# In the United States Court of Federal Claims

**OFFICE OF SPECIAL MASTERS**

**No. 15-792V**

Filed: April 15, 2022

| | |
|---|---|
| HEATHE HELLER and JENNA HELLER, parents of H.H., a minor,<br><br>Petitioners,<br><br>v.<br><br>SECRETARY OF HEALTH AND HUMAN SERVICES,<br><br>Respondent. | TO BE PUBLISHED<br><br>Aicardi–Goutières syndrome (AGS); Type I Interferonopathy; Pentacel vaccine; influenza vaccine; Prevnar vaccine; insufficient proof of causation |

*Margaret Guerra*, Margaret M. Guerra, Attorney at Law, Fort Worth, TX, for Petitioners
*Adriana Teitel*, U.S. Department of Justice, Washington, DC, for Respondent

## DECISION ON ENTITLEMENT[1]

**Oler**, Special Master:

On July 27, 2015, Heathe Heller ("Mr. Heller") and Jenna Heller ("Mrs. Heller") (collectively "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") alleging,

[1] This Decision will be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet**. As provided in 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Decision's inclusion of certain kinds of confidential information. To do so, each party may, within 14 days, 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, this Decision will be available to the public in its present form. *Id.*

[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).

in part, that as a result of his October 17, 2013 vaccinations with influenza and Prevnar[3] and his October 23, 2013 vaccination with Pentacel,[4] H.H. experienced either the onset or the significant aggravation of his degenerative neurologic disorder.

For the reasons discussed in this decision, I find that H.H.'s vaccinations did not cause or significantly aggravate his condition.

## I. Procedural History

On July 27, 2015, Heathe and Jenna Heller, on behalf of their minor son, H.H. filed a petition[5] seeking compensation under the Vaccine Act, alleging that H.H. suffered from dystonia and encephalopathy as a result of the influenza ("flu") and Prevnar vaccines he received on October 17, 2013, and/or the DTaP-IPV-Hib (Pentacel) vaccination he received on October 23, 2013. Pet. at 1.

Petitioners filed medical records on August 3, 2015. ECF No. 10. Petitioners filed additional medical records, affidavits, and expert reports from Dr. Leslie Hollis and Dr. Warren Marks on October 9, 2015. ECF No. 14. Petitioner filed additional medical records on November 9, 2015 (ECF No. 16) as well as a statement of completion on November 9, 2015 (ECF No. 17).

On February 1, 2016, Respondent filed his Rule 4(c) Report, asserting that the case was not appropriate for compensation and should be dismissed. Resp't's Rep. ECF No. 21.

Petitioners filed additional affidavits and exhibits on March 21, 2016. ECF No. 28. Petitioner also submitted a supplemental expert report from Dr. Hollis on the same date. *Id.*

On July 8, 2016, Special Master Hastings held a status conference. ECF No. 35. Special Master Hastings stated to Petitioners' counsel that "as this case proceeds, it is imperative that all the evidence is identified in a manner that does not cause confusion." *See* Scheduling Order of July 8, 2016, ECF No. 35 at 1. Accordingly, Special Master Hastings ordered Petitioners to re-number and re-file all of Petitioner's exhibits that had been filed previously. *Id.* Special Master Hastings noted that "the numbering of these re-filed exhibits shall commence with exhibit number 48, followed by consecutive exhibits numbers thereafter." *Id.*

Accordingly, Petitioners refiled all previously submitted medical records, affidavits, and expert reports on August 26, 2016. Exs. 48-93, ECF Nos. 40-46.

---

[3] Prevnar is a "trademark for a preparation of pneumococcal 7-valent conjugate vaccine." *Prevnar*, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=40909&searchterm=Prevnar (last accessed April 13, 2022).

[4] Pentacel is a "trademark for a combination preparation of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, poliovirus vaccine inactivated, and Haemophilus b conjugate (tetanus toxoid conjugate) vaccine." Dorland's Med. Dictionary Online, *Pentacel*, https://www.dorlandsonline.com/dorland/definition?id=37544&searchterm=Pentacel (last accessed April 13, 2022).

[5] Petitioners filed an amended Petition on November 9, 2015. ECF No. 15.

On December 14, 2016, Respondent filed an expert report from Dr. Kristin Barañano. Ex. A, ECF No. 52. Respondent filed Dr. Barañano's CV at Exhibit B. On the same date, Respondent filed the medical literature associated with Dr. Barañano's report. Exs. A-1 – A-5, ECF No. 52.

On August 25, 2017, Petitioners filed a supplemental expert report from Dr. Warren Marks. Ex. 94, ECF No. 54.

This case was reassigned to my docket on December 5, 2017. ECF No. 59. Petitioners filed additional medical records on March 6, 2018. Ex. 95, ECF No. 61.

On August 17, 2018, Respondent filed a supplemental expert report from Dr. Barañano. Ex. C, ECF No. 67. Respondent filed the medical literature associated with Dr. Barañano's report as Exhibit C-1 on the same date.

On April 29, 2019, Respondent filed an expert report from Dr. Stephen McGeady. Ex. D, ECF No. 70. Respondent filed Dr. McGeady's CV at Exhibit E.[6] Respondent filed the medical literature associated with Dr. McGeady's report on the same day. Exs. D-1 – D-12, ECF No. 71.

On December 31, 2019, the parties filed their pre-hearing submissions. ECF Nos. 75-76. Pre-hearing briefs were filed on January 8, 2020. ECF Nos. 78-79.

On January 8, 2020, Respondent filed two additional pieces of medical literature. Exs. F, G, ECF No. 81.

I held an entitlement hearing on January 22, 2020. ECF No. 88. At the conclusion of the hearing, I held a status conference with the parties during which several items were discussed. *See* Scheduling Order of January 29, 2020, ECF No. 86. I directed Petitioners' counsel to file several documents, including:

1. Any emails and/or records from Dr. Yanick Crow, including the results of the genetic testing done by Dr. Crow.
2. Any medical records from the Panama clinic where H.H. underwent multiple stem cell treatments as referenced in Ex. 96, pg. 36.
3. Medical records from H.H's Boston Children's Hospital visit.
4. Medical records and/or genetic testing results from Atlanta.
5. Any additional photos or videos of H.H. from Halloween 2013.
6. A status report identifying the specific dates of the video clips in Ex. 47.
7. Additional medical records from H.H.'s most recent visits with Dr. Warren Marks.
8. A status report informing the Court as to whether Petitioners wished to file additional expert reports.[7]

[6] Respondent re-filed Dr. McGeady's CV on April 14, 2020. Ex. I, ECF No. 90.

*Id.* at 1-2. In addition, Respondent was ordered to file an updated CV for Dr. Barañano and Dr. McGeady, and the parties were ordered to file medical literature summaries by March 31, 2020.[8] *Id.* at 2.

Petitioners filed a status report on April 14, 2020, stating that they had employed Dr. Lawrence Steinman to provide an additional expert report. Petitioners' Status Report of April 14, 2020, ECF No. 92. Petitioners stated that they had only been able to retrieve some of the medical records that were requested in my January 29, 2020 order, and filed these on the same day. Exs. 97-100, ECF No. 93.

On July 24, 2020, Petitioners filed an expert report from Dr. Steinman. Ex. 101, ECF No. 95. Petitioners filed the medical literature associated with Dr. Steinman's report on the same date. Exs. 101-1 – 101-20, ECF No. 101.

On December 1, 2020, Respondent filed a rebuttal expert report from Dr. McGeady. Ex. J, ECF No. 104.

On February 12, 2021, Petitioners filed a supplemental expert report from Dr. Steinman. Ex. 99,[9] ECF No. 108 (hereinafter "Second Steinman Rep.").

On May 15, 2021, Petitioners filed their post-hearing brief. ECF No. 113. Respondent filed a response on July 8, 2021. ECF No. 116. Petitioners filed a reply on July 15, 2021. ECF No. 118.

On August 9, 2021, the parties filed a joint status report indicating that the record was complete. ECF No. 119.

On March 15, 2022, my law clerk emailed the parties in order to inform Petitioners' counsel that one exhibit referenced during the hearing (a letter from Sheri Huling to Petitioners' counsel which served as the basis for Ms. Huling's affidavit) had not been filed into the record. That same day, I entered an order directing Petitioners to file the letter as soon as practicable *See* Non-PDF Informational Communication of March 15, 2022. Petitioners filed on the letter on March 23, 2022. Ex. 102; ECF No. 120.

This matter is now ripe for adjudication.

---

[7] At the conclusion of the entitlement hearing after we went off the record, I informed Petitioners' counsel that the record, as it currently stood, did not enable Petitioners to meet their burden. I suggested that Petitioners' counsel consider retaining an additional expert neurologist so that Petitioners may be afforded a full and fair opportunity to prosecute their case.

[8] This additional documentation filed on April 14, 2020. ECF No. 90.

[9] Petitioners inadvertently labeled this report as Exhibit 99. Exhibit 99 is already a medical record. To avoid confusion, I have referred to this report as "Second Steinman Rep." in this decision.

## II. Medical Records

### A. Relevant Pre-Vaccination History

H.H. was born on July 14, 2012. Ex. 48 at 1. H.H. was delivered vaginally with no complications. Ex. 49 at 5.

On July 18, 2012, H.H. was seen by Dr. Leslie Hollis at Wise Pediatrics for a newborn visit. Ex. 49 at 5. H.H. was noted as meeting all his newborn milestones: raising his head when prone, making eye contact/regarding faces, startling to noise, following to midline and equal movements. *Id.* H.H. was sleeping three to four hours at a time, and his parents indicated no concerns at this visit. *Id*. Dr. Hollis noted no abnormalities. *Id.* at 5-6. H.H. was scheduled to return in one week for a weight check. *Id.* at 6.

On July 23, 2012, H.H. visited Dr. Hollis at Wise Pediatrics to follow up on an abnormal newborn screen "possibly indicating a VLCAD deficiency."[10] Ex. 49 at 7. Dr. Hollis noted that H.H. "has been doing very well. Weight gain and breastfeeding going well." *Id.* H.H. was observed as "playful, alert and aware" and Dr. Hollis found no abnormalities upon examination. *Id.* Dr. Hollis ordered a Texas newborn screen, a plasma acylcarnitine profile, and a urine organic acids test. *Id.*

On July 27, 2012, H.H. visited Dr. Hollis at Wise Pediatrics for a two-week well child visit. Ex. 49 at 9. His parents had no concerns at this visit. *Id.* Dr. Hollis observed no abnormalities upon examination. *Id.* H.H.'s Texas Newborn Screen was canceled at this visit. *Id.* at 10. H.H. was next scheduled to return for his two-month wellness check.

On August 1, 2012, RN Michelle Johns from Wise Pediatrics left a voicemail for Mrs. Heller, indicating that H.H.'s second PKU (Phenylketonuria) screening was normal. Ex. 49 at 11.

On August 8, 2012, LVN Cozby called Mrs. Heller to inform her that the rest of H.H.'s labs returned normal results. Ex. 49 at 14.

On August 16, 2012, RN Johns called Mrs. Heller and left her a voicemail informing her that "State is requiring a referral to Dr. Basinger[, a] metabolic geneticist since [H.H.'s] first [PKU screening] was abnormal." Ex. 49 at 15. Petitioner called back the same day to confirm an appointment with Dr. Basinger. *Id.* at 16.

