *Id.* She commented that an individual may have persistent antibodies without clinical symptoms. *Id*. Although C.L.'s parents had focused on antibody levels in deciding whether treatment was effective (*see, e.g.*, Pet. Ex. 9, p. 150 (telephone message that parents did not feel comfortable in scheduling an IV steroid infusion without knowing the antibody levels)), Dr. Clardy recommended focusing on clinical improvement, as difficult as it might be to objectively assess, as antibody levels "have been known to persist in patients with clinical remission of symptoms." *Id*., pp. 191. She noted that there had been questionable improvements in the past on language, but no family member had ever seen an improvement in social skills or cognitive function. *Id*., p. 192.

Doctor McKeon's own consultation notes repeated the history of a regression after an influenza vaccination, with the development one month later of self-stimulatory behavior, rocking, humming, and decreased visual contact. Pet. Ex. 9, pp. 193-94. C.L.'s grandfather reported that before the vaccination, C.L. was bright and interactive, but a month afterwards, she would just sit in a corner and refuse to make eye contact. He also reported that she stopped talking and was less affectionate. *Id*., p. 193. Doctor McKeon observed C.L. to run around the room, making some eye contact, but she did

[65] Doctor McKeon is a respected adult neurologist with a focus on autoimmune encephalopathy and has collaborated in research with Dr. Dalmau. Tr. at 382.

[66] Dhamija, Pet. Ex. 11c, reported on 12 pediatric cases of VGKC antibodies (including C.L.'s). Eleven of the patients were seen at the Mayo Clinic. Dhamija, Pet. Ex. 11c at 278. Their symptoms varied widely, ranging from motor tics and episodic flushing to cerebellar ataxia and limbic encephalitis. *Id.* at 276. There were no symptoms common to a majority of the patients. The wide variety of symptoms reported in this article in connection with the presence of VGKC antibodies mirrors Dr. Dalmau's observations, discussed in Section V.B.1.b.(2)(b), below.

not have the social or language skills of child of her age. *Id.* Consistent with the observations of several other physicians, Dr. McKeon noted some coarse facial features.[67] *Id.*, p. 194.

Based on the reports of "the rapid onset" of C.L.'s regression, Dr. McKeon opined that "she may have had an unusual manifestation of an autoimmune encephalitis at that time." Pet. Ex. 9, p. 194. As an alternative, he hypothesized that "the potassium channel autoantibodies, though present, are not related to her developmental problems." *Id.* He cautioned that even if she had experienced autoimmune encephalitis, the "window" for successful treatment of the condition may have passed." *Id.*

Both physicians recommended a full dose trial of IV steroids with Dr. Renaud, but indicated that treatment should be discontinued if no clinical improvement was observed. Pet. Ex. 9, pp. 192, 194.

Thereafter, C.L. continued to receive immunotherapy treatments from Dr. Renaud, who increased her dosage of steroids in September 2012. *See generally* Pet. Ex. 9, pp. 200-06. In December of 2012, C.L.'s mother reported that C.L. was having behavioral side effects as a result of the steroids, including "trying to injure herself and others, [and] trying to kick the car door." *Id.*, p. 217.

Subsequently, some improvements in behavior and skills were noted. C.L. continued to receive ABA therapy, and her family and the ABA therapist felt she had made significant progress. Pet. Ex. 9, pp. 221, 247 (as reported to Dr. Renaud during C.L.'s January and April 2013 appointments). Mrs. Lehner testified that they saw "the biggest gains" in C.L.'s behavior with the increased steroid dose. Tr. at 53. During C.L.'s January and April 2013 appointments with Dr. Renaud, C.L.'s family reported improvements in both her behavior and skills. *See* Ex. 9, pp. 119, 127, 154, 221, 247. C.L.'s antibody levels remained above normal, and continued to fluctuate. *Id.*, pp. 222, 227, 238, 248. In January 2013, C.L.'s parents elected to reenroll her in public school, rather than continue home school plus full time ABA therapy. Pet. Ex. 5, p. 201. However, notwithstanding these noted improvements, C.L. continued to qualify for "special education services as a student with Autism Spectrum Disorder." Pet Ex. 5, p. 214.

As part of reenrolling in public school, C.L. was reevaluated for special education services. While C.L.'s eye contact and joint attention were improved, her communication skills were poor. She did not engage in age appropriate play, did not interact with her peers, preferred repetitive and self-stimulatory behavior, exhibited a

[67] In addition to the other observations of coarse features mentioned above, Dr. Deborah Freese, a pediatric gastroenterologist, saw C.L. in June of 2012 and observed her to be "mildly dysmorphic with frontal bossing and a large head size." Pet. Ex. 9, p. 181.

low frustration tolerance, and sought sensory input by putting things in her mouth, and smelling and touching them. Pet Ex. 5, p. 206. C.L.'s most recently filed IEP indicated that she continued to have needs in the areas of social interaction, behavioral regulation, communication, functional skills as well as academic skills. Pet Ex. 5, pp. 227-35.

g. Seizure Disorder Diagnosis.

At the end of April 2013, C.L. was found unconscious on the playground. School personnel presumed she had hit her head. Pet. Exs. 22, p. 1; 3, p. 131. About a week later, on May 3, 2013, C.L. suffered a seizure witnessed by her father. Pet. Exs. 22, p. 1; 3, p. 131[68]; 9, pp. 251, 254. On May 14, 2013, C.L. was seen by Dr. Chadwick, a pediatric neurologist, for an evaluation of her seizures. She was diagnosed with complex partial epilepsy in addition to autism.[69] Pet. Ex. 22, pp. 1-3. C.L. experienced another seizure several days later and was prescribed Trileptal, with good results in seizure control. *Id*., p. 7. However, C.L. was experiencing "anger, aggression, and agitation issues" with some recent improvement. *Id.* As of February 2014, C.L. continued to receive Trileptal, and IV steroid infusions. Pet. Ex. 9, p. 266. A gain of skills was also reported. *Id.*

5. Other conditions.

C.L.'s medical records also document treatment for a number of minor childhood illnesses and other conditions, including surgery for "lazy eye," evaluation, biopsies, and treatment for gastroesophageal reflux, some alternative tests and treatments for ASD, and many school and therapy records. *See generally* Pet. Exs. 3-6; 13-14; 17; 19. Although I have reviewed these exhibits as a part of the "record as a whole" (*see* § 13(a)), and some are mentioned in passing in the medical records summary above, they are not discussed further in this decision, as they are not relevant to the issues presented in this case.

[68] The history reflected in this record is that Dr. Donald Chadwick witnessed her May 3 seizure; however, based on Dr. Chadwick's records, the history of a witnessed seizure should reflect that C.L.'s father, not Dr. Chadwick, witnessed it.

[69] Doctor Shafrir testified that many individuals with autism eventually develop seizure disorders. Tr. at 131. He also testified that the majority of autistic children will develop seizures by the time they reach their 18th birthday. Tr. at 255. *See also Snyder*, 2009 WL 332044, at *32 ("About 20–30% of children with ASD have or will develop epilepsy over the course of their lives, often beginning during adolescence.").

IV. Experts, Opinions, Diagnoses, and Motion to Exclude.

A. Expert Qualifications.

1. Doctor Frye.

Doctor Frye's curriculum vitae ["C.V."] was not filed in this case, making it difficult to assess his qualifications to offer an expert opinion on autoimmune encephalitis and the role of VGKC antibodies in the condition, much less on whether such a condition would present with symptoms warranting an autism diagnosis. However, I am familiar with Dr. Frye in general, as he has testified as a pediatric neurologist specializing in the treatment of children with neurodevelopmental disorders in other Vaccine Program cases. *See Paluck v. Sec'y, HHS*, 786 F.3d 1373 (Fed. Cir. 2015); *Bast v. Sec'y, HHS*, 2012 WL 6858040, at *3 (Fed. Cl. Spec. Mstr. Dec. 20, 2012).

At the time Dr. Frye wrote his expert report in this case he was an Assistant Professor of Pediatrics and Neurology at the University of Texas Health Science Center. Pet. Ex. 10 at 3.

2. Doctor Shafrir.

Doctor Shafrir is board certified in neurology, with special qualifications in child neurology and clinical neurophysiology. Pet. Ex. 11a at 2; Tr. at 128. After his residency training, Dr. Shafrir completed a fellowship in pediatric neurophysiology and epileptology at Miami Children's Hospital. Pet. Ex. 11a at 1; Tr. at 128.

He is primarily a clinician, and is currently in private practice in Baltimore, MD, where he sees patients five days a week. Tr. at 130; Pet. Ex. 11a at 3. He also teaches residents at Sinai Hospital, and is an Assistant Professor at the University of Maryland School of Medicine. Tr. at 128-29; Pet. Ex. 11a at 3. Doctor Shafrir has an interest in autism spectrum disorders and currently sees approximately 200 ASD patients, but he has no specialized training in the diagnosis, management, or treatment of ASD. Tr. at 130-31, 203. He explained that he did not see most of his ASD patients actively, because there was very little that he could do for them by way of treatment. Tr. at 130-31. Most of his ASD patients had already been evaluated or tested for ASD by the time he saw them. Tr. at 132. He did not appear to place much value on ASD diagnostic criteria (Tr. at 134-35, 206-07), and indicated that he did not order many tests to try to determine if there was a cause for the disorder in individual patients (Tr. at 136-37).

He has treated approximately three patients in his career with autoimmune encephalitis. Tr. at 139. He has not conducted any research in ASD,[70] autoimmune encephalopathies, or voltage-gated antibodies. Tr. at 203-04. He has no expertise in autoimmunity in particular or immunology in general. He has never treated a patient with VGKC antibodies, although he had "seen two patients" with NMDAR encephalitis. Tr. at 208, 227. However, he claimed, based on his reading of published medical literature, that he was an expert on "how different antibodies can cause autoimmune encephalopathy." Tr. at 217. In one of many tangential answers to relatively straightforward questions, Dr. Shafrir testified that his "life is dedicated to autism." Tr. at 148.

3. Doctor Angela Vincent.

Petitioners filed a June 4, 2013 email message from Dr. Vincent to their attorney, Ms. Sheila Bjorkland, as Pet. Ex. 21, as well as the email correspondence from Dr. Vincent, as Pet. Ex. 20. Although petitioner's counsel characterized Dr. Vincent's June 4, 2013 letter as an "Expert Report," the letter is better characterized as a medical record describing testing and a commentary on the significance of the results. A C.V. for Dr. Vincent was not included; however, I note that she co-authored a number of the medical journal articles that were filed as exhibits by both parties.

In the June 4, 2013 message, Dr. Vincent noted that she is a clinical immunologist with 35 years of experience researching diseases of the nervous system caused by autoantibodies to membrane receptors, ion channels, or related proteins. Pet. Ex. 21, p. 1. Her group of researchers made some early discoveries in antibodies thought to be involved with neurological symptoms, including the first description of the potassium channel antibodies in 1995, and developed the first test for the antibodies. *Id*. Her laboratory tests over 50,000 samples per year. *Id*. Doctor Dalmau testified that Dr. Vincent is a leading contributor to the field of autoimmune neurology with whom he has published but, to his knowledge, she is not a medical doctor and does not see patients. Tr. at 379-80, 448.

Based on the information provided, she clearly possessed the qualifications to test C.L.'s blood for the presence of VGKC autoantibodies and to opine on the significance of the results. She did not offer an opinion on the role of the influenza vaccination in causing the antibodies.

[70] Doctor Shafrir has published an abstract on Landau-Kleffner Syndrome. Tr. at 204. Landau-Kleffner Syndrome is an acquired epileptic aphasia presenting in childhood and is a condition that frequently resembles autism spectrum disorders. *See* DORLAND'S at 1861.

4. Doctor Dalmau.

Doctor Dalmau is a world-class expert in the areas of autoimmune encephalopathy and encephalitis and voltage-gated potassium channel antibodies. He is a neurologist with specialties in neuroimmunology and neuro-oncology. Tr. at 293-97. He also has a Ph.D. in immunology and cancer-associated immunology.[71] Tr. at 293. After his residency training in Spain, Dr. Dalmau completed a fellowship in neurology at New York Hospital, Cornell University, and a fellowship in medical oncology at Memorial Hospital for Cancer and Allied Diseases in New York, NY. Res. Ex. K at 1.