On August 23, 2012, Dr. Heather Crawford sent a letter to Dr. Hollis noting that H.H was under evaluation for a VLCAD deficiency, which could cause hypoglycemia, cardiomyopathy, elevated ammonia levels, abnormal liver function tests, and death should H.H. have prolonged

[10] A VLCAD deficiency "is a condition in which the body is unable to properly breakdown certain fats (called very long-chain fatty acids) into energy, particularly during periods without food (fasting)." National Institutes of Health, National Center for Advancing Translational Sciences, VLCAD Deficiency, https://rarediseases.info.nih.gov/diseases/5508/vlcad-deficiency#:~:text=VLCAD%20deficiency%20is%20a%20condition,periods%20without%20food%20(fasting) (last accessed April 8, 2022).

fasting or poor dietary intake due to illness. Ex. 89 at 14. She noted that H.H.'s blood glucose needed to be maintained at about 70 mg/dL. *Id.*

On September 18, 2012, H.H. visited Dr. Hollis at Wise Pediatrics for his two-month well-child visit. Ex. 49 at 18. H.H.'s parents had no concerns at this visit. *Id.* H.H. was recorded as meeting all his developmental milestones: grasping a rattle, presenting a social smile, cooing, responding to a bell, following past midline, and parent/child interaction. *Id.* H.H. weight 11.7 pounds. *Id.* Dr. Hollis noted no abnormalities upon examination. *Id.* at 18-19. H.H. received his Prevnar-13, Hepatitis B, Pentacel, and Rotarix vaccines at this visit. *Id.* at 19. H.H. was next scheduled to be seen for his four-month well child appointment. *Id.*

On November 14, 2012, H.H. was seen by Dr. Hollis at Wise Pediatrics for his four-month well child visit. Ex. 49 at 21. H.H. was noted to be sleeping "more than 10 hours per night". *Id.* His parents voiced no concerns at this visit. *Id.* H.H. was noted to be meeting all his developmental milestones: raising his body on his hands, steady head control when held upright, no head lag when pulling to sit, rolling "prone to supine", grasping his rattle, playing with his hands/bringing his hands together, turning to sound, following objects 180 degrees, and laughing/squealing. *Id.* H.H. weighed 14.06 pounds. *Id.* Dr. Hollis observed no abnormalities upon examination. *Id.* at 22. H.H. received his Prevnar-13, Pentacel, and Rotateq vaccinations at this visit. *Id.* H.H. was next scheduled to return for his six-month well child visit. *Id.*

On January 23, 2013, H.H. was seen by Dr. Hollis at Wise Pediatrics for his six-month well visit. Ex. 49 at 26. H.H. was noted to be meeting all his developmental milestones: rolling over both ways, sitting with minimal support, no head lag when pulling to sit, bearing weight, transferring objects from hand to hand, laughing/babbling and imitating sounds, turning towards voices, "raking raisin", looking "for yarn" and reaching for objects/working for toys. *Id.* at 27. H.H. weight 16.87 pounds at this visit. *Id.* Dr. Hollis noted no abnormalities upon examination. *Id.* at 27-28. H.H. received his Prevnar-13, HiB, Pediarix, Rotateq, and flu vaccinations at this appointment. *Id.* at 28. Dr. Hollis noted that H.H. had "no problems with previous immunizations." *Id.* H.H. was next scheduled to be seen for his nine-month well child visit. *Id.*

On April 16, 2013, H.H. visited Dr. Hollis at Wise Pediatrics for his nine-month well visit. Ex. 49 at 28. By this point, H.H. had begun eating solid foods, including fruits, Cheerios, and yogurt. *Id.* He was sleeping more than ten hours per night and his parents had no concerns. *Id.* H.H. was noted to be meeting all his developmental milestones: Sitting well, crawling, pulling to stand and cruising, using a pincer grasp, banging two toys together, finger feeding, babbling mama/dada, playing peek-a-boo, indicating his wants, and waving bye-bye. *Id.* Dr. Hollis noted no abnormalities upon examination. *Id.* at 28-29. H.H. weighed 18.77 pounds at this visit. *Id.* at 29. H.H. was next scheduled to be seen for his 12-month well child visit. *Id.*

On July 18, 2013, H.H. was seen by Dr. Hollis at Wise Pediatrics for his 12-month well child visit. Ex. 49 at 33. By this time, H.H. had switched to whole milk from formula, was eating solids to include meats and Gerber Graduates, and was sleeping more than ten hours per night. *Id.* His parents had no concerns at this visit. *Id.* H.H. was noted to be meeting all his developmental milestones: pulling to stand/standing alone for 2-3 seconds, walking with support and taking a few steps, precise pincer grasp, had a 1–3-word vocabulary, using Mama/Dada specifically, drinking

from a cup, understanding "no" and imitating actions. *Id.* H.H. weighed 21.34 pounds at this visit. Dr. Hollis noted no abnormalities upon examination. *Id.* at 33-34. H.H. received his MMRV and Hepatitis A vaccinations at this visit. *Id.* at 34. H.H. was next scheduled to be seen for his 15-month well child visit. *Id.*

On July 29, 2013, H.H. was seen by Dr. Hollis at Wise Pediatrics for a sick child visit. Ex. 49 at 36. Under HPI, Dr. Hollis stated that "Pt has been running fever to 102 for the [past] 3 days. Mom is also sick. He has had nasal congestion for 2 weeks." *Id.* H.H. was diagnosed with purulent rhinitis and prescribed Augmentin. *Id.*

On September 13, 2013, Petitioner called Wise Pediatrics and stated that she was concerned with H.H. "not walking and right foot turned inward." Ex. 49 at 37. LVN Cozby noted that H.H. was scheduled for an appointment in one month and advised Petitioner, per Dr. Hollis, to wait until that appointment to be seen. *Id.*

**B. Post-Vaccination History**

On October 17, 2013, H.H. visited Dr. Hollis at Wise Pediatrics for his 15-month well visit. Ex. 49 at 1. At this visit, H.H. was noted as meeting all of his developmental milestones: Walking alone, crawling up stairs, self-feeding with fingers, using a fork and spoon, talking with a three to six word vocabulary, understanding simple commands, rolling/tossing a ball, stooping to recover a toy, and indicating his wants without crying. *Id.* Upon physical exam, Dr. Hollis noted no abnormalities. *Id.* H.H. received his influenza and Prevnar-13 vaccines at this appointment, although he did not receive Pentacel.[11] *Id.* Dr. Hollis discussed H.H.'s development, growth and nutrition with Petitioner. *Id.* at 2. H.H. was next scheduled to return for his 18-month well child visit. *Id.* at 2.

On October 23, 2013, H.H. was seen by Nurse practitioner Ariane Segura. Ex. 49 at 3. H.H. received his Pentacel vaccination at this visit. *Id.*

On November 11, 2013, H.H. visited Dr. Hollis at Wise Pediatrics for a sick child visit. Ex. 49 at 41. In the HPI, Dr. Hollis stated "Pt has been fussy for the last week. He has run fever to 101.5. His energy level is decreased. Pts development has regressed in the last month. He has stopped crawl[]ing. He is not wanting to play with toys. He will throw toys and food." *Id.* H.H. was noted to be "playful, alert and aware" and in no respiratory distress. *Id.* Dr. Hollis observed no abnormalities until she conducted a neurologic examination. She noted that H.H.'s reflexes were "Brisk, 3+" and his tone was "hypotonic". *Id.* A rapid strep throat test was negative and a CBC returned normal results. *Id.* at 41-42. H.H. was diagnosed with a developmental delay and acute pharyngitis. *Id.* at 42. He was referred to neurology "ASAP" for evaluation. *Id.* Petitioner was instructed to try throat lozenges, fluids, and rest to treat the pharyngitis. *Id.*

On November 12, 2013, H.H. visited Dr. Heather Crawford at Cook Children's Hospital, Department of Clinical and Metabolic Genetics, for "new problem of loss of milestones, elevated

[11] Mrs. Heller testified at the entitlement hearing that Wise Pediatrics was out of the Pentacel vaccine, and she was told to return to get that vaccine at a later date. Tr. at 17.

liver enzymes." Ex. 50 at 1. H.H. was observed to be "healthy-appearing, well-nourished, and well-developed" and in no distress. *Id.* He was "active and alert and [with a] normal mood." *Id.* Upon examination, no abnormalities were found in an examination of his head, eyes, ears, nose, throat, neck, chest, heart, abdomen, back, skin, hair and genitals. *Id.* at 1-2. Upon an examination of H.H.'s musculoskeletal systems, Dr. Crawford noted that H.H. had "normal strength and hypertonicity (noted in lower extremities especially at the ankles). *Id.* at 2. She stated that "his heel cords appear somewhat tight and he may require AFOs at some point in the future." *Id.* A neurologic exam revealed that H.H. was "not walking yet" and was "not speaking yet." *Id.* Dr. Crawford also noted that H.H. had "elevated transaminases" but she "would like to repeat those [tests] once his minor illness has passed." H.H. was diagnosed as "a 16 month old who now presents with a new history of developmental delay with loss of some developmental milestones." *Id.* Dr. Crawford ordered a "baseline genetic and metabolic workup to include looking for chromosomal abnormalities and disorders of fat and protein metabolism." *Id.* Additionally, she ordered an "MRI of the brain to make sure that the gross anatomy of the brain is normal." *Id.* She recommended that Petitioners start H.H. in physical and speech therapy while the cause of his developmental delay was diagnosed. *Id.* Concerning his "elevated transaminases", Dr. Crawford stated that if they were still elevated in a month, she would "expand our evaluation to include an abdominal ultrasound to evaluate the liver and possible evaluate for lysosomal disorders if his regression persists." *Id.*

On November 14, 2013, Dr. Crawford sent a note to Dr. Hollis, providing the details of H.H.'s visit on November 12, 2013. Ex. 50 at 4. Dr. Crawford stated that:

> H.H. is a 16 month old male who is being referred again for an evaluation for developmental delay and possible regression of milestones. He was initially seen in the metabolic genetics clinic after an abnormal newborn screen for possible VLCAD deficiency. However, follow up testing including a skin biopsy to look at fat metabolism proved to be negative. He was then cleared for that screening test with no follow up recommended at that time. However, I was contacted by his PCP, Dr. Hollis, who was concerned about his development. She stated that he was sitting at 6 months, crawling at 7 months and took a few steps at 10 months. He apparently had 3 words at 12 months. Parents now state that he does not take any steps [] nor does he pull to stand anymore. He now has no words. They also feel that his affect is not normal in that he does not laugh spontaneously or much at all. He has been sick with a virus this last couple weeks. He has not had any major illnesses or hospitalizations since birth.

*Id.* Dr. Crawford's notes indicate that H.H. was diagnosed with a developmental delay, specifically a slight delay in gross motor function and fine motor function/ADLs, and a significant delay in language functioning. *Id.*

On the same date, H.H. was admitted to the hospital with worsening symptoms. Ex. 51 at 5. Dr. Michael Aalbers, a neurologist, admitted H.H. to the hospital with "progressive dysarthria,[12]

[12] Dysarthria is "a speech disorder consisting of imperfect articulation due to loss of muscular control after damage to the central or peripheral nervous system." *Dysarthria*, Dorland's Med. Dictionary Online, https://

trouble swallowing, and a fairly dramatic spastic diplegia in the lower extremities." *Id.* at 8. A CT scan demonstrated "mild volume loss with no evidence of upper motor neuron injury." *Id.* Dr. Aalbers also noted that there was "no evidence of bony malformation, [or] concerns for acute transverse myelitis." *Id.* It was noted that H.H. was constipated but had "appropriate bowel and bladder symptoms." *Id.*

After being admitted, H.H. underwent a lumbar puncture to "rule out demyelinating disease versus metabolic etiologies versus dopa-responsive dystonia." Ex. 52 at 5. The lumbar puncture revealed no significant results.

On November 15, 2013, H.H. underwent a brain MRI. Ex. 51 at 1. The clinical indication was "acute onset spastic diplegia." *Id.* Dr. Hayden Head interpreted the MRI. His impression was "Mild enlargement of subarachnoid spaces. If the head circumference is enlarged and/or has been rapidly increasing, the findings would be in keeping with benign enlargement of subarachnoid spaces of infancy, in the appropriate clinical setting. If not, mild diffuse parenchymal volume loss should be considered." *Id.* Dr. Head noted that H.H.'s MRI was "otherwise unremarkable."

On November 16, 2013, H.H. was discharged from the hospital. His discharge summary stated:

> [H.H.] presented to the emergency department and upon evaluation by Dr. Aalbers of neurology was found to have significant dystonic posturing of the lower extremities, prompting his admission. He was admitted to the floor in stable status. The workup included an MRI of the brain, which was within normal limits. An MRI of the complete spine was significant only for a fatty film, suggesting a possible tethered cord.

Ex. 51 at 5. Dr. Michael Perry, H.H.'s discharging physician, stated that "during admission, [H.H.'s] irritability decreased significantly, and he was able to feed fairly well." *Id.* H.H. was treated with Sinemet for "presumptive dopa-responsive dystonia" and seemed to respond to the treatment. *Id.* Dr. Perry noted that confirmation of diagnoses would depend on CSF results. *Id.* H.H.'s family was instructed to call the hospital if H.H. had increased irritability, increased tone, intolerance to medication, or any other concerns. *Id.* at 6.

On November 21, 2013, Dr. Elisabeth Brockie, DO, of Quest Diagnostics – Dallas provided lab results for H.H.'s lactate and plasma acylcarnitine. Ex. 50 at 54. She noted that "several very-long-chain and long-chain-hydroxy acylcarnitine species were minimally to mildly elevated" in the sample she tested. *Id.* She noted that the results were "not sufficient" to rule out a mitochondrial fatty acid disorder. *Id.* She noted that these results have been seen in "liver disease, some mitochondrial disorders, metabolic stress, certain glycogen storage disorders, and generalized sickness of not metabolic origin." *Id.* An amino acids lab result reported on the same day showed "elevated" amino acids but did "not suggest a specific inherited metabolic disorder." *Id.* at 56.

---

www.dorlandsonline.com/dorland/definition?id=15144&searchterm=dysarthria (last accessed April 8, 2022).

On November 22, 2013, H.H. was seen by Dr. Aalbers at Cook Children's Hospital. Ex. 52 at 8. Problems reviewed included "cough, spinal cord disease, dystonia, screening finding, speech delay and delayed milestone." *Id.* In the patient history, Dr. Aalbers noted that H.H. was at the clinic "emergently secondary to concerns of rapidly advancing metabolic neurodegenerative disease" and that since his discharge from the hospital on November 16, 2013, H.H. had progressively lost meaningful use of his right hand. *Id.* at 9. Upon examination, Dr. Aalbers found no abnormalities in H.H.'s eyes, ears, nose, mouth, throat, heart, respiratory systems, gastrointestinal symptoms, musculoskeletal systems, or skin. Upon conducting a neurologic examination, Dr. Aalbers noted that H.H. had "weakness, trouble walking, and poor attention." *Id.* at 10. H.H.'s mental status was described as "somnolent." *Id.* His grasp of language was considered "dysfluent and dysarthric" and his "fund of knowledge" was "delayed for age. *Id.* During a motor exam, Dr. Aalbers observed the following:

> Motor spastic, rigidity, hypotonic axial, hypertonia appendicular, and dystonia diffuse and normal bulk and no focal weakness; Patient has internal rotation and supination with dystonic posturing of the thumb in the right hand that was not present 4 days ago with intermittent scissoring of the lower extremities dystonic spastic posturing of the feet with plantarflexion striatal toes bilaterally patient has appropriate head[] control with increased tone and cogwheeling on the right but good range of motion of his fingers.

*Id.* at 10. Finally, in examining H.H.'s spine, Dr. Aalbers observed "no tenderness and decreased ROM" in H.H.'s cervical spine. *Id.* Dr. Aalbers' initial impression was "rapidly progressive ascending dystonia with encephalopathy – Concern for mitochondrial disease versus lysosomal storage disease/inborn error of metabolism." *Id.* at 11. Dr. Aalbers also provided his impression of H.H.'s testing from his hospital stay (November 14, 2013 – November 16, 2013):

> In the interim the patient was admitted to the hospital with subsequent concerns for rapidly progressive dysarthria choking with exacerbation dystonic posturing in the lower extremities. Patient matter and lumbar puncture which demonstrated no evidence of pleocytosis with normal lactate pyruvate urine organic acids and repeat [] acylcarnitine profile.
>
> Subsequent neuroimaging demonstrates numerous white matter hyperintensities particularly along the insula bilaterally however this is still within the normal range of normal myelination for [a] 16- month-old, there is perhaps mild volume loss in the midline particularly midline stratum without signal change.
>
> MRI of his lower spine demonstrates a mildly tethered cord that would not explain the dystonia or striatal toe [but] may explain the constipation rapid exag[g]eration of symptoms.

*Id.* at 11. Dr. Aalbers noted that "within a week [of his discharge, H.H. developed] increased encephalopathy and now has los[t] meaningful[] use of his right hand with cogwheeling of his left despite being on 25 100 mg of Sinemet secondary to a working diagnosis of rapidly progressive

to responsive dystonia." *Id.* A metabolic geneticist did not suspect that H.H. had a "fatty acids oxidation disorder based on the fibroblast and repeated carnitine profiles" and an EEG demonstrated "no evidence of epilep[t]iform [discharges]." *Id.* Dr. Aalbers' differential diagnosis was "rapidly progressive primary mitochondrial disease." *Id.* Dr. Aalbers stated that he would order testing for lysosomal storage diseases, and "full scale mitochondrial studies." *Id.* H.H.'s parents were instructed to continue Sinemet 25 100 and observe H.H. for worsening encephalopathy or new symptoms. *Id.*

That same date, H.H. underwent an EEG. Ex. 52 at 47. Dr. Howard Kelfer, interpreting the EEG, stated that "this tracing, recorded while awake and during sleep, is mildly abnormal. The background activity is somewhat slow for age. The findings are indicative of a mild to moderate diffuse disturbance of brain function. There is no definite epileptiform activity." *Id.*

On November 23, 2013, Dr. Thomas Lohmann provided the results of H.H.'s genetic testing conducted using a microarray analysis, stating that "no deletions or duplications of known or potential clinical significance were detected by microarray analysis." Ex. 50 at 61.

On November 27, 2013, Medical Neurogenetics Laboratories ("MNG Labs") provided the results of the testing ordered by Dr. Aalbers. Ex. 52 at 19. Under "neurotransmitter metabolics", H.H.'s 5-Hydroxindoleacetic acid was slightly elevated, with a value of 215 mnol/L (reference range 67-189 nmol/L). *Id.* Dr. Keith Hyland, Ph.D, interpreting the results stated that "this is unlikely to be of any clinical significance." *Id.* at 20. Under "tetrahydrobiopterin and neopterin profile", H.H.'s neopterin was extremely elevated, with a value greater than 300 nmol/L (reference range 8-33 nmol/L). *Id.* H.H.'s tetrahydrobiopterin was also extremely elevated at 118 nmol/L (reference range 9-33 nmol/L). Dr. Hyland noted that "elevations of neopterin and tetrahydrobiopterin have been described in the Aicardi-Goutieres syndrome" and "we have also noted a similar abnormal pterin pattern in HIV infection." *Id.* All other testing was normal. *Id.* at 19-20, 23.

On December 3, 2013, H.H. was seen by Dr. Aalbers for "neurological regression." Ex. 52 at 25. Dr. Aalbers noted generally the same problems he had observed during H.H.'s November 22, 2013 visit. *Id.* at 25-26. Under "Impression", Dr. Aalbers stated that H.H.'s diagnosis was "rapidly progressive dystonia and encephalopathy" with "concern for possible Accardi-Gutierres [sic]". *Id.* at 28. Dr. Aalbers stated that H.H had:

> Rapidly progressive dystonia, now with lo[ss of] meaningful [use] of his left hand and spastic dystonic scissoring of the lower extremities. In the interim [h]is neurotransmitter results surprisingly showed marked elevation to biopterin in the option which is commonly seen in patients with inflammatory encephalitis such as [] AGS. Of concern the patient had previously unexplained transient elevations of liver enzymes which is consistent with AGS as is progressive encephalopathy and dystonia spasticity.

*Id.* at 28. Dr. Aalbers also noted that H.H.'s MRI was "confusing", noting that "there are patchy white matter hyperintensities throughout however given his chronological age patchy hypomyelination can be normal." *Id.*

To confirm the diagnosis, Dr. Aalbers arranged for HIV testing, repeat of H.H.'s neurotransmitters studies, and planned to contact experts in AGS. *Id.* H.H. was referred to Dr. Heather Crawford for additional genetic testing in connection with AGS. *Id.*

On December 3, 2013, H.H. was seen by Dr. Crawford at Cook Children's Hospital, Department of Clinical and Metabolic Genetics for a follow up evaluation for "developmental regression with dystonia." Ex. 50 at 11. No abnormalities were found upon an evaluation of H.H.'s head, eyes, ears, nose, mouth throat, neck, genitals, back, skin, or hair. *Id.* at 11-12. A musculoskeletal exam revealed that H.H. had "normal strength and hypertonicity (noted in lower extremities especially at the ankles, feet held inward position); Pt now holds hand in a fist when trying to reach for objects and when crawling, then afterward hand relaxes when trying to hold a bottle." *Id.* at 11. A neurologic exam revealed that H.H. was "not walking yet" and "not speaking yet." *Id.* H.H. was assessed as "a 16 month old who now presents with a new history of developmental regression and onset of progressive dystonia in the last 2-3 months." *Id.* at 12. He was diagnosed with delayed milestones, unspecified encephalopathy, speech delay ("expressive language disorder"), and dystonia ("unspecified extrapyramidal disease and abnormal movement disorder"). *Id.*

In the discussion notes, Dr. Crawford stated:

> [H.H.] continues to have dystonia in the lower extremities, however his hands are now becoming involved. He is still unable to crawl or pull [to] stand. He is now having difficulties sitting alone. His clinical picture is very concerning for either a metabolic or neurogenetic disorder. He had CSF studies done that included neurotransmitters which showed an extremely elevated neopterin and tetrahydrobiopterin. The lab's interpretation stated that only Aicardi-Goutières syndrome and HIV infection would cause such high values. Dr. Aalbers and myself have discussed this case at length. He does not have the typical presentation of AGS as he does not have any calcifications in the brain and did not present with thrombocytopenia, hepatosplenomegaly with elevated liver enzymes after birth. However, there are milder presentation[s] of this syndrome where the calcification can develop after 1-2 year of age. Therefore, this disorder remains on our differential. I got permission from the family to contact a Dr. Yanick Crow in England who is a world expert on AGS to get his opinion.

*Id.* Dr. Crawford recommended that the lumbar puncture be repeated, as well as a test for IFN-alpha in the CSF. *Id.* She stated that, aside from AGS, "mitochondrial disorders are still in the differential as he has had an elevated lactate in the past, however repeat was normal." *Id.* Dr. Crawford ordered sequencing of H.H.'s mitochondrial genome and stated that " [S]ince his differential is still so wide at this point, we will proceed with whole exome sequencing which will include the mitochondrial genome. This will also look at the 5 genes known to be associated with Aicardi-Goutieres syndrome." *Id.* Dr. Crawford encouraged "intensive therapies to help condition his muscles and help with regaining milestones." Finally, Dr. Crawford ordered additional biochemical labs for diagnostic purposes. *Id.*

On December 4, 2013, Dr. Crawford sent a note to Dr. Hollis, providing the details of H.H.'s visit on December 3, 2013. Ex. 50 at 14. Dr. Crawford stated that:

> [H.H.] was last seen in the metabolic genetics clinic on 11/12/2013. At that time, some metabolic labs were ordered as well as PT and ST. However, 2 days after our clinic visit, parents felt that he was worsening. They felt he had difficulty swallowing, increase[d] tone in his legs and increased irritability.

*Id.* Dr. Crawford noted that H.H. was admitted to the hospital on November 14, 2013 by Dr. Aalbers in the neurology department. She stated that:

> [Dr. Aalbers] felt that he had significant dystonic posturing of his lower extremities. This led to an emergent MRI of the brain and a lumbar puncture for CSF studies. He also had some other metabolic labs drawn during that admission. His irritability improved and he was feeding well by time of discharge on Saturday 11/16/13. He was started on sinemet during this admission due to the suspicion of dopa-responsive dystonia. There was a slight improvement in his tone by discharge from the hospital.

*Id.* Dr. Crawford further noted that:

> Since discharge from the hospital, he continues to get physical therapy. Parents felt that he was [sleepier] and the increased tone has returned to his legs. His hands appear to be affected as the parents state that he does not use them as much as before and he seems frustrated when trying to use his hands, but he is not able to open them up to use them. *Id.*

Dr. Crawford noted that "[H.H.] was seen back in clinic by Dr. Aalbers on 11/22/13 and he felt that his right hand was more dystonic." *Id.* A swallow study conducted in the hospital returned normal results, and an EEG did not demonstrate any seizure activity although "there was mildly slow background activity." *Id.* Dr. Crawford noted that "CSF neurotransmitter studies done on 11/14/13 returned and were abnormal. The neopterin and tetrahydrobiopterin were significantly elevated." *Id.* Lab testing revealed "several long chain acylcarnitine elevated right at the cutoff ranges" and a "pattern of mildly elevated acids not in a pattern for specific disorder." *Id.* at 15. A brain MRI revealed "mild cerebral volume loss, myelination normal for his age." *Id.* Dr. Crawford's notes again indicated that H.H. was diagnosed with a developmental delay, specifically a slight delay in gross motor function and fine motor function/ADLs, and a significant delay in language functioning. *Id.*

On December 9, 2013, H.H. underwent an EEG which returned normal findings. Ex. 52 at 45.

On December 18, 2013, H.H. was seen by Dr. Richard Roberts at Cook Children's Hospital Neuroscience Center for a consultation regarding his tethered spinal cord. Ex. 53 at 1. In the HPI, Dr. Roberts noted that H.H. was a

> 16-month-old patient who was referred to neurosurgery for findings of a tethered spinal cord on MRI. The patient was initially worked up for rapid onset of developmental delay and hypertonia and a possible loss of motor skills. In the course of workup the patient had [an] MRI which showed a thickened and fat infiltrated filum terminale. The patient also suffers from constipation. Prior to the rapid neurologic changes the patient also dragged his right foot.