At the time of the hearing, Dr. Dalmau served as the director of laboratories involving neuro-oncology and neuroimmunology at the University of Barcelona in Spain. He also serves on the faculty of the University of Pennsylvania in Philadelphia and the University of Barcelona in Spain. Res. Ex. LL at 2; Tr. at 293-94. He has been a reviewer for over 25 medical journals and sat on the editorial board of four neurology journals. Res. Ex. LL at 6.

Doctor Dalmau is an award-winning researcher in the field of neuroimmunology and at the time of the hearing, was a consultant in neuroimmunology for the National Institutes of Health ["NIH"]. Tr. at 294-95; Res. Ex. LL at 3. The current focus of Dr. Dalmau's research is on three aspects of autoimmune encephalitis: studying known disorders; identifying new disorders, antibodies, and target antigens; and studying mechanistically how antibodies act on the brain. Tr. at 298-99. He is the primary author of or a primary contributor to approximately 270 published articles, of which nearly 95% deal with autoimmune disorders. Tr. at 299. The articles published most recently have largely dealt with autoimmune encephalopathies and encephalitis. *Id.*

His clinical practice involves many patients with autoimmune encephalitis, predominantly referral patients seeking confirmation of an immune-mediated disorder diagnosis. Tr. at 297-98. Twenty percent of these patients are children, all of whom have autoimmune neurological conditions. *Id.* Based on these credentials, Dr. Dalmau was offered as an expert in neuroimmunology with special expertise in autoimmune encephalopathy and autoimmune encephalitis without objection. Tr. at 299-300. The hearing in this case was the first time he has testified. Tr. at 300.

5. Doctor Gorman.

Doctor Gorman is a board-certified neurologist, with special qualifications in child neurology. He specializes in pediatric neuroimmunology. Res. Ex. MM at 10, 16; Tr. at 454-55, 485. After his residency, Dr. Gorman completed a fellowship in child neurology and multiple sclerosis. Res. Ex. MM at 1-2.

[71] Because Dr. Dalmau completed his residency in Spain, he is not eligible for board certification in the United States. Tr. at 292.

At the time of the hearing, Dr. Gorman was the director of the pediatric multiple sclerosis program, the neuroimmunology program, and the inpatient neurology service at Boston Children's Hospital. Res. Ex. MM at 2-3. He was an assistant professor at Harvard Medical School and taught at Boston Children's Hospital. *Id*. at 2; Tr. at 455. His clinical practice was limited to pediatric neuroimmunology patients, whom he saw one full day a week, with the remainder of his time involving a research practice in multiple sclerosis, and in other aspects of neuroimmunology distinct from multiple sclerosis. Tr. at 456-57. He has numerous peer reviewed publications and has served as a reviewer for several medical journals. Tr. at 457; Res. Ex. MM at 4, 12-14. Doctor Gorman saw ASD patients in the context of providing autoimmunity consultations and as part of his in-patient attending responsibilities; but he did not represent himself as having any special expertise in ASD. Tr. at 495.

B. Petitioners' Motion to Exclude Dr. Gorman's Testimony.

Prior to discussing the expert opinions on diagnosis and causation, I first deal with petitioners' mid-hearing motion to exclude Dr. Gorman's testimony as cumulative. The issue was first raised by oral motion at the hearing on January 28, 2014. Tr. at 451-53. Given that nothing precluded petitioners from raising the issue in a pre-hearing status conference or by written motion prior to the hearing, and the fact that Dr. Gorman was present and prepared to testify, I elected to hear his testimony and decide later whether to consider it in making my decision. *Id.*

In the post-hearing order, I directed petitioners to file a written motion summarizing their arguments for excluding Dr. Gorman's testimony. Order, issued Jan. 30, 2014. Petitioners filed their Motion to Exclude ["Pet. Motion"] on March 10, 2014; respondent filed a Response to Petitioners' Motion ["Res. Response"] on April 7, 2014; and petitioners filed a Reply to Respondent's Response ["Pet. Reply"] on April 10, 2014.

Petitioners argued that Dr. Gorman's testimony should be excluded as violating the "rules of fundamental fairness" because: (1) Dr. Gorman conceded he would defer to Dr. Dalmau's expertise[72] regarding VGKC encephalopathy, and thus any testimony by Dr. Gorman regarding autoimmune encephalopathy and VGKC antibodies would be cumulative and duplicative; (2) Dr. Gorman's testimony regarding the onset and causation of ASD was beyond his expertise; and (3) his testimony on ASD was beyond the scope of his expert reports and "amounted to trial by ambush." *See generally* Pet. Motion. Despite my instructions that petitioners provide specific objections, Tr. at 475,

[72] It is unsurprising that Dr. Gorman would defer to Dr. Dalmau's expertise regarding VGKC antibodies and autoimmune encephalopathy, as few experts anywhere in the world possess Dr. Dalmau's knowledge. That does not automatically make Dr. Gorman's testimony cumulative. I note that the motion to exclude was made prior to hearing his testimony. Thus, petitioners were only assuming that the testimony would be cumulative. Further, as discussed above in the post-hearing brief on the matter, petitioners failed to cite any specific examples of cumulative testimony offered by Dr. Gorman.

petitioners failed to cite any specific examples of cumulative testimony offered by Dr. Gorman. Rather, petitioners asserted that as Dr. Gorman deferred to Dr. Dalmau's expertise "it is a matter of simple logic than any testimony he offered regarding VGKC antibodies and [C.L.'s] situation was merely cumulative." Pet. Reply at 1. Petitioners argued Dr. Gorman's testimony on VGKC antibodies "was anecdotal of his own experience and not specific to C.L.'s situation." *Id.* at 1-2. I disagree with all of petitioners' arguments.

At the hearing Dr. Gorman testified consistent with his revised opinion[73] that C.L. did not have an autoimmune encephalopathy, let alone one related to VGKC antibodies. Consistent with his initial opinion in this claim, he testified that the vaccination was not responsible for the antibodies and that C.L. evidenced significant developmental delay prior to her influenza vaccination. He also testified about C.L.'s autism spectrum disorder diagnosis and his disagreements with some of Dr. Shafrir's testimony about ASD.

The Vaccine Act vests the special master with the authority to determine the weight to be afforded evidence, while requiring the special master to consider the entire record. §§ 13(a)(1), 13(b)(1). The statute further provides that the rules established to

[73] Doctor Gorman initially agreed with Dr. Frye that C.L. suffered an autoimmune encephalopathy related to VGKC antibodies, but he also opined at the same time that her condition was not caused or exacerbated by her influenza vaccination. Res. Ex. A at 2-5. His opinion was that C.L. suffered "significant developmental delay" prior to her November 25, 2005 influenza vaccine, that the extent of that delay was underestimated, and that if the VGKC antibodies played any role in her condition, they were likely present before the vaccination. *Id.* at 4. He clearly disagreed with Dr. Frye's "sweeping general statements about purported links between various vaccinations and lupus, Guillain Barré syndrome, and autoimmune thrombocytopenia," as well as "potential mechanisms of autoimmunity," which Dr. Gorman did not find relevant to C.L.'s case. *Id*. He pointed specifically to the "lack of scientific evidence" linking influenza vaccine to VGKC antibody disorders. *Id.* at 5. After Dr. Dalmau submitted his opinion in this case explaining that recent research had established that only certain types of VGKC antibodies appeared to play a causal role in autoimmune encephalitis, Dr. Gorman changed his initial opinion that C.L. suffered an autoimmune encephalopathy. Res. Ex. W. After considering the opinion and evidence submitted by Dr. Dalmau, reviewing additional medical literature, and having recently evaluated a patient with elevated VGKC antibodies himself, Dr. Gorman indicated that he was in agreement with Dr. Dalmau that C.L. "did not have an autoimmune encephalopathy related to VGKC complex antibodies." Res. Ex. W at 1. I note that it appears that Dr. Gorman and Dr. Frye had previously collaborated on a publication, which perhaps explains why he was willing to accept Dr. Frye's opinion on the presence of an autoimmune encephalopathy, but disagreed with his conclusions on the role of the vaccine in triggering it, as the latter was a matter in which Dr. Gorman had expertise. *See* Res. Ex. B at 7 ("Clinical Communications" category on Dr. Gorman's C.V. reflecting a publication with "R. Frye"); *see also id*. at 7-8 ("Original Articles" category, reflecting publications on the role of vaccines and infections in neurological demyelinating disorders (references 4, 5, and 12)). At the hearing, Dr. Gorman summarized the reasons for his changed opinion as including information from Dr. Dalmau about the technical limitations of the radioimmunoassay testing performed on C.L.; the lack of any control establishing the normal range for such antibodies by the Mayo Clinic; the testing by Dr. Vincent for the pathogenic antibodies, which was negative; the rapidly expanding volume of scientific literature about VGKC antibodies; and his personal experience with two patients and Mayo Clinic testing results. Tr. at 467-72.

govern Vaccine Act proceedings should "include flexible and informal standards for admissibility of evidence." § 12(d)(2)(b). Vaccine Rule 8(b)(1), which controls the admission of evidence, including expert testimony, in cases filed in the Vaccine Program, indicates that "[i]n receiving evidence, the special master will not be bound by common law or statutory rules of evidence but must consider all relevant and reliable evidence governed by principles of fundamental fairness to both parties." Petitioners in general often benefit from this approach, as *Daubert* and its progeny are rarely used to exclude witnesses; instead, the *Daubert* factors are used to weigh and evaluate expert testimony.[74]

Doctor Gorman, unlike Dr. Dalmau, is a board certified *pediatric* neurologist who specializes in *pediatric* neuroimmunology. As such, Dr. Gorman is clearly qualified to testify and opine in the areas of *pediatric* neurology and immunology, which encompass the topics of ASD, autoimmune encephalopathy, and VGKC antibodies.[75] As to his supposed lack of qualifications to opine on ASD, Dr. Gorman has the same general qualifications as Dr. Shafrir, another pediatric neurologist. I note that at least two of the physicians who treated C.L. were pediatric neurologists (Drs. Renaud and Chadwick) and Dr. Janousek was identified as a neurologist. Although Dr. Shafrir saw children with ASD, he did not appear to have any special qualifications, apart from his training as a pediatric neurologist, to do so, and Dr. Gorman saw children with ASD as a part of his pediatric neuroimmunology practice. Thus, Dr. Gorman was at least as qualified on the topic of ASD as Dr. Shafrir, and more qualified than Dr. Shafrir on the immunological and autoimmune aspects of the causation theory petitioners chose to present.

The fact that Dr. Gorman conceded the expertise of Dr. Dalmau, who, according to petitioners' own expert, is a "pioneer in this field [having] essentially discover[ed] the

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[74] For example, much of the evidence pertaining to the causation theories presented in the OAP test cases and considered by the special masters was excluded, based on its lack of reliability, by the state and federal judges in the autism cases litigated outside the Vaccine Program. *See Blackwell v. Wyeth*, 408 Md. 575, 971 A.2d 235 (2009); *Doe v. Ortho-Clinical Diagnostics*, Inc., 440 F. Supp. 2d 465 (M.D.N.C. 2006); *Redfoot v. B.F. Ascher & Co.*, No. C 05-2045 PJH, 2007 WL 1593239 (N.D. Cal. June 1, 2007).