*Id.* Dr. Roberts explained the benefits and risks of surgical release of tethered spinal cord to H.H.'s parents, who indicated they wished to proceed with surgery. *Id.*

On December 19, 2013, H.H. underwent surgery to release his tethered spinal cord. Ex. 53 at 7. During surgery Dr. Roberts collected cerebrospinal fluid to be tested by neurology. *Id.* at 8. Dr. Roberts noted that the procedure was successful and H.H. tolerated the procedure well. *Id.* He was taken to recovery in stable condition. *Id.*

Following surgery, H.H. was seen by Dr. Aalbers. Ex. 55 at 1. Dr. Aalbers noted that the lumbar puncture showed "remarkably high elevations of biopterin and neopterin; the highest neopterin levels we have ever seen." *Id.* Dr. Aalbers noted that the differential diagnosis in a patient with new-onset dystonia and significantly elevated neopterin levels was likely "Aicardi-[Goutières] syndrome." *Id.* H.H.'s brain MRI was "completely normal", but in the interim, he continued to regress developmentally and was no longer using his arms. *Id.* Dr. Aalbers also wrote that H.H.'s elevations of his liver enzymes (325 for the AST and 472 for the ALT) were also indicative of possible AGS. *Id.* He noted that H.H. had been "intermittently lethargic, tired more so than usual over the last 3 or 4 months without significant weight gain." *Id.* at 2.

Dr. Aalbers laid out next steps for H.H.'s treatment. Ex. 55 at 3. He ordered an ultrasound of H.H.'s liver and spleen, noting that "fluctuating liver inflammation and spleen inflammation can be consistent with Aicardi-Goutieres syndrome with subsequent resolution of the syndrome." *Id.* at 3-4. Dr. Aalbers also ordered a repeat EEG, noting that "patients can have stages of encephalopathy that come and go, which may explain why his abnormal EEG subsequently improved, and now that he is having progressive upper extremity symptoms, the EEG would again be abnormal." *Id.* at 4.

Dr. Aalbers noted that AGS was incredibly rare. Ex. 55 at 4. He discussed that H.H.'s thallium levels were elevated and this could "inhibit glutathione levels and cause similar symptoms of encephalopathy" to AGS. *Id.* Dr. Aalbers recommended that H.H.'s parents discontinue all homeopathic medications until thallium levels could be resolved. *Id.* In the context of AGS, Dr. Aalbers noted that H.H. was likely in the early onset of the disease and repeat imaging could now show evidence of early-onset leukodystrophy. *Id.* He also ordered testing for H.H.'s CSF interferon alpha. *Id.*

Accordingly, H.H. underwent an EEG on the same date. Ex. 53 at 12. Dr. Fernando Acosta, interpreting the results, stated that "this is an abnormal EEG due to mild generalized background slowing. This may be consistent with an encephalopathic state. No electrographic nor electroclinical seizures were recorded." *Id.*

On December 20, 2013, while still in the hospital, H.H. was seen by Lori Thompson, CPNP for a consultation regarding his elevated transaminases. Ex. 54 at 1. In the history of present illness section, Ms. Thompson noted that H.H. had a "complex past medical history," including "abnormal newborn screening, concern[s] for a possible VLCAD", and "metabolic genetics." *Id.* Ms. Thompson noted that the workup thus far had been "within normal limits." *Id.* She noted an unremarkable family history. *Id.* Upon a musculoskeletal examination, she noted "diminished deep tendon reflexes over lower extremities, spastic tone. His tone is spastic, dynamic, dystonic, and posture has hypotonia." *Id.*

In the medical history, Ms. Thompson noted that H.H. "was a normally developing male until approximately 15 months of age and he began losing milestones. He cannot walk, sit up, roll over. He lost his verbal skills, but he is able to babble and is being followed by neurology for progressive dystonia." Ex. 54 at 1. She noted that AGS was a concern and that H.H. was being "worked up by neurology" and by gastroenterology to follow his liver transaminases and evaluate for the source of the elevation. *Id.*

On January 2, 2014, NMG labs reported the results of the repeat neurotransmitter studies ordered by Dr. Aalbers on December 3, 2013. Ex. 52 at 71. H.H.'s neopterin was elevated, with a value of 270 nmol/L (reference range 7-65 nmol/L), while his tetrahydrobiopterin was also elevated, with a value of 69 nmol/L (reference range 18-58 nmol/L). *Id.* Dr. Hyland, interpreting the results stated that "the concentrations of tetrahydrobiopterin and neopterin were above our reference ranges. Elevations of neopterin and tetrahydrobiopterin have been described in [] Aicardi-Goutières syndrome." *Id.* at 72.

On January 6, 2014, MNG labs reported no abnormalities in H.H.'s sialic acid metabolism. Ex. 52 at 69.

On January 14, 2014, H.H.'s HIV testing was returned as "non-reactive." Ex. 52 at 39. His urine sample contained elevated 3-hydroxybutyrate, elevated 3-hydroxyisobutyric, elevated 2-et-30hpropionic, elevated methylsuccinic, and low 3-OH-3-methylgutaric. *Id.* at 40-41.

On January 16, 2014, H.H. visited Dr. Samson Cantu at Cook's Children's Hospital for his abnormal liver enzymes. Ex. 55 at 9. Dr. Cantu noted that H.H. had a history of tethered cord repair, hypertonia, elevated liver enzymes all of unclear etiology. "Pt has had an extensive work-up thus far with inconclusive findings. Since release from hospital he has had no jaundice, and increased bruisability …. He has intermittent constipation responsive to miralax." *Id.* Dr. Cantu also noted that H.H.'s liver ultrasound was normal. *Id.* Upon examination, Dr. Cantu observed H.H. as developmentally delayed. *Id.* at 11. All other systems were normal, including H.H.'s back following surgery. *Id.* Dr. Cantu planned to repeat the liver panel, check H.H.'s CK level and potentially perform a liver biopsy, depending on the results of the liver panel. *Id.*

On January 17, 2014, Quest Diagnostics returned the labs ordered by Dr. Cantu. Ex. 80 at 8. Under "hepatic function panel", H.H.'s globulin was measured low at 1.7 g/dL (reference range 2.1-3.5 g/dL), leading to a high albumin/globulin ratio of 2.8 g/dL (reference range 1.0-2.5 g/dL). *Id.* His indirect bilirubin was low at 0.1 mg/dL (reference range 0.2-0.8 mg/dL). *Id.* His AST was

high at 117 u/L (reference range 3-56 u/L), and his ALT was high at 129 u/L (reference range 5-30 u/L). *Id.*

On February 4, 2014, H.H. was seen by Dr. Warren Marks to review the results of his testing with genetics and neurology. Ex. 56 at 1. Dr. Marks indicated to H.H.'s father that H.H.'s likely diagnosis was AGS and they were awaiting genetic confirmation. *Id.*

On the same day, H.H. visited Dr. Crawford at Cook Children's Hospital, Department of Clinical and Metabolic Genetics to discuss his disease and diagnosis. Ex. 50 at 23. Dr. Crawford stated that "[H.H.] has had 2 lumbar punctures that showed an elevated neopterin. This is seen only in Aicardi-Goutieres syndrome (AGS) and HIV infection. We ruled out HIV infection and pursued testing for AGS…" *Id.* at 24. Dr. Crawford noted that blood testing and CSF both "showed elevated levels of IFN-alpha which is diagnostic for AGS." *Id.* In discussing H.H.'s possible diagnosis with his family, Dr. Crawford stated that

> [H.H.] appears to be hav[ing] a later-onset presentation for AGS as he presents after a long period of normal development. He then presented with developmental regression and developed progressive dystonia that is characteristic of the disease. This disease can lead to a severe encephalopathy that can result in severe intellect[u]al disability and physical disabilities. There is a spectrum for this disease, so ther[e] are milder cases that have been reported in the literature depending on which gene is involved. Typica[l]ly, these children have a regression phase, followed by irritability, then a slow progressive encephalopathy phase. These children[] typically develop peripheral spasticity, truncal hypotonia, dystonic posturing upper limbs and poor head control, all of which [H.H.] is currently displaying.

*Id.* Dr. Crawford noted that Dr. Crow's lab in England was working on DNA testing to determine which of H.H.'s genes were involved in his disease. *Id.* She noted that AGS is "now known to be associated with mutation in 6 different genes." *Id.* Dr. Crawford stated that "there are currently no treatments known to affect or slow disease progression" and the H.H. would need "to continue aggressive therapies due to his hypotonia and dystonia." *Id.*

Regarding AGS in particular, Dr. Crawford noted that it is an "autosomal recessive disorder, therefore recurrence risks for future pregnancies is 25%.... Therefore, if DNA testing confirms [H.H.] is affected, parents are obligate carriers." *Id.*

On March 6, 2014, Petitioner received the results of H.H.'s genetic testing. Ex. 50 at 40. Only one significant mutation was found, a VLCAD deficiency in the gene ACADVL. *Id.* at 42.

On the same date, H.H. was seen by Dr. Marks for evaluation. Ex. 56 at 18. Dr. Marks noted that H.H.'s eyes were "clear and anicteric and non cooperative with fundoscopic testing." *Id.* He observed H.H. to be "awake (but not very interactive)" and that he was nonverbal. *Id.* Upon conducting a motor examination, Dr. Marks noted "motor spastic, rigidity, hypotonic axial, hypertonia appendicular, and dystonia diffuse (and severe generalized dystonic posturing - trunk and extremities with rigidity)." *Id.* He was non-ambulatory, and had decreased range of motion in

his spine. *Id.* Dr. Marks noted that the diagnosis for H.H. was still "possible AGS" but "with negative genetic markers thus far." *Id.* at 19. Dr. Marks also considered a retroviral infection as a possible cause. *Id.* He noted that H.H. suffered from extreme irritability and ordered further testing. *Id.*

On March 13, 2014, H.H. was seen by Dr. Kenneth Collins for an infectious diseases consultation. Ex. 57 at 1. Dr. Collins noted that he was "consulted because [H.H.] is being referred to the infectious diseases clinic over the next couple of weeks for possible retroviral infection causing developmental delay." *Id.* Under medical history, Dr. Collins noted that H.H.'s "mother reports that she breastfed consistently until 10/09[/2013]. Within a day or 2 of stopping breastfeeding he seemed to trip and fall when he was crawling." *Id.* Dr. Collins noted that HH.'s mother reported that H.H. was "completely normal" at his 15-month checkup. *Id.* Following the checkup, she "stopped breastfeeding, and within a week he was falling. About 8 days later, after stopping breastfeeding, he got his 15-month shots. After that time he developed increased inability to crawl and this progressed over the next couple of months." *Id.* Under a review of systems, Dr. Collins noted that after H.H. "started falling in mid-October his parents noticed that he had a fever for about a week, with a red throat that resolved." *Id.*

Upon examination, Dr. Collins noted that H.H. was irritable, made good eye contact, and appeared hypertonic. Ex. 57 at 2. His impression was "progressive dystonia with regression of developmental milestones from 10/2013 through the end of 12/2013, with no improvement in milestones since then. He is now not eating very well and requires a G button" *Id.* at 3. He also had "continuous elevation in liver enzymes with negative hepatitis, cytomegalovirus, and Epstein-Barr virus serologies." *Id.* Dr. Collins wanted to recheck H.H. for HIV, but he thought it was unlikely that this was the explanation for H.H.'s condition.

On the same date, H.H. was evaluated for placement of a G button. Ex. 58 at 1. It was noted that "over the last 2 weeks, he is refusing to eat or drink very much. He maybe drinks 6-10 ounces of PediaSure per day and not really eating unless mom forces him to." *Id.* H.H. was also dehydrated, urinating 2 times per day "in the last 5 days." *Id.* He had also lost three pounds since his 15-month checkup. *Id.*

On March 15, 2014, H.H. underwent surgery for insertion of a gastrostomy tube. Ex. 59 at 1. H.H. was noted as tolerating the procedure well and the operation was successful. *Id.* at 2.

On March 25, 2014, H.H. was seen for a lumbar puncture for diagnostic studies. Ex. 56 at 38. Dr. Marks noted that H.H.'s working diagnosis "has been Aicardi-Goutieres syndrome versus retroviral infection based on his markedly elevated CSF neopterin levels." *Id.* Various samples were taken for neurotransmitter and other testing. *Id.*

On March 27, 2014, Dr. Marks received the results of H.H.'s updated neurotransmitter testing. Ex. 56 at 358. H.H.'s neopterin was extremely elevated at 239 nmol/L (reference range 7-65 nmol/L) and his tetrahydrobiopterin was also elevated at 75 nmol/L (reference range 18-58 nmol/L). *Id.* Dr. Hyland, the Ph.D. who interpreted the testing, noted that these findings were consistent with a diagnosis of AGS. *Id.* at 363.