[75] I note that some of the medical journal articles filed addressed VGKC antibodies in adults, while others focused on the antibodies in children. For example, the following articles focus on children: Dhamija, Pet. Ex. 11c; Y. Hacohen, et al., *Paediatric autoimmune encephalopathies: clinical features, laboratory investigations and outcomes in patients with or without antibodies to known central nervous system autoantigens*, J. NEUROL. NEUROSURG. PSYCHIATRY, 84: 748-55 (2013), filed as Pet. Ex. 23a [hereinafter "Hacohen, Pet. Ex. 23a"]; and J. Suleiman, et al., *VGKC antibodies in pediatric encephalitis presenting with status epilepticus*, NEUROLOGY, 76: 1252-55 (2011), filed as Pet. Ex. 23b [hereinafter "Suleiman, Pet., Ex. 23b"]. These articles focus on adults: J. Lilleker et al., *VGKC complex antibodies in epilepsy: Diagnostic yield and therapeutic implications*, SEIZURE, 22:776-79 (2013), filed as Pet. Ex. 23d [hereinafter "Lilleker, Pet. Ex. 23d"]; S. Wong, et al., *An effective immunotherapy regimen for VGKC antibody-positive limbic encephalitis,* J. NEUROL., NEUROSURG. & PSYCHIATRY 81: 1167-69 (2010), filed as Res. Ex. F [hereinafter "Wong, Res. Ex. F"]; E. Lancaster, et al., *Investigations of Caspr2, an Autoantigen of Encephalitis and Neuromyotonia*, ANN. NEUROL., 69: 303-11 (2011), filed as Res. Ex. Q [hereinafter, "Lancaster, Res. Ex. Q].

entity of autoimmune encephalitis" does not render Dr. Gorman unqualified to testify. Pet. Ex. 16 at 1; *see also* Tr. at 139, 520 (acknowledging Dr. Dalmau's expertise and qualifications). Nor does the fact that Dr. Gorman's testimony overlapped to some degree with Dr. Dalmau's testimony make Dr. Gorman's testimony inadmissible. While a special master might chose to preclude a party from offering the opinions of two medical experts within the same field, nothing in the Vaccine Rules or the Act itself requires one to do so. Moreover, while Dr. Dalmau has specialized in the area of autoimmune encephalopathy and encephalitis and, in particular, the VGKC antibodies at issue in this case, he primarily treats adults; whereas Dr. Gorman specializes in pediatric neuroimmunology and has published on the role of vaccines and infections. *See* Section IV. A.; n.72, *supra*. Thus, they bring some differences in background to their understanding of the causation issues in question.

Petitioners had ample opportunity to move to exclude Dr. Gorman's testimony prior to the hearing, rather than blindsiding respondent, not to mention the special master, with the issue for the first time at hearing.

Petitioners' argument that Dr. Gorman's changed opinion should preclude his testimony was, essentially, unsupported by law or practice. In more than nine years as a special master, I have seen many experts modify their opinions under a variety of circumstances, and in particular, many petitioners' experts change their theories in mid-hearing.[76] Doctor Gorman's changed opinion is certainly a matter to be considered in determining how much weight to give to his opinions,[77] but to preclude him from testifying because he had changed his opinion is simply not warranted.

I conclude that Dr. Gorman should not have been precluded from testimony based on his changed opinion in this matter, nor on his concession of Dr. Dalmau's superior knowledge regarding autoimmune encephalopathy and encephalitis and VGKC

[76] To some degree, Dr. Shafrir did so in this case, acknowledging at the end of the hearing that Dr. Dalmau's explanations had changed his opinion and conceding that C.L. did not have the pathogenic antibodies associated with autoimmune encephalitis. *See* Section V.B.1. b, below.

[77] A trier of fact might well question the expertise and reliability of an expert who does such an about-face on a diagnostic issue, but Dr. Gorman's candid acknowledgment that he was wrong speaks volumes about his honesty and credibility. The causes of autoimmune encephalitis are a "cutting edge" area of medical and scientific research, about which Drs. Frye, Gorman, and Shafrir were all simply wrong because new evidence became available between the filing of this claim and the hearing. I suspect that even Dr. Dalmau might have expressed some agreement with Dr. Frye about a connection between VGKC antibodies and autoimmune encephalitis at a point before Dr. Dalmau became suspicious about the wide variety of symptoms attributed to VGKC antibodies, and before he completed his more recent research identifying only certain VGKC antibodies as causal of autoimmune encephalitis—antibodies not present in C.L. I have excluded consideration of experts' testimony based on matters that reflected on their credibility, *see, e.g.*, *Raymo v. Sec'y, HHS*, No. 11-0654V, 2014 WL 1092274, at *16 (Fed. Cl. Spec. Mstr. Feb. 24, 2014), but see no basis here to exclude categorically all of Dr. Gorman's testimony. I found his willingness to admit an error refreshing.

antibodies, although they are factors to be considered in the weight accorded to his testimony. I add that Dr. Dalmau's testimony did not require buttressing by Dr. Gorman.

As to Dr. Gorman's testimony regarding ASDs in general, and C.L.'s ASD diagnosis in particular, I find his testimony permissible. As I pointed out at the hearing, Dr. Gorman has opined consistently that C.L.'s neurological injury pre-dated her November 25, 2005 vaccination. Tr. at 453 (citing Res. Ex. A); s*ee also* Res. Reply at 5 ("Dr. Gorman has consistently stated that [C.L.'s] well-documented early developmental delays mark the onset of her neurologic condition and that her influenza vaccination played no role." (citing Res. Ex. A; Res. Ex. I at 3; Res. Ex W; Tr. at 462-66, 480, 500, 511-12)). Further, the medical records are replete with references to C.L.'s ASD diagnosis, and Dr. Shafrir discussed ASD in his testimony. Thus, petitioners cannot claim to be surprised regarding Dr. Gorman's thoughts about C.L.'s ASD diagnosis and symptoms.

It was not fundamentally unfair to hear this testimony. To the contrary, the rules of fundamental fairness require that respondent be allowed to respond to the evidence offered by petitioners and, as a pediatric neurologist, Dr. Gorman was qualified to offer testimony in counterpoint to that of Dr. Shafrir on ASD.

Finally, while I am overruling petitioners' objections, my ultimate findings in this case would be unchanged even were I to exclude Dr. Gorman's testimony. In particular, the testimony he offered on ASD was encompassed in the medical journal articles that Dr. Dalmau referenced in his expert reports.

C. Diagnoses.

C.L. has received two diagnoses relevant to the issue of causation. Her ASD diagnosis is not in dispute, but the parties are in disagreement about whether C.L. truly experienced autoimmune encephalopathy or encephalitis[78] and, if so, whether that condition is responsible for the symptoms resulting in the ASD diagnosis.

When the injury or diagnosis itself is disputed, and "the proposed injuries differ significantly in their pathology," the special master may "first find which of [the] diagnoses was best supported by the evidence presented in the record before applying the *Althen* test so that the special master could subsequently determine causation relative to the injury." *Broekelschen v. Sec'y, HHS.,* 618 F.3d 1339, 1346 (Fed. Cir. 2010).

[78] The medical records establish that C.L. received a diagnosis of probable autoimmune encephalitis during the first round of treatment with Dr. Renaud. However, this diagnosis did not appear in Dr. Renaud's later records, although she continued to treat C.L. for the condition. The fact that C.L. has VGKC antibodies is not in dispute.

1. Autism Spectrum Disorder.[79]

a. Diagnostic Criteria and Characteristics.

The terms "autism spectrum disorder," "autistic disorder," or "autism" refer to a class of neurodevelopmental disorders marked by "qualitative impairments in the development of social and communication skills, often accompanied by stereotyped and restricted patterns of interests and behavior." Landa, Res. Ex. EE, at 138. Symptoms of the onset of the disorder must occur before the child is three years old. *Id.*

Parents of children diagnosed with ASD often report that they first became concerned about some aspect of their child's behavior at about 18 months of age. Landa, Res. Ex. EE, at 139. However, concerns may arise at other points during the first year of life. *Id.* Eighty percent of parents of children subsequently diagnosed with ASD have observed abnormal behaviors in their child by two years of age, typically involving speech and language development and, less frequently, involving social, play, sensory, motor, or medical problems, or problems relating to eating, sleeping, and behavior. *Id.* at 139-40.

Regression or loss of skills is reported in a substantial minority of children with ASD. Loss of language skills or vocabulary is often observed in these children, although social skills loss is seen as well. Lord, Res. Ex. R, at 936; Rogers, Res. Ex. S, at 141 (loss of eye contact described in 90% of children with regression as well as loss of social interests). More than 90% of children with regression had only single-word speech prior to the loss of vocabulary; only 3% had developed phrase speech prior to their regression. Rogers, Res. Ex. S, at 141. C.L. had only single words, and not many of them, at the time of her regression.

Rogers described three different patterns of autism onset: (1) developmental concerns present from birth, with parents reporting atypical behaviors across the first year of life; (2) early milestone achievement followed by a developmental plateau, where the children fail to develop the social and communicative skills that differentiate children with ASD from those with typical development; and (3) a clear developmental loss of previously-demonstrated skills—a regression. Rogers, Res. Ex. S at 140. Further study of children who present with regression has demonstrated that "a very

[79] This subsection discusses the diagnostic criteria in effect at the time of C.L.'s initial diagnosis, the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision ["DSM-IV-TR"]. The DSM-IV-TR has since been replaced by the DSM-5. The symptoms recognized by the medical community at large as those of an ASD have not changed, but the criteria for diagnosis have been refined, and the distinctions drawn in the DSM-IV among the diagnoses of autistic disorder, PDD-NOS, and Asperger's disorder have been eliminated. *See* American Psychiatric Association*, Autism Spectrum Disorder Fact Sheet*, http://www.dsm5.org/Documents/Autism%20Spectrum%20Disorder%20Fact%20Sheet.pdf (highlighting the differences between DSM-IV and DSM-V) (last visited July 15, 2015).

small proportion of children with autism exhibit a period of truly typical ("normal") development; only approximately 15% of children who later lose skills appear to have had a full repertoire of expected skills in their infancy." *Id*. Good recovery after regression is rare, and children with regression develop similarly to children with autism but no regression. *Id*., p. 141. This pattern of children with a clear loss of skills, but whose prior development was not entirely normal, appears to describe C.L.'s developmental trajectory. There were early behavioral concerns significant enough that the parents raised them in several pediatric appointments, and her language was clearly not normal prior to the influenza vaccination and regression.

b. Testing.

C.L. has consistently scored in the autistic range on several different diagnostic tests, and received the diagnosis from several different specialists in this field. Pet. Ex. 4, pp. 50-71; Pet. Ex. 5, pp. 31-33, 70-74, 78; Pet. Ex. 9, pp. 231-37; Pet. Ex. 17. More recent school system testing has confirmed that the diagnosis has persisted in spite of all the therapies employed to treat C.L. Pet. Ex. 5, pp. 201-14.

c. Opinions Regarding ASD Diagnosis.

Doctor Shafrir's testimony was inconsistent regarding his opinion about C.L.'s ASD diagnosis. He first testified that C.L. has autism. Tr. at 214. When asked later if she had autism, he equivocated, saying that she has "autistic regression." Tr. at 215.

Doctor Janousek diagnosed C.L. with an encephalopathy but, according to petitioners, he thought she had an ASD, albeit one with a more pronounced regression than he thought was usual. It is unclear what he considered, besides petitioners' reports, in determining that the level of regression was unusual, as the descriptions of C.L.'s language and social skills loss in her medical and therapy records do not reflect a profound regression.

In contrast, Dr. Dalmau described C.L.'s regression as part of "the natural course of the autism." Res. Ex. J at 3. C.L.'s pattern of development included the failure to begin to put words together in phrases before the regression,[80] followed by a loss of language and social skills and a relatively poor recovery. Moreover, C.L. has a number of other risk factors that have been associated with the diagnosis of ASD: twin birth, prematurity, dysmorphic features, and a twin with a diagnosis on the autism spectrum.[81] *See* Res. Ex. J at 3 (Dr. Dalmau's expert report); *Dwyer*, 2010 WL 892250, at *34-35,

[80] Doctor Shafrir conceded that C.L. was developmentally delayed before she received the influenza vaccine, but thought that the delays were mild. Tr. at 150. However, it is not the degree of impairment that is significant; it is the fact that C.L. was displaying a delay in language prior to losing language.

[81] C.L.'s twin's trajectory differed from C.L.'s in that the twin showed delayed development earlier, but later became higher functioning than C.L. Pet. Exs. 7, pp. 8, 51; 9, pp. 191, 233; Tr. at 107.

44. He thought the ASD diagnosis accounted for all of C.L.'s symptoms. Tr. at 373, 376-77; *see also* Tr. at 473-74 (Dr. Gorman agreed).

2. Autoimmune Encephalopathy or Encephalitis.

Petitioners' causation theory rests on the conclusion that C.L. experienced autoimmune encephalitis, as exemplified by a sudden regression involving loss of language, eye contact, and social skills. No one contests the fact of the regression; the parties differ in their assertions regarding when and how fast the regression occurred, as well as about its cause. Petitioners claim that the symptoms leading to C.L.'s ASD diagnosis are evidence of an autoimmune encephalopathy. Pet. Exs. 10, 11, 16, 23 (expert reports of Drs. Frye and Shafrir).

a. Definitions and Characteristics of Autoimmune Encephalitis.

Not surprisingly, given his expertise in autoimmune encephalitis, Dr. Dalmau provided a great deal of the background information about encephalopathy, encephalitis and, in particular, autoimmune encephalitis. The terms encephalopathy and encephalitis were used interchangeably throughout the record in this case. Tr. at 323. Doctor Dalmau explained that encephalopathy is the broader or umbrella term and encephalitis is one form of encephalopathy. *Id*. He defined encephalopathy as a "dysfunction of the brain" and added that "any dysfunction is an encephalopathy." Tr. at 316; *see also* DORLAND'S at 622. Encephalitis is a brain dysfunction associated with inflammation. Tr. at 316-17; *see also* DORLAND'S at 619. By definition, autoimmune disorders involve inflammatory reactions that produce antibodies. Tr. at 317, 323. Inflammation of the brain can be demonstrated by the presence of inflammatory cells in cerebral spinal fluid or the brain or based on inflammation observed on MRI. Tr. at 319.

Clinical symptoms associated with autoimmune encephalopathies vary based on the antibodies involved. Tr. at 316; *see, e.g.*, Hacohen, Pet. Ex. 23a at 752 (showing symptom data for NMDAR and VGKC encephalitis). However, there are core general symptoms that most autoimmune encephalopathies share. Tr. at 316. In general, the presentation is subacute, which Dr. Dalmau described as falling between an acute encephalopathy (where symptoms evolve in hours or days) and a chronic encephalopathy (where symptoms continue for months). Tr. at 316-17; *see, e.g.,* Dalmau, Ex. 16b, at 63-64 (NMDAR encephalitis patients develop psychiatric symptoms within a few days).

Doctor Dalmau observed that the presentation of autoimmune encephalitis is "not subtle." Tr. at 322; *see, e.g*., Dalmau, Ex. 16b at 64. Children have symptoms that raise the suspicion of a viral disorder or viral encephalitis. Tr. at 322. They frequently present with seizures, headache and, about 50% of the time, with fever. Tr. at 317; *see, e.g.*, Hacohen, Pet. Ex. 23a at 752. Most will have an abnormal EEG. Tr. at 317 (referencing Hacohen, Pet. Ex. 23a at 752 (100% of the VGKC complex encephalitis

patients had abnormalities on EEG)). In autoimmune limbic encephalitis,[82] MRIs often show abnormalities. Tr. at 318. Doctor Dalmau explained the medical literature indicates that, with or without seizures, the patient's "EEG is almost always abnormal in [cases of these autoimmune] encephalopathies." *Id.*; *see, e.g.*, Hacohen, Pet. Ex. 23a at 752. In most cases of autoimmune encephalitis, there will be evidence of brain inflammation on spinal tap, MRI, or autopsy of the brain. Tr. at 319.

b. C.L.'s Symptoms.

Doctor Frye described C.L.'s symptoms after the influenza vaccination as encompassing sleeping and feeding difficulties within a month of the vaccination. He asserted that she lost words and stopped babbling, waving, and pointing at objects. Pet. Ex. 10 at 1. C.L.'s parents testified about a fever after vaccination that was treated with Advil. Tr. at 23. They did not report she was acutely ill. In December 2005, about a month after the influenza vaccination, they took her to her pediatrician for sleeping and feeding difficulties. Pet. Ex. 3, p. 42. There was no indication in the records that C.L. had been ill in the intervening month, and Dr. Snook did not remark that she was ill appearing.

C.L. did not experience her first seizure until nearly eight years after her vaccination. Around the time of the seizure, she was being treated with steroid Solu-Medrol every two weeks, according to the record of her treating physician, Dr. Chadwick. Pet. Ex. 22, p. 1. The Mayo Clinic's records indicate C.L.'s last steroid infusion before her seizures was on March 2, 2013, and her next treatment after her seizures was on July 17, 2013. Pet. Ex. 9, pp. 247, 262. Steroid treatment is noted to prevent seizures in those with autoimmune encephalopathies, according to Dr. Shafrir. Tr. at 514-17.

c. Opinions Regarding Diagnosis.

Some of C.L.'s treating physicians also attributed her ASD symptoms to an autoimmune encephalopathy, based at least in part on her "sudden" regression,[83]

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[82] Limbic encephalitis can be defined as "an inflammatory brain disorder of paraneoplastic or non-paraneoplastic origin . . . causing memory deficits, temporal lobe seizures or affective disturbances." E. Haberlandt et al., *Limbic encephalitis in children and adolescents*, ARCH. DIS. CHILD., 96 (2): 186-191 (2011), filed as Res. Ex. C [hereinafter "Haberlandt, Res. Ex. C"], at 186. Limbic encephalitis can be, but does not have to be, caused by a tumor or its metastases. *Id.*; *see also* DORLAND'S at 1400 (defining "paraneoplastic" as "pertaining to changes produced in tissue remote from a tumor or its metastases"). It can also be caused by antibodies produced without a tumor. Haberlandt, Res. Ex. C at 189.

[83] The records from Drs. Renaud, McKeon, and Clardy do not reflect that any of these physicians examined C.L.'s medical, school, and therapy records from the period between August 2005 and the two mid-February 2006 calls to Dr. Snook's practice, seeking a referral to Dr. Janousek. Nor does it appear that they reviewed any of the medical histories provided to school personnel, therapists, and physicians closer in time to the events between the vaccination and the referral request. Thus, characterizations of

accompanied by the presence of VGKC antibodies. Doctor Renaud first made a diagnosis of possible autoimmune encephalitis after C.L. tested positive for VGKC antibodies. She later changed that diagnosis to "probable autoimmune encephalitis" when immunotherapy was somewhat effective in reducing the level of antibodies. However, when C.L.'s parents brought her back to Dr. Renaud in 2011, she did not return to her earlier diagnosis of autoimmune encephalitis, noting instead only that C.L. was positive for VGKC antibodies. Nevertheless, she continued to treat C.L. with steroids, a treatment predicated on the notion that the antibodies were contributing to C.L.'s symptoms.

Doctor Shafrir testified that C.L. suffered autoimmune synaptic encephalitis.[84] Tr. at 207. Later, he explained that C.L. did not have acute encephalitis, or encephalitis, but rather something that he characterized as a "subacute encephalopathy." Tr. at 269. He maintained that C.L. has a "probable autoimmune encephalopathy" under the Zuliani criteria[85] based on her clinical symptoms, VGKC antibodies, and response to immunotherapy. Tr. at 277-81, 514. He did not point to any specific symptoms she displayed after the November 25, 2005 vaccination as evidence that she had an encephalopathy, other than her regression. He opined that C.L. responded favorably to treatment for an autoimmune encephalopathy as evidence that autoimmune encephalopathy is the correct diagnosis. Tr. at 187-90.

In early 2013, after an increase in C.L.'s steroid dose, C.L.'s parents and Dr. Renaud noted improvements in her condition. Pet. Ex. 9, pp. 119, 127, 154, 221, 247. In February 2014, Dr. Renaud noted that C.L. continued to gain new skills. *Id.*, p. 266. However, C.L.'s January 2013 IEP found that, while C.L.'s eye contact and joint attention had improved, her communication skills were poor, she did not engage in age appropriate play, lacked the skills to interact with her peers, preferred repetitive and self-stimulatory behavior, exhibited a low frustration tolerance, and sought sensory input by putting things in her mouth, and smelling and touching them. Pet Ex. 5, p. 206. In June 2013, Dr. Chadwick noted that C.L. was experiencing "anger, aggression, and agitation issues, though this has gotten better of late." *Id.* at 7.

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the regression as sudden and occurring within two weeks to a month after the vaccination by these physicians must be based on parental reports made years after the events in question.

[84] Dr. Dalmau explained that VGKC complex antibody encephalitis is not synaptic. Tr. at 309-11.

[85] *See* L. Zuliani, et al., *Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition*, J. NEUROL. NEUROSURG. PSYCHIATRY 83: 638-45 (2012), filed as Pet. Ex. 23n [hereinafter "Zuliani, Pet. Ex. 23n"]. Initially, Dr. Shafrir maintained that C.L. had "a definite autoimmune encephalopathy" based on the Zuliani criteria. Pet. Ex. 23 at 11 (Dr. Shafrir's second expert report, citing Zuliani, Pet. Ex 23n). After Dr. Dalmau testified that the Zuliani criteria covered only neuronal surface antibodies and that the VGKC antibodies present in C.L. were not neuronal surface antibodies (Tr. at 356-62), Dr. Shafrir retreated from this position (Tr. at 513-14).

Doctor Dalmau testified that C.L.'s clinical condition is distinct from other patients with autoimmune encephalopathy and encephalitis that he has seen personally or who are described in the medical literature. Tr. at 301. According to Dr. Dalmau, children with an autoimmune encephalopathy or encephalitis share a core group of symptoms with a subacute presentation, including: seizures, headache, and fever. Tr. at 317. An EEG performed on a patient with encephalopathy is almost always abnormal. Tr. at 318 (citing Hacohen, Pet. Ex. 23a). Inflammation typically accompanies autoimmune encephalopathy, which can be found by performing a spinal tap, a biopsy, or an MRI. Tr. at 319. Doctor Dalmau noted that C.L.'s EEGs and MRI were normal. Tr. at 322. He also pointed out that, despite having being seen by physicians (Drs. Snook and Janousek) within a few weeks or months after her November 25, 2005 influenza vaccination, none of C.L.'s physicians ordered a spinal tap. He considered this evidence that her physicians did not see any evidence that C.L. had a subacute encephalopathy. *Id.*

Further, Dr. Dalmau explained that it is not clear that C.L. has responded favorably to the immunotherapy treatments. Rather, he attributed the improvements noted by her parents and Dr. Renaud to her ongoing ABA therapy.[86] Tr. at 339, 437. Doctor Gorman also testified that ABA therapy has been the most beneficial therapy C.L. received. Tr. at 490. He noted that there have been improvements reported throughout the period after her initial diagnosis, and attributed her improvements to her increased maturity and intensive ABA therapy.

Although the filed photos and videos show C.L. has learned some new skills and has some improvements in behavior, it is very difficult to draw any causal conclusions from the videos provided. *See* Pet. Exs. 29-35.[87] None of the filed photographs were from the months immediately following C.L.'s influenza vaccination. The videos are similarly unhelpful. The video that most closely predates C.L.'s November 2005 vaccination was from April 26, 2005 (Pet. Ex. 33) and the video most proximate to the time after the vaccination was from September 2007 (Pet. Ex. 34).

D. Factual Findings.

Based on the contemporaneous medical, school, and therapy records, the early histories provided by petitioners, the observations and testing performed resulting in an autism diagnosis, the opinions of treating providers and the experts, and the evidence in the medical literature, I make the following factual findings:

[86] ABA therapy "is the recommended and clinical standard (evidence based) for treatment of children and adolescents with autism." Pet. Ex. 13, p. 12.

[87] Petitioners' Exs. 31-35 were filed on February 22, 2014 (ECF Docket No. 79); however, the docket text and event code did not specifically identify this filing as containing exhibits. Instead, the filing is identified as a "Status Report."

1. C.L. had symptoms of delayed development and ASD prior to the administration of the November 25, 2005 influenza vaccination. These included language delay, behavioral difficulties (including temper tantrums and irritability), being a "picky eater," and mild gross motor delay.

2. Evaluations after the vaccination showed a progression of her speech, sleep, eating, and behavior problems, the continuation of some of these older problems, and the onset of new problems, including loss of eye contact and social skills, as well as some loss of vocabulary. However, the histories provided at these early evaluations did not pinpoint the influenza vaccination as the turning point.[88] Rather, they variously referred to concerns developing when C.L. was two, two and one-half, and 26-27 months of age. The most frequently referenced time periods were when the initial speech delay was noted at the two year well-child visit, and when she was two and one-half, which was in late January 2006. Petitioners also used the onset of feeding problems to date when signs of regression developed and placed it at around two years of age. Pet. Ex. 14, p. 13.