On March 31, 2014, H.H. was seen by Dr. Jason Kennedy at Cook Children's Hospital, Department of Orthopedics Services for neuromuscular decline. Ex. 60 at 1. Dr. Kennedy noted that H.H. suffered from a "yet undiagnosed neuromuscular decline." *Id.* Interpreting an AP pelvis radiograph, Dr. Kennedy noted that H.H. had "encased tone throughout his upper and lower extremities" and could "achieve a plantigrade position of the feet." *Id.* He noted that H.H. had "increased tone at his hip abductors and [had] increased neck-shaft angles on the x-ray" and his "Shenton's lines appear[ed] intact." *Id.* Dr. Kennedy ordered a repeat AP pelvis radiograph in six months. *Id.*

On April 17, 2014, H.H. visited Dr. Cantu. Ex. 61 at 12. Dr. Cantu noted that H.H. had a "history of hypotonia of unclear etiology" and that he had an "extensive work-up by neurology with unclear diagnosis, although it has been suggested he may have a variant of Aicardi." *Id.* at 13. H.H.'s parents reported that "over the past few weeks, he has begun to [spit]-up/reflux much more often" and that they were concerned with his level of reflux. *Id.*

On April 22, 2014, H.H. visited Dr. Marks for follow up regarding neurological regression. Ex. 56 at 329. Dr. Marks noted that H.H. did "not have words at 19 months" and his "affect has become more flat." *Id.* at 330. He was diagnosed with "progressive encephalopathy and dystonia with loss of milestones and worsening dystonia. Interferonopathy with elevated [sic] neopterin clinically suggestive of Aicardi-Goutiere[s] Syndrome." *Id.* at 333.

On May 21, 2014, H.H. was seen by Dr. Kyriacos Panayides because the neurology department wanted a port added to his G button for IVIG treatments. Ex. 59 at 4. The medical records note that H.H. was throwing up about thirty minutes after feeding. *Id.* He had pain during feedings and was irritable at night. *Id.* A pH probe study was scheduled to attempt to locate the source of the issue; H.H. had no fever or associated symptoms. *Id.* Dr. Panayides diagnosed H.H. with "gastroesophageal reflux that is not responding to medical treatment." *Id.* He ordered a UGI study, noting that "if there is horrid reflux, a fundoplication will be performed at the same time as the port. If the UGI is equivocal then a formal pH probe study will be done when the port is placed." *Id.*

On May 23, 2014, H.H. was seen by Dr. Jane Keng for consultation regarding feeding intolerance, vomiting and pain behaviors. Ex. 62 at 1. Nurse notes from that date indicate that the reflux was not acidic in nature. Ex. 63 at 1. Dr. Keng noted that H.H.'s CBC was normal, sodium was 147, and his bicarbonate was 21. *Id.* at 2. She noted that his AST was elevated at 119 and his ALT was elevated at 125. *Id.* Dr. Keng's impression was that the intolerance, pain, and vomiting may be due to gastroesophageal reflux disease and she suggested that H.H. be placed on external pain medication rather than IV morphine. *Id.*

On June 23, 2014, H.H. was admitted to the hospital for a follow up with Dr. Marks after placement of his gastronomy feeding tube. Ex. 56 at 325. A review of his mental status noted that he was "awake (but not very interactive)." *Id.* at 328. He was nonverbal. *Id.* A motor system exam revealed "motor spastic, rigidity, hypotonic axial, hypertonia appendicular (and severe generalized dystonic posturing – trunk and extremities with rigidity)." *Id.* His reflexes were "1+ equal throughout and brisk throughout." His plantar reflex was "upgoing bilaterally (spontaneous extensor responses)." *Id.* H.H. was "unable to perform heel-to-shin bilaterally." *Id.* He was noted

to have "prominent scissoring." *Id.* He was non-ambulatory and had decreased range of motion in his spine. *Id.* His abdominal surgical wound was partially healed. *Id.* He was assessed with "progressive encephalopathy and dystonia with loss of milestones and worsening dystonia. Interferonopathy with elevated neopterin clinically suggestive of Aicardi-Goutiere[s] Syndrome but with negative genetic testing by two different labs." *Id.* Dr. Marks stated that because of the negative genetic testing, he was "inclined to try several months of IVIG treatment." *Id.* He noted however, that after a literature review, it did "not appear that IVIG, steroids, [or] azathioprine [would be] particularly effective" if H.H. did in fact have AGS. *Id.* at 329. Nevertheless, H.H. began IVIG treatments in June 2014 which lasted for six months. *Id.*

On October 6, 2014, H.H visited Dr. Kennedy for a follow up. Ex. 60 at 25. Dr. Kennedy discussed with H.H.'s parents that H.H. had "neuromuscular hip dysplasia and increasing migration." *Id.* Dr. Kennedy suggested Botox in the gastrocsoleus complex as treatment. *Id.*

On November 3, 2014, H.H. was seen for a lumbar puncture and Botox injections. Ex. 56 at 84. In a patient history obtained from H.H.'s mother, it was noted that H.H. developed "sudden regression after vaccines at 15 mo[nths] old." *Id.* at 104. Nurse notes from that date also indicate that H.H. suffered from an "autoimmune response to vaccines." *Id.* at 106. The notes from the procedure indicate that H.H. "has laboratory findings consistent with Aicardi-Goutières syndrome." *Id.* Dr. Marks noted that H.H. had "been on 6 months of IVIG therapy and is here for follow [] up studies." *Id.* Labs conducted that same day revealed that H.H.'s IGG serum was elevated at 2280 mg/dL (reference range 407-1009 mg/dL) and his CSF IGG/albumin ratio was elevated at 0.26 (reference range 0.09-0.25). *Id.* at 92. His neopterin was extremely elevated at 300 nmol/L (reference range 7-65 nmol/L) and his tetrahydrobiopterin was elevated at 87 nmol/L (reference range 18-50 nmol/L). *Id.* at 93.

On February 4, 2015, H.H. was seen by Dr. Michel Fayad at Boston Children's Hospital. Ex. 97 at 3. It was noted that H.H. had a history of regression at the age of 15 months and "the regression happened around the time of his immunizations." *Id.* at 2. Dr. Fayad noted that neither metabolic work-ups or genetic work-ups showed any results and the possibility of an autoimmune process was still something to look into. *Id.* at 3. Upon examination, he noted that H.H. was unable to sit, crawl, or roll over, but socially he was "very interactive." *Id.* at 2.

On March 6, 2015, Dr. Marks provided a letter stating that he was the "pediatric neurologist caring for [H.H.]." Ex. 56 at 294. He stated that H.H. had been seen in the neurology clinic for "autoimmune encephalitis" and that "he has received IVIG infusions." *Id.* Dr. Marks also noted that H.H. "has a gastrostomy tube for feeding." *Id.* at 33.

On March 20, 2015, H.H. was seen by Dr. Lesley Hall, Dr. Miriam Bloom, Dr. Sally Evans, Dr. Adeline Vanderver, and Amy Fizzino, MGC at the Myelin Disorders Clinic. Ex. 81 at 1. In summarizing the visit, Dr. Vanderver noted that H.H. was seen "in the context of developmental delay, dystonia, abnormal MRI and elevated CSF interferon/neopterin/tetrahydrobiopterin with a clinical diagnosis of Aicardi Goutieres Syndrome, but negative genetic testing and no visible intracranial calcifications on an early CT scan." *Id.* In summarizing H.H.'s clinical picture, Dr. Vanderver noted that:

> [H.H.] [h]ad been fine until about 15 months of life, hitting all milestones on time. In late October he had his 15-month vaccination (dTaP, flu, pneumonia). Approximately a week later his crawling was deteriorating. He also had a fever of about 102. Two weeks later he had rapid decline of motor function over 4 days, with loss of ability to crawl, sit, talk, or use his arms purposefully. He was extremely irritable. Per parents recollection he was not encephalopathic.

*Id.* Dr. Vanderver further noted that IVIG treatments beginning in June 2014 and lasting six months "did not seem to improve things significantly." *Id.* Dr. Vanderver noted that since that time, H.H. had been "fairly stable" and possibly even showed improvement in August 2014, "where he started to try to support himself in sitting and reaching for objects" as well as trying to use language. *Id.* at 2. Dr. Vanderver noted that H.H. does, however, continue to have significant crying and apparent discomfort. *Id.* Family history, birth history, and social history were reviewed and found to be unremarkable in relation to H.H.'s symptoms. *Id.* at 3-4.

Upon examination, Dr. Vanderver noted that H.H.'s sleep was "poor" with multiple awakenings during the night with crying. Ex. 80 at 2. H.H. also presented with sweating and a faster respiratory rate while crying. *Id.* His parents estimated that he cried about thirty percent of the day. *Id.* H.H. had dystonic posturing and crying, occasionally with…myoclonic jerks. *Id.* His neurologic examination showed that H.H. was able to "briefly regard" the examiner, but he had "no vocalizations with communicative intent and did not demonstrate receptive skills" during the examination. *Id.* at 4. Dr. Vanderver's impression was "developmental delay, dystonia, and encephalopathy." *Id.* at 6. Dr. Vanderver planned to follow up with Dr. Crow (AGS expert) to facilitate genetic resolution of H.H.'s suspected heritable interferonopathy. *Id.*

On April 1, 2015, H.H. was seen by Dr. Eric Hubli for an enlarged soft palate. Ex. 76 at 23. Dr. Hubli did not see signs of an enlarge palate, but saw signs of a possible upper airway issues for which he recommended a pulmonary evaluation. *Id.* at 26.

On April 2, 2015, H.H. visited Dr. Michelle Marcincuk for a sleep consultation due to his persistent snoring. Ex. 72 at 13-14. In the HPI, Dr. Marcincuk noted the following was "reported by parent": "Pt got vaccines about 1.5 years ago. Within 3 [] months had dev regression." *Id.* at 14. She noted that per H.H.'s mother, genetic testing was negative. She noted that Dr. Hubli (seen on April 1, 2015) believed he had low muscle tone and currently suffered from dysphagia due to low muscle tone. *Id.* Upon examination, she noted that his affect was "consistent with encephalopathy" and that he suffered from hypotonia and spasticity. *Id.* Dr. Marcincuk diagnosed H.H. with obstructive sleep apnea and hypertrophy of his tonsils and adenoids. *Id.* Dr. Marcincuk explained to H.H.'s parents that corrective surgery would likely be required. *Id.*

On April 14, 2015, H.H. was seen by Dr. Sami Hadeed for complaints of stridor. Ex. 69 at 21. In the patient history, Dr. Hadeed completed notes, which summarized a history provided by Mrs. Heller. These notes indicate that H.H. was "reportedly in perfect health until 15 months of age when he developed neurological problems that his parents attributed to immunization. [H]e was subsequently diagnosed with autoimmune encephalitis." *Id.* at 22. H.H.'s parents stated that H.H. had "noisy breathing" since birth, but this had gotten "markedly worse since he developed neurological problems specially since December." *Id.* H.H. had been seen by Dr. Marcincuk, who

diagnosed him with tonsillar and adenoidal hypertrophy, and recommended a tonsillectomy and adenoidectomy, along with a flexible fiberoptic bronchoscopy. *Id.* Upon examination of H.H.'s lungs, Dr. Hadeed noted "retractions, intercostal retractions, subcostal retractions, and strider inspiratory and clear to auscultation and no distress." *Id.* at 24. A review of H.H.'s musculoskeletal systems indicated "contractures", and an examination of his reflexes showed abnormalities of his deep tendon reflexes. *Id.* Dr. Hadeed assessed H.H.'s stridor as secondary to pharyngomalacia and his snoring as suggestive of a severe obstructive sleep apnea. *Id.* at 25.

On April 23, 2015, H.H. was seen by Dr. Cantu for a follow up of his feeding problem and gastroesophageal reflux disease. Ex. 80 at 23. In the history of present illness, Dr. Cantu noted that H.H. had a history of developmental delay, static encephalopathy, swallow dysfunction, and gastrostomy-tube dependence. *Id.* Per H.H.'s mother, he was gaining weight well. *Id.* at 24. H.H. was in a wheelchair. *Id.* at 25.