3. Contrary to the later assertions that the onset of her regression was sudden, occurring within two weeks to a month after the influenza vaccination, I find that the onset was more gradual. C.L. saw several therapists and her pediatrician in December 2005-January 2006. Yet, her parents did not seek a referral to a neurologist until February 13-14, 2006, when they made two telephone calls to Dr. Snook asking to see Dr. Janousek. As Dr. Shafrir testified, they may have been in denial because C.L.'s twin had already been diagnosed with an ASD. Tr. at 147-48. But, given the timing of the telephone requests, which closely followed an OT evaluation that revealed "substantial delays in sensory processing skills, oral[-]motor strength and coordination and decreased muscle tone" (Pet. Ex. 14, p. 12), plus the problems mentioned at the February 9, 2006 speech session,[89] it is more likely that these two events constituted

[88] For example, at the December 19, 2005 St. Francis evaluation that Dr. Shafrir relied upon to show a significant regression after the vaccination (Tr. at 147-52), C.L.'s parents reported that they became concerned six months previously about her speech and language development as C.L. was not gaining new words, was unable to combine words, and most of her sounds came out as "da-da." Pet. Ex. 14, p. 2 (emphasis added). Mrs. Lehner attributed this report to a rounding error and indicated that her first concerns regarding C.L.'s speech were in August 2005 at her two year check-up. Tr. 26-27. Apparently Dr. Snook's concern about C.L.'s gross motor development at 15 months of age was not specifically mentioned, but Mrs. Lehner reported that C.L. "met most of her developmental milestones late" and exhibited "signs of regression in terms of her communication development at the same time that she started having the feeding difficulties around 2 years of age." Pet. Ex. 14, p. 13.

[89] Mrs. Lehner reported that C.L. was "doing more lining up of items at home." Pet. Ex. 14, p. 17 (emphasis added). C.L. made eye contact with and smiled at the therapist during a game, and used the words "bubble" and "quack." *Id.* During her feeding therapy session, she made poor eye contact. *Id.* Her response to bath time had improved, according to Mrs. Lehner's report, but C.L. had decreased tolerance for changes in her routine. *Id.*, p. 18. She tolerated only 15 minutes of the feeding therapy that day. *Id*.

the" tipping point" after months of a gradual loss of words, eye contact, and other social skills, as well as the emergence of new autism symptoms.

4. C.L. did not experience the symptoms commonly associated with autoimmune encephalitis, including seizures, headache, and fever.[90] Nor did she have an abnormal EEG, commonly present in children with an autoimmune encephalopathy or encephalitis. Her MRI did not show any evidence of inflammation.

5. The diagnosis of ASD, accompanied by a regression or loss of skills, fully accounts for all the symptoms C.L. displayed leading up to her formal diagnosis in June 2006. The parties filed a number of medical journal articles describing regression in autism, and C.L.'s losses, age, and subsequent clinical course of gradual improvements with "good and bad days" fit squarely within the clinical course of ASD.

6. The seizure disorder diagnosis is fully compatible with the ASD diagnosis. It is much less compatible with autoimmune encephalitis. Although seizures are a frequent symptom of autoimmune encephalitis, they occur during the initial presentation, according to Dr. Dalmau and the medical literature submitted. Doctor Shafrir noted that immunotherapy, including steroids, were used to treat seizures that were possibly or probably autoimmune in nature. However, C.L.'s seizures abated only with antiepileptic drugs.

7. The evidence regarding response to immunotherapy treatment is the most amorphous, but I conclude that the objective evidence in the form of school and test records (the same type of evidence of clinical improvement that Drs. Clardy and McKeon suggested relying upon before continuing with treatment (Ex. 9, pp. 191-94)), demonstrates that any response was minimal at best. In contrast to the responders to immunotherapy cited in the medical literature filed, C.L.'s behavioral improvements were minimal, and best explained by her age and ABA therapy. The immunotherapy did not change her diagnosis, cognitive functioning, or speech, and sometimes failed to affect even her antibody levels. Her antibody levels were not a good correlate for improvement, which, in itself is evidence that the antibodies were unrelated to her behavioral and cognitive problems. C.L.'s antibodies never reached the purportedly normal level used by the Mayo Clinic.

Because I conclude that C.L. did not have autoimmune encephalitis after her allegedly causal vaccination, conducting a causation analysis under the *Althen* and *Pafford* criteria may not be necessary. However, the fact that ASD is the correct

[90] Although petitioners testified that C.L. experienced a few days of fever after her vaccination, there is no documentation of this and it was never mentioned in subsequent medical records. Even if she did have a transient fever after vaccination, the type of fever and other symptoms suggestive of encephalitis are, in Dr. Dalmau's words, "not subtle." Such symptoms would prompt parents, particularly those who took their child to the pediatrician for colds and ear infections, to seek medical treatment.

diagnosis does not entirely foreclose the theory advanced by petitioners, in that autistic symptoms may be caused, in rare cases, by other conditions. *See Snyder,* 2009 WL 332044, at *45, nn. 124-26 (discussing evidence that prenatal exposures to drugs or viruses may result in autistic-like symptoms in children and listing some case reports of autism symptoms resulting from herpes or cytomegalovirus infections after birth and even in adulthood). I thus continue with the *Althen* analysis.

V. Causation Analysis.

A. Summary of Causation Determination.

To some extent, Dr. Gorman's changed opinion provides, in a microcosm, a summary of what happened in the scientific exploration of autoimmune encephalitis and, in particular, the role of voltage-gated potassium channel antibodies in encephalitis. Had this case been tried several years earlier, my causation determination might well have been different—and wrong. Science and medicine are not immutable, and this case demonstrates how additional research may prove that a much desired hypothesis, one that provides some hope of improvement by treating devastating neurological impairments with immunotherapy, is simply wrong. And, in the weighing of contrary opinions on diagnosis and causation, this case also illustrates the importance of expert qualifications, research, and clinical experience in selecting an expert. This was not a battle of the experts; it was a rout.

The clear weight of the evidence is that the VGKC antibodies present in C.L. do not cause autoimmune encephalitis. There is no reliable evidence that such antibodies are triggered or caused by influenza or influenza vaccinations. Finally, C.L. had symptoms of ASD prior to the allegedly causal vaccination, making it even less likely that the loss of some language and social skills, characterized by Dr. Shafrir as an autistic regression, that occurred after this vaccination were caused by it.

B. Applying *Althen*.

1. *Althen* Prong One.

a. Legal Standards.

Althen requires that a petitioner in an off-Table causation case present a reliable medical theory by explaining how the vaccine administered can cause the injury in question. *Althen*, 418 F.3d at 1278. This first prong of *Althen's* three part causation test has also been characterized as the equivalent of the "Can it cause?" inquiry used in toxic tort litigation. *See Pafford*, 2004 WL 1717359, at *4.

The medical theory must be a reputable one, although it need only be "legally probable, not medically or scientifically certain." *Knudsen,* 35 F.3d at 548-49. The

Supreme Court's opinion in *Daubert* likewise requires that courts determine expert opinions to be reliable before they may be considered as evidence. "In short, the requirement that an expert's testimony pertain to 'scientific knowledge' establishes a standard of evidentiary reliability." 509 U.S. at 590 (footnote omitted). The Federal Circuit has stated that a "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly,* 592 F.3d at 1324.

b. The Theory.

Petitioners changed their theory as the hearing progressed. After first contending that the VGKC antibodies present in C.L. were pathogenic themselves, Dr. Shafrir waffled. At the conclusion of the hearing, he conceded that only the CASPR2, LGI1, and Contactin-2 antibodies in the VGKC complex (antibodies not present in C.L.'s serum sample) had been shown to be pathogenic:

> [N]ext is the fact that I would definitely change my mind about the pathogenicity. I think that Dr. Dalmau made a very nice statement of what is pathogenic, which is only three known antibodies in neurological disorders that have to meet like [sic] Witebsky's criteria.[91]

Tr. at 514. Nevertheless, he continued to assert that "it is definitely very likely, I have to say more than 50 percent likely, that there was something in [the] antibodies that [C.L.] has, it is a marker of autoimmune process that is taking place." Tr. at 518. Although he conceded that he could be wrong, he did not believe that he was,

> because we have proof that finding the antibodies lead [sic] to treatment, but lead [sic] to a dramatic improvement in the patient, both in epilepsy patients and in autistic patients. But supposed that we would find not, there is something in it, we will find one of these other antibodies or other target protein of those antibodies and we will find that some of them is [sic] really involved with autism. . . . [C.L.] will be the first patient every [sic] described to have this problem. So, we don't have any way that we can base our—my opinion on previous testing that is going like this. So, my opinion is based on the fact that . . . some influenza vaccines have the capacity to produce autoimmune disease, that [C.L.] has an antibody with very high levels, not in the typical levels that are found in the general population that is leading to a productive treatment, which means that it is a very substantial support to the presence of an autoimmune process and that the treatment helped her. So, I think that this is enough for me to say

[91] Doctor Shafrir was referring to E. Witebsky, et al., *Chronic Thyroiditis and Autoimmunization,* J.A.M.A. 164(13): 1439-47 (1957), filed as Res. Ex. V. Doctor Dalmau discussed this article in his initial expert report, citing the article as the basis for the "accepted criteria by which to define an antibody as pathogenic (causing a disorder)," and which were "modified as science progressed." Res. Ex. J at 9.

> that we had a mechanism and we had a mechanism that can explain cause and effect in this particular case. And this is why I think, I don't change my mind based on it, and I think that Dr. Dalmau's testimony helped me to make it much clearer, helped me to remove a lot of errors or misconceptions that they had in the initial way that I presented it.

Tr. at 519-20. In referring to epilepsy, Dr. Shafrir referenced the "Lilleker" article (Tr. at 514-17), referring to Lilleker, Pet. Ex. 23d.[92] In referring to proof that treating autoantibodies resulted in improvement in autistic patients, he may have been referring to C.L. herself or to a paper he cited in his December 11, 2013 expert report, O. Scott, et al., *Anti*-N-*Methyl-D-Aspartate (NMDA) Receptor Encephalitis: An Unusual Cause of Autistic Regression in a Toddle*r, J. CHILD NEUROL., (Epub) 1-4 (Oct. 3, 2013), filed as Pet. Ex. 23e.

It remains somewhat unclear whether Dr. Shafrir now believes that the type of VGKC antibodies C.L. has are pathogenic, or merely a marker for some autoimmune process, but it is clear that he thinks the presence of the antibodies demonstrates that C.L. had autoimmune encephalitis and that the influenza vaccine is responsible for the antibodies and thus the encephalitis. It is equally clear that he thinks C.L.'s autism diagnosis is the result of this purported encephalitis.

The theory advanced has two parts. First, petitioners contend that the VGKC antibodies are pathogenic, or a marker of autoimmune neurologic disease, and can cause symptoms like those C.L. displayed. Pet. Pre-hearing Memorandum, filed Jan. 7, 2014, at 11-13. Second, petitioners allege these antibodies can be caused by an autoimmune response to an influenza vaccination. *Id.* I note that at the hearing, Dr. Shafrir testified that even if C.L. had never been tested for the antibodies, he would still opine, based on the timing of the vaccination and her declining scores on language testing after the vaccination, that the influenza vaccination was responsible for C.L.'s regression. Tr. at 214-16. However, he did not directly argue this theory.

(1) Are the Antibodies Pathogenic or a Biomarker?

Petitioners' theory of causation crumbled because the first cornerstone of their theory—that the VGKC antibodies C.L. had are either pathogenic themselves or are markers for something else that can produce autoimmune encephalitis—was refuted by research that reflected a new and more nuanced understanding of these antibodies. Doctor Dalmau conclusively demonstrated that only certain types of the group of

[92] The Lilleker study reviewed 144 patients who developed unexplained epilepsy as adults. Six of these patients were found to have VGKC antibodies >400pM (one of whom had LGI1 antibodies and one of whom had CASPR2 antibodies). The six patients were given immunotherapy and experienced improved seizure control. Lilleker, Pet. Ex. 23d at 776.

antibodies erroneously termed VGKC antibodies are pathogenic. The history of how he came to this conclusion is illustrative.