On April 27, 2015, H.H. was seen for a follow up with Dr. Kennedy. Ex. 60 at 14. In interpreting an AP pelvis radiograph, Dr. Kennedy noted that H.H. "appeared to have more well-seated hips today" and his tone was "much improved." *Id.*

On April 28, 2015, H.H. was admitted to the hospital for several procedures. Ex. 72 at 1. H.H. first underwent a bronchoscopy. Ex. 69 at 19. The procedure went well, and H.H. was diagnosed with moderate to severe pharyngomalacia and moderate laryngomalacia. *Id.*

On the same date, H.H. underwent a successful tonsillectomy and adenoidectomy. Ex. 69 at 41, Ex. 72 at 4. He was admitted to the PICU following the procedure. *Id.* A physical exam the next day revealed hypotonia and abnormal deep tendon reflexes. *Id.* It was also noted that he had a swallow dysfunction. *Id.* at 45. An examination by Dr. Hadeed revealed that H.H. was in severe pain but calmed down following administration of morphine. Ex. 70 at 13. In the HPI, Dr. Hadeed noted that H.H. had suffered from autoimmune encephalitis since 15 months of age. *Id.*

On April 29, 2015, labs were taken, measuring H.H.'s hemoglobin to be high, with a value of 13.2 g/dL (reference range 11.5-13.0 g/dL). Ex. 72 at 9. His sodium bicarbonate was also high, measuring at 7220 $mm^3$ (reference range 1500-5000 $mm^3$). His Eosinophils and Eosinophil Count Test (EOC) was low, measuring at 10 $mm^3$ (reference range 30-800 $mm^3$). *Id*. In the interpretation section of the results, it was noted that these findings were consistent with methicillin resistant staphylococcus aureus. *Id.* at 10.

On the same date, H.H. underwent an allergy panel. Ex. 77 at 1-2. H.H was noted to be allergic to cow's milk. *Id.* at 2.

On April 30, 2015, H.H. was discharged from the hospital. Ex. 72 at 1. He was scheduled for a sleep study a month later to observe if further surgery was needed. *Id.* at 2.

On May 3, 2015, H.H. was admitted to the hospital emergency room with fever, lethargy, poor perfusion, mild hypoxemia and concern for sepsis. Ex. 69 at 1. Under pertinent medical history during triage, nurse notes indicated that H.H. suffered from dystonia and encephalopathy, along with "auto immune response to vaccines", among other conditions. Ex. 71 at 14. H.H. was

given IV broad-spectrum antibiotics and admitted to the intensive care unit for further evaluation and treatment. *Id.* While in the hospital, H.H. was treated for parainfluenza bronchitis, sepsis syndrome, hypoxemia secondary to bronchitis, acute respiratory distress secondary to bronchitis, acute respiratory failure, fever secondary to bronchitis, and severe pharyngomalcia. *Id.* His hospital discharge records indicate that he suffered from autoimmune encephalitis and encephalopathy and developmental delay secondary to autoimmune encephalitis. *Id.*

On June 24, 2015, H.H. was seen by Dr. Marks for a follow up appointment. Ex. 56 at 389. His condition was largely unchanged. *Id.* at 389-391. At this point he was standing, albeit with "max support." *Id.* at 389.

On November 2, 2015, H.H. was seen by Dr. Kennedy for follow up of his hip dysplasia. Ex. 95 at 67-68. His parents reported that they were able to get him on a horse for therapy and that he was scissoring less. *Id.* at 68. Dr. Kennedy noted that his tone was increased throughout and he had had good response to Botox, which may be useful to try again. *Id.* at 71.

On February 29, 2016, H.H. was seen by Dr. Kennedy for hip tightness. Ex. 95 at 59-60. H.H. was non ambulatory and was extremely inflexible. *Id.* at 61-62. Dr. Kennedy recommended Botox injections. *Id.* at 62.

On March 4, 2016, H.H. was seen by Dr. Marc Mazade at the infectious diseases clinic as a new patient. Ex. 95 at 54, 57. It was noted that H.H. "stopped vaccines after 15 months due to neurologic condition that developed after vaccine administration." *Id.* at 56. The following patient history was obtained from Mrs. Heller and entered into the notes section of the record by Dr. Mazade:

> [H.H.] is a now 3-year-old boy who was seen by Dr. Whitworth in pediatric infectious diseases consultation as an inpatient on March 14, 2014 in regard to dystonia and progressive developmental delay. He has subsequently been diagnosed with encephalitis of an autoimmune nature presumably due to vaccinations two weeks previously. He is referred back to Infectious diseases now for possible recurrent C difficile infection. … His immunizations are on hold due to the concern for immunologically mediated neurologic injury.

*Id.* at 57.

On May 18, 2016, H.H. was seen by Dr. Marks at the spasticity clinic Ex. 95 at 49. H.H. was noted to be wheelchair bound, keeping his hands loosely fisted throughout the exam. *Id.* at 53. His mother reported that normally he was able to open them easily. *Id.* Dr. Marks noted "dystonic-type UE movements present. LEs scissor when he is lifted. *Id.*

On July 7, 2016, H.H. received Botox injections in his hips. Ex. 95 at 223. The procedure was uneventful and H.H. was discharged home. *Id.*

On August 29, 2016, H.H. was seen by Dr. Kennedy for a follow up exam following a Botox injection. Ex. 95 at 41-42. Dr. Kennedy noted that H.H. had "further migration of

progression of his neuromuscular hip dysplasia" and corrective surgery would soon likely be required. *Id.* at 45.

On November 1, 2016, H.H. was seen by Dr. Abigail Collins at the Neurology Clinic at Children's Hospital Colorado for treatment with medical marijuana. Ex. 98 at 1. H.H. was still wheelchair-bound at this time. *Id.* at 3. It was noted that H.H. had not been treated with immunomodulatory therapies to address his ongoing inflammation. *Id.* at 5. A physical exam was largely unchanged from previous exams, although it was noted that H.H. was having difficulty with lateral tongue movements. *Id.* Dr. Collins suggested continuing a trial of medical marijuana for tone. *Id.* at 6. She also strongly recommended that H.H, undergo immune-mediated treatments (such as steroids or Rituximab) after her review of the medical records. *Id.*

On December 5, 2016, H.H. was seen by Dr. Kennedy following treatment in "Colorado for treatment with distilled cannabinoids for his overall spasticity and neurologic function." *Id.* at 38. Dr. Kennedy noted that he continued to have decreased range of motion to his hips, most notably to his right hip. *Id.* at 39. H.H. had no issues with his spine. *Id*. Dr. Kennedy discussed surgery for bilateral adductor releases and bilateral proximal femoral varus derotational osteotomies with H.H.'s parents. *Id.* at 40. H.H. was scheduled for surgery on December 8, 2016. *Id*.

On December 8, 2016, H.H. underwent surgery for bilateral adductor releases and bilateral varus derotational osteotomies of the femora. Ex. 95 at 199. The procedure was uneventful and H.H. was discharged home on December 12, 2016.

On December 21, 2016, H.H. visited Dr. Kennedy for a follow up after his hip surgery. Ex. 95 at 31. This was his first visit post-surgery. *Id.* at 34. Dr. Kennedy observed no complications from his surgery and explained that H.H. could begin gentle therapy. *Id.* at 34-35.

On January 16 , 2017, H.H. again visited Dr. Kennedy for a follow up after his hip surgery. Ex. 95 at 27. At this point, he had no weight bearing restrictions, but was still reluctant to fully extend his hips. *Id.* at 30-31. H.H. was noted to be healing well and improving gradually with his flexibility. *Id.*

On February 27, 2017, H.H. had another follow-up with Dr. Kennedy after his hip surgery. Ex. 95 at 22. H.H.'s examination was fairly unremarkable and his mother reported continued improvement in stretching of his lower extremities. *Id.* Dr. Kennedy noted that H.H. had tightness in his "gastrocs", but as he continued to improve, this should resolve. *Id*. at 26.

On May 1, 2017, H.H. visited Dr. Marks. Ex. 95 at 17. The medical record noted that he stopped receiving vaccines "after 15 months due to [a] neurologic condition that developed after vaccine administration." *Id.* at 18. H.H.'s mother clarified that he was up to date on all vaccines except those normally received at four years old. *Id.*

On May 22, 2017, H.H. visited Dr. Marks for a follow-up 5.5 months post hip surgery. Ex. 95 at 15. He was noted to be "doing better" and making progress on his hip flexion contractures. *Id.* at 16. Dr. Marks scheduled a follow up appointment for four months later. *Id.*

On June 26, 2017, labs ordered by Dr. Marks found H.H.'s glucose elevated at 121 mg/dL (reference range 60-115 mg/dL). Ex. 95 at 77. A neurotransmitter study ordered the same date (but reported on August 7, 2017) found H.H.'s neopterin levels to be normal, at 47 nmol/L (reference range 7-65 nmol/L) and his tetrahydrobiopterin to be normal as well at 26 nmol/L (reference range 18-50 nmol/L). *Id.* at 78. All other results were also within normal ranges. *Id.* at 77-92.

That same day, H.H. underwent an MRI of his brain. Ex. 95 at 147. The MRI indicated that H.H. had lost white matter volume over the past three years. *Id.* The corpus callosum was complete but "quite thin". *Id.* There was also "increased abnormal T2/FLAIR hyperintensity in the periventricular white matter, extending into the centrum semiovale in the frontal regions and in the periventricular white matter." *Id.* Dr. Hayden Head, interpreting these results, noted that these findings were concerning for a cerebral neurodegenerative process. *Id.* at 148. Finally, it was noted that H.H.'s "maxillary sinuses are nearly completely opacified. There is also opacification of most of the bilateral mastoid air cells." *Id.* Dr. Head requested clinical correlation for sinusitis and ear infection. *Id.* at 148.

On July 9, 2017, H.H. was seen by Dr. Jian Tong at Cook Children's Emergency Department with complaints of seizure. Ex. 95 at 105. The seizure started with "eyes twitching then full body twitching upon ambulance arrival." *Id.* Upon arrival of EMS, H.H. had "lip smacking and eye rolling…and he also began to develop [] right upper extremity and then left upper extremity tonic-clonic twitching." *Id.* at 114. He had no history of seizures. *Id.* at 105. Under medical history, it was noted that H.H suffered from "vaccine dystonia." *Id.* The seizure lasted approximately one hour and H.H. was reportedly playful and active prior to symptoms. *Id.* He had no fever prior to the seizure. *Id.* Upon arrival at the emergency department, H.H. had a fever of $103^{o}$ F, a white blood cell count of 21, and hypoxia, with O2 saturation 86% on room air. H.H. was intubated. *Id.* Upon admission, H.H. was chemically sedated and paralyzed. *Id.* at 110. His O2 saturation was 97% on mechanical ventilation. *Id.* He had "coarse breathing sounds bilaterally." *Id.* He was also tachycardic. *Id.*

While still in the hospital, H.H. was seen by Dr. Ryan Meyer, who noted that H.H. had a past medical history "significant for autoimmune encephalopathy thought to be vaccination related with severe dystonia" at normal baseline prior to the onset of seizure. Ex. 95 at 114. Dr. Meyer noted that a blood gas was obtained which revealed a pH of 6.97 and a $CO_2$ of 111. *Id.* H.H. was transferred to the PICU and continued to receive ventilation. *Id.*

Later that day, an electroencephalogram was conducted by Dr. Adrian Lacy. Ex. 95 at 126-27. Dr. Lacy noted that H.H. was "a 4-year-old patient with a prior history of developmental delay and dystonia, who is admitted with febrile seizure, manifesting with right face and arm clonus and right eye deviation, as well as impaired mental status." *Id.* at 126. Upon examination, Dr. Lacy observed that "The hypersomnolence and generalized slowing seen in states of maximal stimulation during the recording are reflective of diffuse nonspecific neuronal dysfunction as may be seen in multiple encephalopathic or sedated states." *Id.* at 127.

On July 10, 2017, Dr. Meyer observed significant improvement in H.H.'s condition. Ex. 95 at 133. An EEG taken overnight showed no seizure activity and no epileptiform activity. *Id.*

Dr. Lacy, also examining H.H. that day, stated that H.H. appeared to return to his prior baseline. *Id.* at 134. Under impression, Dr. Lacy wrote:

> This is a very interesting almost 5-year-old patient with a prior history of acute encephalopathy with dystonia occurring at approximately 16 months of age, which has been previously associated with vaccinations by parents, although the significance of this is unclear, who has had extensive testing and have some chemical parameters consistent with Aicardi Goutieres syndrome, for which the range of onset and symptomatology may be relatively wide. However, the patient does not have any gene mutations associated with this syndrome, and variants of uncertain significance in his whole exome sequencing have not been shown to be associated. He is being treated symptomatically for his dystonia, and recent neuroimaging shows progressive white matter volume loss consistent with an ongoing neurodegenerative process of uncertain origin…. The origin of the seizure at this time is of uncertain cause, but the patient was not known to have fever prior to the onset of seizure, and has not had fever since, has no evidence for encephalitis currently by examination or by spinal fluid study. EEG is strongly suggestive of postictal slowing in the left posterior temporal region, which is strongly concordant with the patient's seizure semiology.