(a) NMDAR Encephalitis.

I begin by discussing NMDAR encephalitis because it was the first autoimmune encephalopathy identified, and because Dr. Shafrir relied on several medical journal articles discussing NMDAR encephalitis for parts of his theory.

In 2005, Dr. Dalmau and other researchers discovered the first autoimmune encephalopathy. As he wrote in 2011:

> In 2005, a syndrome of memory deficits, psychiatric symptoms, decreased consciousness, and hypoventilation was reported in four young women with ovarian teratomas. Specific autoantibodies to the N-methyl D-aspartate receptor (NMDAR) were soon detected in these and eight other patients with similar neurological symptoms, seven of whom also had ovarian teratomas. During the following 3 years we identified 419 other patients with this syndrome, many of them children and young adults with or without an associated tumour. The discovery of this disorder, termed anti-NMDAR encephalitis, has changed the diagnostic approach to clinical problems as diverse as catatonia, subacute memory disturbance, seizures, abnormal movements, and limbic encephalitis. It has also led to the discovery of other autoimmune synaptic encephalitides mediated by antibodies against the AMPA receptor (AMPAR); the γ-amino-butyric acid-B receptor (GABAB-R); and leucine-rich, gliomainactivated 1 (LGI1), which is the main autoantigen of limbic encephalitis previously attributed to voltage-gated potassium channels.

Dalmau, Pet. Ex. 16b at 63. The significant level of recovery from NMDAR encephalitis with immunotherapy treatments[93] encouraged further research into autoimmune encephalopathies; voltage-gated potassium channel antibodies quickly became one of the targets for further research, testing, and treatment.

Anti-NMDAR encephalitis is probably the best studied and described of the autoimmune encephalitides. Moreover, there is more proof of the causal nature of the antibodies in this type of autoimmune encephalitis than in any other: the causal antibodies are found in the brain and "have been shown to affect the brain receptors

[93] Patients with NMDAR encephalopathies are divided into two groups: those with tumors (paraneoplastic presentations) and those without tumors. Tumor resection (if a tumor is found) and immunotherapy (corticosteroids, IVIG, and plasma exchange) as the first line of therapy and the use of rituximab and/or cyclophosphamide as the second line of therapy, resulted in recovery or only mild sequelae in about 75% of patients, with those who had tumors removed making the greatest recovery. Dalmau, Pet. Ex. 16b at 63.

and cause a decrease in their function." Res. Ex. J, at 4. Doctor Dalmau emphasized that this "direct link between the antibodies and a well-described specific syndrome" was shown to produce "the same disease in all subjects."[94] *Id*.

(b) VGKC Encephalitis.

Given that VGKC antibodies had already been identified and a test developed to measure them,[95] these antibodies were initially considered as another possible cause of autoimmune encephalopathies, because problems with the potassium channels in neuronal cells could be a reason for encephalopathic symptoms.

For many years, patients with a very wide variety of symptoms were reported in the medical literature as having "positive" VGKC antibodies. Res. Ex. J at 8, 10. However, the initial optimism about a causal role for VGKC antibodies was tempered because of the wide variation in symptoms reported. Doctor Dalmau reported that it was nonsensical to attribute so many symptoms to one cause. *Id.* at 8. Moreover, the testing method for VGKC antibodies could not identify a specific target protein and these antibodies were found only in serum, not in cerebral spinal fluid. *Id*. This led researchers, including Dr. Dalmau, to conclude that the VGKC antibodies did not play a direct role in any of these disorders. *Id.* (citing J. Honnorat, *Is Autoimmune Limbic Encephalitis a Channelopathy?*, LANCET NEUROL., 9: 753-55 (2010), filed as Res. Ex. O [hereinafter "Honnorat, Res. Ex. O"], at 754 ("antibodies against voltage-gated potassium channels were also found in a broad spectrum of immunological disorders and therefore these antibodies probably did not have a direct role in all of these syndromes")).

Contrary to Dr. Frye's opinion, Pet. Ex. 10 at 2 (citing the 2008 Tan study, Pet. Ex. 10i) regarding VGKC antibodies as markers for several neurological problems as the result of their "antigen-specific crosslinking" (*id.*), the current scientific understanding is that these antibodies do not target the potassium channel itself. Pet. Ex. J at 7-8; Tr. at 301-03. Thus, according to Dr. Dalmau, a positive VGKC antibody test does not reflect that antibodies against the potassium channel are present.[96] Tr. at 303.

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[94] The article about the California encephalitis project (Dr. Dalmau was a co-author and the person who conducted the antibody testing in the study) noted specific differences in clinical presentation in NMDAR encephalitis from those in other types of encephalitis. Seizures were more common; intubation rates were significantly higher; and movement disorders and language dysfunction were more likely to occur, with language dysfunction occurring about twice as often as in cases with viral causes. Gable, Pet. Ex. 16a at 899-900. Autonomic instability occurred in nearly half the NMDAR cases and psychiatric symptoms (including psychosis) occurred in two-thirds of the NMDAR cases. *Id.* at 901-02.

[95] Doctor Dalmau testified that the term voltage-gated potassium channel antibodies was initially used beginning in about 1995 to describe antibodies found using radioimmunoassay (RIA). Tr. at 301-02; Res. Ex. J at 7. Specific proteins are not identified by this test. Tr. at 303; Res. Ex. J. at 7-8.

[96] Doctor Dalmau had other problems with the Mayo Clinic testing on C.L. He noted that the Mayo laboratory website stated that VGKC antibody testing would not be performed on children under age 18

However, within this large group of VGKC-positive patients, two distinct subsets of patients were identified, patients with limbic encephalitis alone and those with neuromyotonia and limbic encephalitis (Morvan's syndrome). Res. Ex. J at 8. This led researchers to believe these patients had an autoimmune disorder, but not one related to the entire complex of VGKC antibodies. *Id.* In 2010, Dr. Dalmau and his colleagues identified that the patients suffering from limbic encephalitis had antibodies directed against the LGI1 protein within the larger VGKC complex. *Id.* (citing M. Lai, et al., *Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series*, LANCET NEUROL., 9: 776-85 (2010), filed as Res. Ex. G [hereinafter "Lai, Res. Ex. G"]). In 2011, Dr. Dalmau and his colleagues identified a group of patients suffering from Morvan's syndrome. However, all of the Morvan's syndrome patients had antibodies directed against the specific protein CASPR2, not VGKC. *Id.* (citing Lancaster, Res. Ex. Q). As Dr. Dalmau explained in his initial expert report, "these patients did have an autoimmune disorder—it just was not related to VGKC." *Id.*

While the relevant medical community may once have thought—perhaps even as late as January 2011, when Dr. Frye authored his opinion—that VGKC antibodies in general were disease-causing, based on the more recent research discussed by Dr. Dalmau only the antibodies against three specific proteins in that complex appear to cause autoimmune encephalopathies. As Dr. Dalmau observed, C.L.'s "family and physicians were hoping to find a treatable cause of her developmental delay" when she was referred to Dr. Renaud at the Mayo Clinic in 2008. Res. Ex. J at 3. When testing for VGKC antibodies was positive, they made "an automatic assumption of a relationship" (*id*.), but the later developments and discoveries discussed above cast considerable doubt on the causality assumption. The only "VGKC complex" antibodies for which causality of autoimmune encephalitis has been demonstrated are those against the proteins LGI1 or CASPR2. *See generally* Tr. at 333-36. C.L. did not have either of these proteins in her VGKC antibodies.[97] Pet. Ex. 21, p. 1. The type of VGKC

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because normal values had not yet been established for the pediatric population. Res. Ex. J at 10. He commented:

> Neither Dr. Renaud nor other doctors treating [C.L.], nor the other expert witnesses, make note of the experimental nature of the VGKC testing and that the Mayo Clinic Lab itself does not even know what the normal range of values in children is. So, [C.L.] was diagnosed and treated for a disease based on the results of an experimental research test for which the normal results in children are not known.

Res. Ex. J at 10. Doctor Gorman expressed similar concerns, grounded in his own experiences with the Mayo Clinic testing. Tr. at 468-72. He was particularly concerned that the VGKC antibody testing performed by the clinic did not include testing for specific autoantibodies such as CASPR2 or LGI1.

[97] According to Dr. Vincent, C.L. also tested negative for antibodies against the protein Contactin-2. Pet. Ex. 21, p. 1. Antibodies against the protein Contactin-2 have been implicated in a minority of patients with encephalitis. E. Lancaster & J. Dalmau, *Neuronal autoantigens—pathogenesis, associated*

antibodies for which C.L. was positive were those "with affinity to Kv 1.1, 1.2, and 1.6 type channels." Pet. Ex. 9, p. 78.

(c) Conclusion Regarding Significance of Antibodies.

Notwithstanding Dr. Shafrir's opinion, there is no reliable evidence that C.L.'s specific antibodies are pathogenic or even markers for disease. Doctor Dalmau's vastly greater expertise in this area of medicine provides a firm foundation for his opinions that VGKC antibodies are associated in the literature with too many conditions to be meaningful as a biomarker for disease. In contrast, Dr. Shafrir's opinions are wishful thinking premised on unverified and unsupported assumptions. Doctor Dalmau's testimony that VGKC antibodies have never been found to cause any neurological dysfunction was effectively unrebutted. Tr. at 412. There is no evidence that heightened levels of VGKC antibodies are indicative of any disease at all, unless they are associated with the specific proteins, LGI1 or CASPR2.[98] Tr. at 416-17; *see also* Pet. Ex. 21, p. 1.

Petitioners also failed to produce preponderant reliable evidence that VGKC antibodies are biomarkers of autoimmune encephalopathy or any other disease. Dr. Frye's report was written in 2011, around the time Dr. Dalmau and other research scientists demonstrated that only certain types of the group of antibodies erroneously termed VGKC antibodies are pathogenic. Accordingly, Dr. Frye's report is outdated and therefore unreliable. Doctor Shafrir lacks the necessary experience to rebut Dr. Dalmau's testimony on VGKC antibodies. He has never treated a patient with positive VGKC antibodies. Tr. at 208. Additionally, while he purports to be an expert on how "antibodies can cause autoimmune encephalopathy" (Tr. at 217), he has no formal training in immunology, nor does he publish in the field of immunology, or in the area of antibodies and autoimmune encephalopathy.

Finally, while Dr. Vincent is clearly qualified to opine regarding C.L.'s VGKC antibodies, she essentially conceded that only VGKC complex antibodies against the specific proteins LGI1, CASPR2, and Contactin-2 are biomarkers or causal of disease, and that C.L. does not possess these specific antibodies. Pet. Ex. 21, pp. 1-2. While Dr. Vincent believed that "high levels of VGKC-antibodies generally indicate the presence of a disease that can be treated with immunotherapies with considerable hope of improvement" (*id.*, p. 2), this statement of belief and hope is not tantamount to reliable evidence that VGKC antibodies in general are pathogenic. Other evidence demonstrates that these antibodies have been found in individuals with no neurological

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disorders and antibody testing, J. NAT. REV. NEUROL., 8: 380-90 (2012), filed as Res. Ex. BB [hereinafter "Lancaster & Dalmau, Res. Ex. BB"], at 383. "However, antibodies against contactin-2 usually occur in association with those targeting LGI1 or Caspr2, and have been identified in other disorders, raising doubts about the importance of these antibodies." *Id.*

[98] C.L. does not have antibodies to these specific proteins. Pet. Ex. 21, p. 1.

impairments. J. Suleiman, et al., *Autoantibodies to neuronal antigens in children with new-onset seizures classified according to the revised ILAE organization of seizures and epilepsies,* EPILEPSIA, 54 (12): 2091-2100 (2013), filed as Res. Ex. KK [hereinafter "Suleiman, Res. Ex. KK"].

While it remains possible that some additional component of VGKC antibodies may someday be identified as pathogenic or as a biomarker for disease, the wide variety of reported symptoms, coupled with the failure to identify any other candidate components after several years of research, makes this increasingly unlikely. Petitioners' experts' opinions are contrasted, not favorably, with that of Dr. Dalmau—a world leader in this field—who cogently explained at the hearing that, based on the state of science today, there is no evidence that C.L.'s VGKC antibodies are either biomarkers or pathogenic.

(2) Can the Influenza Vaccine Cause VGKC Antibodies?

Petitioners similarly failed to present preponderant evidence that the influenza vaccination causes VGKC antibodies or VGKC-mediated autoimmune encephalopathy. Doctor Shafrir was not only unable to explain coherently his theory of causation, he also relied upon studies and reviews which focused either on a different vaccine or a different type of injury. In essence he parroted certain key phrases, such as "molecular mimicry," and pointed to journal articles without explaining how the articles supported his theory of causation in this case. The vague nature of his testimony about molecular mimicry underscored his lack of formal training or specialized experience in the fields of immunology and autoimmunity upon which the theories he put forward are based. Doctor Frye's report possessed the same problems.[99]

(a) Molecular Mimicry.

Doctor Shafrir relied on "molecular mimicry" to explain how influenza vaccine could trigger an autoimmune reaction (the production of antibodies that targeted an individual's own body, rather than the pathogen against which they are intended), but both the cases he cited and his extremely vague testimony about how this happens failed to explain the theory as it applies to influenza vaccine and brain injury.

[99] Doctor Frye also advanced a medical theory of causation with little support and outside his area of expertise. Extrapolating from medical literature indicating that autoimmune reactions such as systemic lupus erythematosus, Guillain Barré Syndrome ["GBS"], and autoimmune thrombocytopenia have been reported following various vaccinations, he opined that a particular vaccine (influenza) can cause another condition (an autoimmune encephalopathy). Pet. Ex. 10 at 2. He indicated, without providing detail regarding a specific theory, that "[v]arious theories of pathogenesis have been suggested, including molecular mimicry and bystander activation." *Id*. at 2 (citing N. Toplak & T. Avčin, *Influenza and Autoimmunity*, CONTEMP. CHALLENG. AUTOIMMUN., 1173: 619-26 (2009), filed as Pet. Ex. 10k [hereinafter "Toplak & Avčin, Pet. Ex. 10k"]; A. Balofsky, et al., *The new H1N1 and HPV vaccines and old fears*, CURR. OPIN. RHEUMATOL., 22: 431-35 (2010), filed as Pet. Ex. 10a [hereinafter "Balofsky, Pet. Ex. 10a"]).

Doctor Shafrir relied on two journal articles to establish that molecular mimicry was a plausible mechanism for causation in this case, the same two articles cited by Dr. Frye. Tr. at 164-65 (citing Balofsky, Pet. Ex. 10a; Tolpak & Avčin, Pet. Ex. 10k). These articles do not explain either molecular mimicry or how the influenza vaccination can cause VGKC antibodies to develop. The Tolpak & Avčin article discussed the 1976-77 swine flu vaccine and GBS and indicates that molecular mimicry is one possible explanation for how that particular vaccine resulted in a significant increase in cases of GBS. Tolpak & Avčin, Pet. Ex. 10k at 619, 624-25. The article does not suggest that any specific autoantibodies were involved in the immune system attack on the body's own peripheral nerves in GBS, nor is it a primer on what molecular mimicry involves in general. The authors noted that their research group demonstrated "an induction of [unspecified] autoantibodies after influenza vaccination in apparently healthy adults," with molecular mimicry as a possible explanation. *Id.* at 621. There was no indication that such autoantibodies were pathogenic or actually involved in causing GBS or any other condition. Further, despite the changes in autoantibodies found in subjects after influenza vaccination, no subject "developed clinical signs of overt autoimmune disease." *Id.* at 624. This article focused primarily on adjuvants and is thus irrelevant to the influenza vaccine C.L. received, as Dr. Shafrir conceded that the influenza vaccine administered to C.L. did not contain an adjuvant. Tr. at 229.

The Balofsky article focused on how vaccinations containing adjuvants might lead to autoimmune injury. Balofsky, Pet. Ex. 10a at 432-34. The authors did not explain molecular mimicry in general, stating only that "inactivated or recombinant antigens were also associated with autoimmunity. The most probable mechanism by which this occurs is molecular mimicry between the infectious antigen and self-antigens, as well as other mechanisms like epitope spreading, bystander activation and polyclonal activations." *Id.* at 432 (citation omitted).

Doctor Shafrir's brief foray into immunology during his testimony was limited to noting that since C.L. had received another influenza vaccination prior to the allegedly causal one on November 25, 2005, her "immune cells and lymphocytes that carry the memory of the molecular receptors for influenza antibodies – antigens, and there are – the production of antibodies will be much faster and much more intense after the second vaccination." Tr. at 166.

When cross-examined about how molecular mimicry would be involved in the production of VGKC antibodies, Dr. Shafrir was hard-pressed to formulate a coherent response:

> Q: I was a little confused on direct about your medical theory. You mentioned . . . Exhibits 10k and 10a. . . . Can you just restate for me what your medical theory – what the mechanisms you think could potentially be involved here are?

A: This is an article published by the Shoenfeld group [referring to Balofsky, Pet. Ex. 10a] that talks about the mechanism by which the influenza vaccination causes autoimmunity in general.

Q. And what is your – what were those theories or what was discussed in that article that you're adopting in this case?

A: All the discussion of the molecular mimicry and bystander activation and the role of the adjuvant.

Q: Is there adjuvant in influenza vaccine?

A: I don't think in this vaccine – in this particular one she had adjuvant. And as I said, adjuvant is not important here because it's not the first vaccination.

Tr. at 229. It was painfully obvious that Dr. Shafrir was not familiar with these two articles, despite his reliance upon them.

(b) Medical Literature.

As evidence the influenza vaccine could cause VGKC antibodies and autoimmune encephalitis, Dr. Shafrir relied on reports in medical journal articles[100] dealing with a different type of autoimmune encephalitis (the NMDAR encephalitis discussed in Section V.B.1.b.(1)(a), above), which, in a few of the reported cases, identified a bout of influenza or a different type of influenza vaccine as an antecedent event to the encephalitis. He characterized this very weak evidence as showing the presence of "a high association between the influenza vaccination preceding the onset" of NMDAR autoimmune encephalitis. Tr. at 167.

The Dalmau study mentioned three NMDAR autoimmune encephalitis patients with antecedent vaccinations (two who received the H1N1 vaccine, and one who received a common childhood vaccine), but did not draw any conclusions regarding a causal relationship. Dalmau, Pet. Ex. 16b at 66. These three patients were among the hundreds of patients Dr. Dalmau's research group has studied with anti-NMDAR[101] encephalitis. Doctor Dalmau testified that researchers commonly list antecedent events

[100] *See* Dalmau, Pet. Ex. 16b; Hung, Pet. Ex. 16c; J. Takanashi et al., *Late Delirious Behavior with 2009 H1N1 Influenza: Mild Autoimmune-Mediated Encephalitis?*, PEDIATRICS, 129 (4): e1068-71 (2012), filed as Pet. Ex. 16e [hereinafter "Takanashi, Pet. Ex. 16e"].

[101] NMDAR antibodies are not VGKC complex antibodies. Tr. at 415-16.

when the cause of a phenomenon is unknown, in the hope that with enough reports, possible causes might be identified and studied. Tr. at 325; Res. Ex. J at 4.

The Hung article was a case report of a 14 year old girl with NMDAR encephalitis who had an H1N1 vaccination one month prior to developing neurological symptoms. Hung, Pet. Ex. 16c at 362. The Takanashi study, Pet. Ex. 16e, discussed five children in Japan who developed "late-onset (>3 days after fever) and long-standing (>48 hours) delirious behavior" after suffering H1N1 influenza and who tested positive for NMDAR antibodies. Takanashi, Pet. Ex. 16e at e1068.

Doctor Shafrir also pointed to the Dhamija article, Pet. Ex. 11c, a case series authored in part by two of C.L.'s physicians,[102] reporting on 12 patients with VGKC antibodies. Of the 12 patients, only C.L., Patient 11, had received an antecedent vaccination.[103] Relying upon a case report involving C.L. to establish that a vaccine could cause C.L.'s condition is circular reasoning.

This evidence fails to demonstrate that Dr. Shafrir's theory has sufficient indicia of reliability to be persuasive. Only C.L.'s own case, reported in Dhamija, Pet. Ex. 11c at 276, involved the seasonal influenza vaccine and VGKC antibodies. The Dalmau study, Pet. Ex. 16b, and Hung case report, Pet. Ex. 16c, involved different vaccines, different antibodies, and actual encephalitis. The Takanashi article, Pet. Ex. 16e, did not involve vaccination at all, but instead looked at a single case report of an H1N1 viral infection, followed by NMDAR encephalitis. A report of vaccination prior to developing symptoms of an injury is not tantamount to establishing that the antecedent event caused the injury. Tr. at 325.

Doctor Dalmau, the lead author of Pet. Ex. 16b, testified that, based on his own experience in investigating and researching autoimmune encephalitis, vaccination does not play any role in its development. Tr. at 405 ("we don't find this association").

Reasoning by analogy, petitioners attempted to show that because NMDAR antibodies are pathogenic, VGKC antibodies are disease-causing, too. But VGKC antibodies, other than LGI1 and CASPR2, "have absolutely nothing to do with NMDA[R] antibodies." Tr. at 415-16. NMDAR antibodies and LGI1 and CASPR2 are neuronal

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[102] C.L.'s treating physician, Dr. Renaud, as well as her consulting physician, Dr. McKeon, are among the named authors of this review from the Mayo Clinic.

[103] The article identified the symptoms as "[g]lobal developmental regression, autism, [and] insomnia" with onset one to four weeks after vaccination. Dhamija, Pet. Ex. 11c at 276. The article also reported that the patient improved on IVIG, and relapsed when IVIG was stopped. While the report of timing could arguably be based on what petitioners reported to the Mayo Clinic physicians, I find the description of a global regression inaccurate and the report of improvement on IVIG and relapse when therapy stopped to be exaggerated. This causes me to question the reliability of the other matters reported in this case series.

surface antibodies. Tr. at 358, 446. The significance of the type of antibody in causing encephalitis is that neuronal surface antibodies "bind to cell surface determinants of membrane associated proteins on neuronal cells and are likely to be pathogenic." Zuliani, Pet. Ex. 23n at 638; Tr. at 306, 414. Neuronal surface antibodies react with the surface of neurons. Tr. at 358. NMDAR antibody encephalopathy is a well-defined disease, the function of the antibodies is understood, and an animal model for the disorder exists. Tr. at 334, 358; Zuliani, Pet. Ex. 23n at 3.

(c) Epidemiology.

Finally, Dr. Shafrir made the broad assertion that "the epidemiology links the receipt of [a] vaccine and actual [autoimmune] disease." Tr. at 175. Assuming, arguendo, that he is correct, he did not point to any study linking any autoimmune disease to vaccination. As evidence for this sweeping statement, Dr. Shafrir once again pointed to literature discussing vaccines and injuries distinct from the seasonal influenza vaccine and autoimmune encephalopathy at issue in this claim. He mentioned the association between the 1976-77 H1N1 (swine) influenza vaccine and GBS, as well as literature associating childhood narcolepsy following H1N1 vaccination in Scandinavian countries. Tr. at 175-76.[104] He offered no meaningful testimony explaining how these studies were relevant to establishing C.L.'s seasonal influenza vaccination caused her injury. Tr. at 175-77. C.L. did not receive the H1N1 vaccine, or suffer from either GBS or narcolepsy.

(3) Conclusions Regarding *Althen* Prong 1.

I find that Doctor Shafrir failed to muster plausible, much less preponderant and reliable evidence that the influenza vaccine cause VGKC antibodies to develop. He failed to coherently explain his theory of *how* C.L.'s vaccination caused her to develop them. Moreover, he proffered no reliable or convincing evidence that the presence of such antibodies can produce an autoimmune encephalopathy. In effect, he conceded there is no evidence the influenza vaccination leads to the development of VGKC antibodies. Tr. at 167.