*Id.* at 135.

On July 11, 2017, H.H. was discharged from the hospital. Ex. 95 at 130. In the discharge summary, it was noted that:

> [H.H.'s] condition and new changes were discussed extensively with his attending neurologist, Dr. Warren Marks. The management of Aicardi-Goutieres syndrome is unclear, but it is felt by world-wide authorities that rituximab and other B-cell immunotherapy is not effective. The management of seizures is not different with Aicardi-Goutieres syndrome than with epilepsy syndromes. The plan arrived at in discussion with Dr. Marks and family was for the patient to be discharged home with Diastat to be used as rescue if needed, continue seizure precautions and first aid and ER warnings, repeat EEG following discharge at baseline to evaluate for need for initiation of antiepileptic therapy, and Dr. Marks will seek authorization for a new medication, which is designed to inhibit the JAK-1 pathway, and experimental use for AGS.

*Id.* at 131.

On August 23, 2017, H.H. was seen by Dr. Kennedy for a follow up appointment. Ex. 95 at 6. Dr. Kennedy noted H.H. liked to attempt standing. *Id.* at 10. He had had stem cell treatment done in Panama, though H.H.'s mother reported no effect as of yet. *Id.* At the time, Petitioner was still awaiting news from Dr. Vanderver or Dr. Crow regarding H.H.'s molecular diagnosis. *Id.*

On October 2, 2017, H.H. was seen by Dr. Kennedy for a follow up after his hip surgery. Ex. 95 at 1. He was noted to be comfortable and his hip flexion contractures were improving. *Id.*

at 5. Dr. Kennedy noted that H.H. was not progressing towards ambulation at this point, although he had "wide, symmetric abduction of the hips and [was] continuing to improve." *Id.*

On November 29, 2017, H.H. visited Dr. Marks. Ex. 96 at 98. H.H.'s mother stated that at the time, the only medication he was on was Botox. *Id.* at 101. She denied any new concerns regarding H.H.'s condition. *Id.* at 102. Upon examination, Dr. Marks noted that H.H.'s hypertonia seemed improved since his last visit. *Id.* He had bilateral Achilles contractures and his hips were "very tight." *Id.* He was "attentive and cooperative" and engaged well with others. *Id.* Dr. Marks' assessment was "progressive encephalopathy and primary dystonia with loss of milestones and worsening dystonia" and "interferonopathy with elevated neopterin clinically consistent [with] Aicardi-Goutiere[s] Syndrome or other autoimmune mediated event." *Id.*

On October 1, 2018, H.H. was seen by Dr. Marks for planned Botox injections in his lower extremities. Ex. 96 at 1-2. Dr. Marks described H.H.'s condition as "autoimmune [encephalitis] – presumed Aicardi Goutiere[s] syndrome." *Id.* at 2.

On December 10, 2018, H.H. was seen by Dr. Marks for a neurologic exam. Ex. 96 at 5. Dr. Marks noted that per his parents, H.H. had been less active since he received Botox injections, with intermittent dilated pupils and coolness of his extremities. *Id.* H.H. was observed to be somnolent and nonverbal. *Id.* His pupils were pharmacologically dilated and he had generalized truncal hypotonia. *Id.* He had increased reflexes and bilateral striatal toes. *Id.* at 6. Dr. Marks noted that H.H.'s dystonia was worsening. *Id.* Regarding AGS, Dr. Marks noted that H.H. had "negative genetic testing by two different labs for all seven known AGS genes – however that only covers 95% of AGS cases." *Id.*

On January 10, 2018, H.H. was seen by Dr. Kennedy for a pre-op discussion regarding his G button and removal of hardware. Ex. 96 at 69. H.H.'s mother reported that he was "tight" in his adductors. *Id.* Upon examination, his neurological condition was largely unchanged. *Id.* Upon a musculoskeletal examination, Dr. Kennedy noted that H.H.'s hip flexion contractures were improving, and that his ankles could be "fatigued to a neutral positioning." *Id.* at 73. H.H.'s radiographs showed that he had "well-seated" hips. *Id.*

On January 23, 2019, H.H. was seen by Dr. Marks. Ex. 96 at 10. Dr. Marks noted that H.H. was deteriorating with motor regression – "severe quadriparesis dystonia/spasticity with bulbar involvement." *Id.* Dr. Marks noted that H.H. was "more alert" and his extremities seemed cool rather than warm. *Id.* His examination was largely unchanged from December 10, 2018. *Id.* at 11-12. Dr. Marks noted that H.H. did not have independent sitting and no standing, and that he appeared lethargic. *Id.* at 11-12.

Dr. Marks noted that H.H.'s dystonia was currently being treated symptomatically. Ex. 96 at 13. He stated that the "best plan would be a JAK 1/2 inhibitor", noting that he had discussed the idea with Dr. Janik Crow and Dr. Vanderver (CHOP). *Id.* He also stated that "JAK 1/2 inhibition would appear [to be] the best treatment even if [H.H.'s injury was] triggered by [an] immune response to external stimulus such as immunization." *Id.*

On the same date, H.H. was seen for an MRI of the brain. Ex. 96 at 15. Dr. Hayden Head, interpreting, found "cerebral white matter volume diffusely moderately diminished, with associated continued thinning of the corpus callosum." *Id.* at 16. He also noted a "persistent thin band of abnormal T2/FLAIR hyperintensity in the periventricular white matter" and "abnormal T2/FLAIR hyperintensity with suspected volume loss of bilateral insula." *Id.* Further, "the third ventricle [was] substantially larger, while still maintaining a non-obstructed appearance." *Id.* "The lateral ventricles and fourth ventricle [were] mildly larger. The subarachnoid spaces and cerebella fissures [were] newly prominent." *Id.* Trace fluid was noted in the mastoid air cells, "markedly decreased" from H.H.'s previous MRI. *Id.* Dr. Head's impression was "enlargement of ventricles and subarachnoid spaces" and he was concerned for progressive neurodegeneration. *Id.* He also noted that there was "no significant change of already existing abnormalities" and that "for Aicardi-Goutieres syndrome, the severity of findings is quite mild." *Id.*

H.H.'s neurotransmitters were also measured at this visit. Ex. 96 at 14. His neopterin was elevated at 176 nmol/L and his tetrahydrobiopterin was also elevated at 42 nmol/L.

On July 22, 2019, H.H. visited Dr. Shirley Tetteh at Cook Children's Hospital Emergency Department. Ex. 96 at 17. H.H. presented with "seizure-like activity" at home, for which his home health nurse administered two doses of Diastat. *Id.* at 18. His mother stated that his seizure lasted for about four hours and H.H. was febrile approximately two hours into the seizure. *Id.* Per the ED nurse's note, H.H. was actively seizing upon arrival. *Id.* Dr. Tetteh also noted that three weeks prior, H.H. had received his third regimen of stem cell treatment in Panama. *Id.* H.H. was admitted to the hospital. *Id.* Upon examination, it was noted that H.H. "appeared thin" and had increased tone in both his upper body and lower body. *Id.* at 39-40. He also had abnormal muscle tone. *Id.* at 40. H.H. was admitted to the hospital on the same date. *Id.* at 17.

On September 4, 2019, H.H. was seen by Dr. Marks and his MA, Ms. Kim Sunday. Ex. 96 at 56. His examination was largely unchanged from his neurological baseline. *Id.* at 58-60.

No additional medical records pertinent to this decision have been filed.

## III. Petitioners' Affidavits and Testimony

### A. Affidavits

#### 1. Heathe Heller

Mr. Heller is H.H.'s father. He testified that H.H. was born with no complications and was otherwise healthy prior to his October 17 and 23, 2013 vaccinations. Ex. 64 at 1-2. H.H. was developmentally on track for a 15-month old child. *Id.* at 2. H.H was "able to walk with one hand assistance, crawl on his own, and climb." *Id.* H.H. was also able to say some words like "Mama" and "Dada", and interact with family members by waving, kissing, and playing with the family dog. *Id.*

The first time Mr. Heller noticed a change in H.H.'s health and behavior was one week after his 15-month checkup where he had received his vaccinations and flu shot. Ex. 64 at 2. H.H.

lost the ability to do many of the things he had been able to do prior, including crawling, feeding himself, talking, waving, and standing. *Id.* H.H. also seemed to be more irritable, and in a lot of pain. *Id.* In early November of 2013, Mr. Heller remembered that H.H. ran a fever of 102º F for two days and was recommended by Dr. Hollis to see a neurologist. *Id.* In December 2013, H.H. was referred to many specialists and had many tests and procedures performed. *Id.* H.H. still does not have a diagnosis but has general diagnoses of dystonia and encephalopathy. *Id.* at 2-3.

2. Jenna Heller

Mrs. Heller gave birth to H.H. with no complications and he was a healthy child who experienced normal minor illnesses. Ex. 65 at 1-2. H.H. was a happy, outgoing, and energetic child; he liked to play with golf clubs, hit golf balls, and play with the family dog. *Id.* at 2. Mrs. Heller took H.H. to his 15-month vaccinations in October 2013, where he received his influenza and DTaP vaccinations. *Id.* About a week after his vaccinations, H.H. ran a fever and his overall health declined. Mrs. Heller took H.H. to Dr. Leslie Hollis, who referred him to specialists at Cook Children's Hospital. *Id.* Doctors and specialists have not been able to determine H.H.'s diagnosis but he is being treated for dystonia and encephalopathy. *Id.* Mrs. Heller stated that "The only possible cause for H.H.'s drastic and significant decline in health is a complication resulting from the vaccinations he received at fifteen months, based on the timing and the severity of his problems." *Id.* at 3. It is devastating to see H.H. unable to do the things he used to love so much. *Id.* H.H. is now in a wheelchair and requires a feeding tube to eat. *Id.*

3. Angela Kleinhans

Ms. Kleinhans is H.H.'s aunt. Ex. 92 at 1. Ms. Kleinhans stated that her daughter, H.H.'s cousin, suffered from a vaccine reaction at her four month vaccinations so she has been aware of potential side effects ever since. *Id.* at 2. Ms. Kleinhans stated that H.H. regressed so severely she immediately thought it was related to his vaccinations. *Id.* Ms. Kleinhans also recalled that H.H. was a very normal baby and met his milestones on time. *Id.* Ms. Kleinhans noted that "The weekend after H.H. received his 15 months vaccinations he came down with a really high fever…. A few days [after October 23, 2013] he got sick and he was never the same again." *Id.* Ms. Kleinhans remembered receiving a call from Mrs. Heller to come to her house the weekend of November 1st because she was worried about H.H. and he was now "doing this limp thing with his leg." *Id.* Ms. Kleinhans stated she saw H.H. two times each week after this date and saw H.H. rapidly declining, from walking to limping, to crawling, and then crawling with his right leg dragging behind him. *Id.* at 3. Ms. Kleinhans recalled that the family believed he had simply injured his leg, but around November 8, 2013, Ms. Kleinhans saw that H.H. could no longer crawl or sit up. *Id.* Ms. Kleinhans next recalled that H.H.'s hands "started turning in" and he could no longer hold his head up on his own. *Id.* Ms. Kleinhans stated the Hellers took H.H. to the doctor around November 13, 2013 and in the ensuing weeks, H.H. lost all speech, he would gag on all food he ate, and he lost all motor skills. *Id.*

4. Sheri Huling

Ms. Huling signed her affidavit on March 21, 2016. Ex. 91. Ms. Huling is H.H.'s great aunt and had worked as a pediatric physical therapist for 35 years as the time she signed her affidavit.