There is no evidence, much less reliable evidence, in this record that influenza vaccinations can cause the production of VGKC antibodies, much less that the antibodies are pathogenic or a marker for disease. Unsupported speculation is not a

[104] Doctor Shafrir referenced the journal articles accompanying his third expert report (Pet. Exs. 23o-23q). Tr. at 176-77. These articles include: M. Partinen, et al., *Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland*, PLoS ONE, 7 (3): e33723 (2012), filed as Pet. Ex. 23o; European Centre for Disease Prevention and Control, TECHNICAL REPORT, *Narcolepsy in association with pandemic influenza vaccination*, filed as Pet. Ex. 23p; E. Miller, et al., *Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis*, BMJ, 346: f794 (2013), filed as Pet. Ex. 23q.

basis for finding the medical theory to be reliable or a basis for finding a causal connection between vaccination and injury.

Assuming, arguendo, that the influenza vaccination could cause the production of VGKC antibodies and that such antibodies could cause autoimmune encephalitis, I turn to the second *Althen* prong.

2. *Althen* Prong 2: Lack of a Logical Connection.

Even if petitioners had provided a theory which satisfied the first prong, to satisfy the second prong of the *Althen* test, petitioners must establish a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." *Althen*, 418 F.3d at 1278. In other words, petitioners must show that the received vaccine did, more likely than not, cause the injury in the case at bar. *Pafford*, 451 F.3d at 1356. The sequence of cause and effect need only be "'logical' and legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 548-49; *accord Capizzano*, 440 F.3d at 1326. Evidence from a treating physician may assist petitioner in meeting her burden of proof under the second *Althen* prong. *Capizzano*, 440 F.3d at 1326.

In this case, none of the treating physicians ever specifically identified the influenza vaccine as the cause of C.L.'s purported autoimmune encephalopathy. At best, they described a temporal relationship between the vaccination and a sudden loss of C.L.'s language and social skills—a temporal relationship not borne out by the testing, therapy, and medical records between the vaccination and evaluation by Dr. Janousek.

I am not ignoring the fact that Drs. Renaud and McKeon, as well as Dr. Vincent, thought C.L.'s antibody levels warranted immunotherapy treatment, particularly given the remarkable improvement seen in the majority of patients with true autoimmune encephalitis on treatment. While I have fully considered these treating opinions and note that Drs. McKeon and Vincent are well regarded researchers in this field, they never opined that the antibodies were responsible for C.L.'s autism diagnosis. Their notes reflect the same frustration evident in Dr. Shafrir's testimony. Autism is a devastating diagnosis because there is often so little that can be done to treat it. If there is a scintilla of hope that it could be treated, improved, or even cured by autoimmune therapy, then the possible benefit far outweighed the risk of treatment. Unfortunately for C.L., petitioners, and others with autism diagnoses, the objective evidence in this case is that immunotherapy did not help at all with C.L.'s behavior and cognitive problems or, at best, the small degree of improvement observed is more likely due to ABA therapy and C.L.'s greater maturity. It certainly does not compare to the degree of improvement seen in NMDAR, limbic encephalitis, and Morvan's syndrome patients treated with immunotherapy. *See* Dalmau, Pet. Ex. 16b at 66; Lancaster & Dalmau, Res. Ex. BB at 384-85.

To establish the logical connection, Dr. Shafrir similarly relied on the temporal relationship between vaccination and onset of regression; the presence of the antibodies, the efficacy of immunotherapy, and the presence of an autoimmune encephalopathy/encephalitis. The latter issue was addressed above in Section IV.C 2. In summary, C.L.'s clinical presentation was not consistent with any known autoimmune encephalitis. Likewise, the efficacy of C.L.'s immunotherapy is not supported by objective evidence. *See* Sections III.E.4 and IV.C.2.c, *supra*. I have concluded that the regression was not abrupt or sudden. *See* Section IV.D.3, *supra*. What is left is the presence of the antibodies.

What we know about C.L.'s VGKC antibodies is that they were first discovered in her serum approximately three years after the regression and autism diagnosis. The antibodies have been measured over time and the levels have fluctuated. More often than not, they have declined during immunotherapy, which is what immunotherapy is designed to do—either remove the antibodies by IVIG or plasma exchange or suppress the immune system producing them, via steroid administration or the use of immunosuppressive agents such as rituximab. However, there was no reliably demonstrated clinical correlation between C.L.'s VGKC antibody levels and improvement in cognitive function, language, or behavior.

Moreover, if the antibodies are responsible for C.L.'s autism symptoms, then they were likely present before the vaccination. C.L. showed symptoms of what was later diagnosed as ASD as early as 15 months of age, and had a clear and significant language delay by two years of age. In addition to the language problems which are often the first symptom that prompts parents to seek medical advice, C.L.'s parents reported that she had always enjoyed solitary play, and were concerned enough about her temper tantrums to bring them to the attention of her pediatrician on at least two occasions prior to the vaccination—behaviors often seen in children with ASD. Both parties' experts agreed that C.L. experienced developmental delay prior to her November 25, 2005 vaccination. Tr. at 142 (Dr. Shafrir testifying: "Yes. She did have a developmental delay prior to receiving the influenza vaccine."). Developmental delay, including language delay, is a symptom of an autism spectrum disorder. Luyster, Res. Ex. DD at 1426 ("One of the primary diagnostic criteria for the diagnosis of autism spectrum disorder (ASD) is the presence of a language delay or impairment."); Landa, Res. Ex. EE at 139, Table 1 ("Social, communication, and other developmental disruptions reported before 24 months in age in retrospective and prospective studies of children later diagnosed with autism spectrum disorder.").

In discussing the anomalies in C.L.'s clinical presentation, vis-à-vis the autoimmune encephalopathies with which he was well acquainted, Dr. Dalmau described it as "unprecedented" to have an autoimmune disorder that causes a one-time attack (i.e., C.L.'s regression and presumed encephalitis in late 2005), with the antibodies remaining in her system for three more years, without further neurological

problems manifesting. Res Ex. J at 6; Tr. at 438-39. Yet, C.L. remained stable or improved marginally and slowly, while retaining an ASD diagnosis.

Finally, while it is not necessary to evaluate the possible factors unrelated to her vaccination[105] the evidence clearly demonstrates that C.L. suffers from an autism spectrum disorder, that the symptoms of C.L.'s autism spectrum disorder began prior to her November 25, 2005 vaccination, and that regression is seen in children with autism spectrum disorders. It is Dr. Dalmau's opinion that C.L.'s brain dysfunction is not autoimmune in nature, but representative of her ASD. Tr. at 300; Res. Ex. J at 3. C.L. has been consistently diagnosed or noted to have an autism diagnosis by a variety of her treating medical care providers, autism screening testing, and scholastic placement testing. *See, e.g.*, Pet. Exs. 3, p. 47; 4, p. 52; 5, p. 236; 7, p. 36; 9, pp. 4-5, 234-37; 13, p. 37; 22, p. 10.

Accordingly, while C.L.'s autism diagnosis was not made until June of 2006 (Pet. Ex. 4, pp. 50-52), it was clear that her first symptoms of developmental delay began as early as her October 27, 2004 15 month well child checkup (Pet. Ex. 3, p. 32 (behavior problems, feeding issues, and some mild gross motor delay)), and were readily apparent by her two year well child exam when Dr. Snook noted a language delay (Pet. Ex. 3, p. 41). In fact, by C.L.'s two year well child visit, she had been noted to have behavior problems, poor eating habits, poor sleeping habits, sensitivity to touch, sound, temperature, as well as language delay. Pet. Ex. 3, pp. 36-41. Doctor Shafrir acknowledged that C.L. experienced developmental delay prior to her November 25, 2005 influenza vaccination, but asserted that C.L. "developed a dramatic autistic regression following the vaccination." Pet. Ex. 23 at 12. However, there is no evidence of a *dramatic* regression following C.L.'s November 2005 vaccination—C.L.'s behavior did not rapidly change.[106] What is evident from the medical literature filed in this case is that regression is seen in children with autism. Relying upon the medical literature, Dr. Dalmau explained in his expert report that "a subset of children with autism have significant social and language gains and then, often between 15 and 30 months experience a dramatic loss of skills." Res. Ex. J at 3. In fact a "sizable minority (15%-47%)" of children with ASD exhibit a developmental course "associated with an idiopathic regression in one or more domains of behavior following a period of normal or

[105] The special master may consider evidence of an alternate cause when determining whether petitioner has established a prima facie case. *Doe 11 v. Sec'y, HHS*, 601 F.3d 1349 (Fed. Cir. 2010).

[106] In his initial report, Dr. Gorman noted that at C.L.'s neurological impairment prior to November 25, 2005, was underestimated by her medical care providers, aside from those providers administering her formal speech and language evaluation. Res. Ex. A at 4. While Dr. Gorman believed that C.L. suffered regression, he thought it was unclear when the regression began, noting that her Bayley Scales of Development score on August 4, 2006 was higher than her pre-vaccination score on September 27, 2005. *Id.*

near normal early development." G. Stefanatos, *Regression in Autistic Spectrum Disorders*, NEUROPYSCHOL. REV., 18: 305-19 (2008), filed Res. Ex. U, at 305.

For the above reasons, I find that petitioners have not demonstrated by a preponderance of the evidence a logical connection between C.L.'s vaccination and her purported injury of autoimmune encephalopathy.

3. Althen Prong 3: Proximate Temporal Relationship.

Merely showing a proximate temporal connection between a vaccination and an injury is insufficient, standing alone, to establish causation. *Grant v. Sec'y, HHS,* 956 F.2d 1144, 1148 (Fed. Cir. 1992). A proximate temporal relationship, even when coupled with the absence of any other identified cause for the injury, is not enough to demonstrate probable cause under the Vaccine Act's preponderance standard. *Moberly*, 592 F.3d at 1323 (citing *Althen*, 418 F.3d at 1278). In this case, Dr. Shafrir did not identify any specific medically appropriate time frame between the influenza vaccination and onset of an autoimmune encephalopathy. He notes "I cannot be accurate about that [a medically acceptable time frame between C.L.'s vaccination and regression] because . . . [w]e can't say . . . exactly when the regression started." Tr. at 193. Doctor Shafrir appeared to speculate, based on injuries distinct from C.L.'s (GBS, NMDAR encephalitis) that anywhere from one week to six weeks is an appropriate time period. Tr. at 192-200. However, he failed to explain in his testimony or within his reports why this is an appropriate time period for C.L.'s purported injury of VGKC autoimmune encephalopathy. Accordingly, I find that petitioners have failed to demonstrate a medical acceptable proximate temporal relationship between C.L.'s vaccination and injury.

VI. Conclusion.

For the reasons discussed above, I find that petitioners have not met their burden under *Althen*. They did not produce preponderant evidence that C.L.'s influenza vaccination caused an autoimmune response. They did not show that it caused the high VGKC antibodies. They did not establish that these antibodies were "clinically significant" in terms of causing an autoimmune encephalopathy. They did not demonstrate that the influenza vaccine could or did cause C.L. to develop an autoimmune encephalopathy. As the Court of Federal Claims has noted, an expert's "conclusions . . . are only as good as the reasons and evidence that support them." *Davis v. Sec'y, HHS,* 20 Cl. Ct. 168, 173 (1990). *See also Perreira v Sec'y, HHS,* 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) ("An expert opinion is no better than the soundness of the reasons supporting it.") (citations omitted); *Dobrydnev v. Sec'y, HHS*, 566 Fed.Appx. 976, 982-83 (Fed. Cir. 2014) (an expert's opinion is only worth as much as the facts upon which it is based) (citing *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993)); *Fehrs v. United States*, 620 F.2d 255, 265

(Ct. Cl.1980) (an expert's opinions "can be no better than the soundness of the reasons that stand in support of them"). Petitioners' experts failed this well-established test.

I conclude that petitioners failed to demonstrate any of the *Althen* factors by preponderant evidence. Petitioners have not demonstrated that C.L.'s injury was either caused in fact or significantly aggravated by the influenza vaccination she received on November 25, 2005. The petition for compensation is therefore **DENIED**. The clerk is directed to enter judgment accordingly.

IT IS SO ORDERED.

s/Denise K. Vowell
Denise K. Vowell
Chief Special Master