*Id.* at 2. Ms. Huling noted that H.H. was crawling, standing, and was able to take steps between furniture before his vaccine on October 23, 2013. *Id.* Ms. Huling stated that a few weeks prior to his October 23, 2013 vaccination, she noticed some tightness in his right heel cord that she directed Mrs. Heller to bring up at H.H.'s next appointment. *Id.* Ms. Huling recommended some stretches for Mrs. Heller to do with H.H. *Id.* Because H.H. was bearing weight on both legs, Ms. Huling was not concerned. *Id.*

Ms. Huling next saw H.H. on October 31, 2013 for Halloween and noticed him fall over when in a sitting position, and fall on a separate occasion when he was standing. *Id.* Ms. Huling described a distinct memory where H.H. was standing in the family driveway as other children were boarding a hayride and noticed H.H. "just falling down while standing." *Id.* at 2-3. Ms. Huling described receiving a call from Mrs. Heller on November 14, 2013. *Id.* at 3. Mrs. Heller was very concerned because H.H. was unable to sit up or crawl and wanted Ms. Huling to see him so she knew what to do. *Id.* Within two minutes of seeing H.H., Ms. Huling averred that she knew there was a "serious neurological insult." *Id.* Ms. Huling noted that H.H.'s trunk "was so hypotonic he would just bend over forward while sitting on the floor and then could not right himself with his arms." *Id.* H.H.'s arms also could not support his body to crawl. *Id.* Everyone left for Cook Children's Hospital immediately. *Id.* H.H. continued to deteriorate over the next few months and is now wheelchair dependent. *Id.*

Ms. Huling testified at the January 22, 2020 entitlement hearing noting discrepancies between this affidavit and a letter she wrote to Ms. Guerra which served as the basis for her affidavit. *See* Tr. at 205-07. Ms. Huling's letter to Ms. Guerra was filed as Exhibit 102. In this letter, Ms. Huling stated that H.H. was crawling, standing, and taking steps between furniture prior to his vaccine on October 17, 2013. Ex. 102 at 1. After his pneumonia and flu vaccine on October 17, 2013, H.H. and Mrs. Heller visited Ms. Huling. Ms. Huling noticed that "over the last <u>few days</u> [H.H.] was having some trouble cruising around furniture and taking steps and [Mrs. Heller] asked me to take a look at him from a therapist perspective." *Id.* at 1 (emphasis added). Ms. Huling noticed that H.H. had right heel cord tightness that was alarming and told Mrs. Heller to bring this matter up at H.H.'s next visit on October 23, 2013. *Id.* Ms. Huling next saw H.H. on Halloween and noted worsening tightness in his right heel cord and described two instances where he fell while sitting and standing. *Id.* The other details provided are similar to what was stated in her affidavit. *See generally id.*; *see generally* Ex. 91.

**B. Testimony**

1. <u>Heathe Heller</u>

Mr. Heller testified at the January 22, 2020 entitlement hearing. Mr. Heller is a gas and oil consultant in Midland, Texas. Tr. at 95-96. Mr. Heller described H.H.'s first year of life as fun because he was such a playful child. *Id.* at 96. Mr. Heller did not accompany Mrs. Heller to the vaccination appointments but his first recollection of something being wrong was when H.H. began dragging his leg. *Id.* at 98. Mr. Heller also testified that he noticed something "was different" on Halloween but couldn't pinpoint a specific date regarding when H.H.'s leg dragging began. *Id.* at 99. After Halloween, Mr. Heller remembered that H.H. would be playing, get tired, and lay down; at some point the other leg started to give out as well. *Id.* at 100. Mr. Heller was not present

when Mrs. Heller drove to "Aunt Sher[i]'s" but remembered being at Cook's Hospital emergency room and talking to Dr. Aalbers. *Id.*

Mr. Heller testified that none of the doctors H.H. has seen have been able to give him a diagnosis. Tr. at 103. H.H. is currently dependent on someone at all times. *Id.* at 104. H.H. now has a full-time nurse and is able to go to school. *Id.* After the Hellers had another child, Mrs. Heller spent more time with their new baby to breast feed him, so Mr. Heller slept with H.H. from 2013-2017, until they moved to Midland and got his own room. *Id.* at 105-06.

2. Jenna Heller

Mrs. Heller testified at the January 22, 2020 entitlement hearing. Mrs. Heller is a licensed professional counselor (LPC), working in the court system as a parenting coordinator and performing custody evaluations for custody cases. Tr. at 7. Petitioners and their family moved to Midland, Texas in 2017 for Mr. Heller's work. *Id.* at 8. Petitioners have three sons, including H.H. *Id.* H.H. was born with no complications but had an abnormal newborn screening with elevated liver enzymes, which was resolved. *Id.* at 9. H.H. had some testing performed for his elevated liver enzymes but the results ended up being negative. *Id.* at 10-11.

Regarding H.H.'s first year of life, Mrs. Heller testified she was a paranoid mom but had no issues with H.H. Tr. at 11. Mrs. Heller took H.H. to Dr. Leslie Hollis for his 15-month checkup and had concerns about whether his language skills were on track and also with him being "pigeon-toed." *Id.* at 13. Mrs. Heller stated she could not remember if it was his right leg or both legs that turned inward. *Id.*

I asked Mrs. Heller about a phone call she made before H.H.'s 15-month appointment about her concern about his ability to walk. Tr. at 15. Mrs. Heller stated she thought H.H. should be able to walk more independently by 15 months but he would take a few steps and resume crawling. *Id.* at 15. Mrs. Heller confirmed that she was concerned about his right foot turning inward on this phone call as well. *Id.* at 15-16. Dr. Hollis assured Mrs. Heller that H.H. was developmentally in range during the 15-month checkup and was meeting the appropriate milestones. *Id.* at 16.

Mrs. Heller testified that H.H. received two vaccinations on October 17, 2013, the flu and pneumonia shots, and that the office had run out of Tdap vaccines so they scheduled for Mrs. Heller and H.H. to return the following week to get the Pentacel vaccination. Tr. at 17. Mrs. Heller said she noticed that H.H. had a fever the weekend after the vaccinations and slept the whole time. *Id.* at 18. The following week was the week of Halloween which is when Mrs. Heller noticed he was dragging his right foot and leg. *Id.* at 18-19. Mrs. Heller also remember arguing with Mr. Heller because he noticed it first and thought H.H. had fallen and injured himself. *Id.* On Halloween, other people noticed something off with H.H. because he typically stood with his friends who are around the same age as he is, but he would just fall over and sit. *Id.* at 19-20. Over the weekend, Mrs. Heller testified that his other leg started to drag as well, prompting Mrs. Heller to call and schedule an appointment with Dr. Hollis. *Id.* at 20. Dr. Hollis "had no clue… what was going on" but said H.H. needed to see a geneticist right away and got an appointment with Dr. Heather Crawford. *Id.* at 21.

H.H.'s first appointment with Dr. Crawford was on November 5, 2013.[13] Tr. at 21. Dr. Crawford knew something was wrong but did not feel like H.H. needed to be admitted; she instructed Mrs. Heller to see Dr. Hollis if he worsened. *Id.* at 22. During this appointment, Mrs. Heller stated that H.H. could no longer crawl. *Id.* He could crawl during the weekend but one leg dragged behind, which is why Mrs. Heller thought it could have been an injury. *Id.* at 23.

Between the two appointments with Dr. Crawford, H.H. went from being unable to crawl, to being unable to sit up. Tr. at 24. Mrs. Heller immediately contacted her aunt, Sheri Huling, and drove H.H. out to Decatur, Texas, where Ms. Huling lived. *Id.* at 24-25. Mrs. Huling did "some of her PT things to try to figure out" what was wrong, and told them to go to Cook's ER. *Id.* at 25. Ms. Huling and Mrs. Heller's mother drove them to Cook's [Hospital] emergency department. *Id.* Ms. Huling said something about H.H. not bending his legs, they were straight and scissoring, and had a tight right (or left) heel cord, like a ballerina. *Id.* Dr. Aalbers was the neurologist on call at the hospital so he is the one who observed H.H. upon arrival. *Id.* Dr. Aalbers believed H.H. was experiencing dopamine responsive dystonia (DRD), and prescribed H.H. dopamine. *Id.* at 26, 27. Mrs. Heller stated that the dopamine made H.H. very sick and did not help him at all. Mrs. Heller remembered reporting back to Dr. Aalbers that the dopamine was not working around two weeks after their visit. *Id.* at 28. Mrs. Heller testified that at some point, Dr. Aalbers called to inform her that H.H.'s "brain cells are dying at a really rapid rate, and we don't know why." *Id.* at 28. The next steps for H.H. was to have his whole genetic exome sequenced, which Dr. Crawford said would take two to four months. *Id.* at 28-29. H.H. continued to get worse; he could pick up food at one point but would bite his fingers when they were in his mouth. *Id.* at 29. At some point, H.H. couldn't bring the food to his mouth anymore and it would fall out of his hands prior to it reaching his mouth. *Id.* H.H. was also not sleeping much at the time and was crying all the time; only over time did the Hellers discover it was because he was in pain. *Id.* at 30.

Around three years, ago, in 2017, there was a huge turn around and it was "kind of like he came out of this fog." Tr. at 30. Dr. Hollis informed them that H.H. probably had a massive migraine all the time and was cramping. *Id.* at 30-31. Somewhere around December 2013 or January 2014, doctors were able to tell the Hellers that H.H.'s neopterin and tetrahydrobiopterin levels were too high, and medical research could only find levels that high in HIV or AGS patients. *Id.* at 31. Drs. Aalbers and Crawford explained that AGS was a very rare genetic disorder, more common in Amish communities. *Id.* at 32. Mrs. Heller testified that she emailed Dr. Crow to get H.H. tested for AGS around Christmas; Dr. Marks had told the Hellers about Dr. Crow and he was the most specialized researcher of AGS. *Id.* H.H.'s first round of testing was negative and there were six or seven known mutations of AGS at the time. *Id.* at 33. Another gene was discovered after the petition was filed but H.H. was still negative for the new gene. *Id.* at 33-34.

H.H. continued to worsen and was given a G tube for his dehydration and eating issues. Tr. at 34. H.H. had a consultation with Dr. Suzanne Whitworth, who asked whether H.H. had any changes in his diet, to which Mrs. Heller informed her that she had weaned H.H. completely off breastfeeding on October 9, 2013. *Id.* at 34, 37. Mrs. Heller clarified that H.H. did not deteriorate after being weaned off of breastmilk but after his vaccinations. *Id.* at 37. Mrs. Heller also disputed

[13] Later in her testimony, Mrs. Heller recognized that she had shifted these events one week forward. Tr. at 86.

Dr. Whitworth's notation that H.H. started falling in mid-October and a "red throat and fever" that lasted about a week. *Id.* at 40-41; *see also* Ex. 57 at 1. Mrs. Heller clarified she does not recall a red or sore throat. *Id.* at 41-42.

Under Dr. Marks' care, H.H. was immediately tested for AGS genes and he was started on Baclofen. Tr. at 43. H.H. also had Botox injections and prescribed Thianicol and Clonidine. *Id.* at 43-44. Mrs. Heller testified that all these various treatments did not help or alleviate H.H.'s symptoms. *Id.* at 45.

Mrs. Heller said she found out about vaccine injuries from her sister-in-law, whose daughter had a vaccine reaction. Tr. at 46. Mrs. Heller said it was always in the back of their minds because there were so many different avenues for them to pursue. *Id.* She kept suggesting things to Dr. Marks so she must have mentioned the vaccinations as some point but Mrs. Heller doesn't know specifically when. *Id.* at 46. Dr. Marks would always call H.H.'s condition AGS-like and be very vague. *Id.* at 47-48. Mrs. Heller recalled travelling to Boston and seeing a neurologist there who told her he had never seen a patient like H.H. before. *Id.* at 49. Mrs. Heller then recalled going to DC to do additional genetic testing, but the testing was also negative. *Id.* at 50.

Mrs. Heller testified that before the petition was filed, Drs. Marks and Crow were still doing some testing but Dr. Marks told the Hellers that he believed that the vaccines triggered and induced H.H.'s condition. Tr. at 51-52. H.H. had been repeatedly tested for the genes associated with AGS which came back negative. *Id.* at 53. In 2015 (she later stated that it was during 2016-2017), Mrs. Heller recalled H.H. coming out of a fog; within six months, his eyes were brighter and seemed happier and would snuggle with his family members and move his arms to reach for people. *Id.* at 53-54. The Hellers returned to Dr. Marks during this time, who was surprised at H.H.'s improvement. *Id.* at 54-55.

Mrs. Heller testified that the first two years of H.H.'s condition were horrible but the last two years (2017-2019) have been amazing. *Id.* at 55. The Hellers slept with H.H. until they had a second child and they slept in entirely separate rooms. *Id.* at 56. The Hellers' second child grew up travelling with H.H. and going to all of this medical appointments. *Id.* Their second child had to grow up quickly as a result. *Id.*

Regarding the November 11, 2013 visit with Dr. Hollis, the medical record notes that H.H. had been fussy for the past week and had been experiencing developmental regression over the last month. Tr. at 60-61. Mrs. Heller denied this record indicated H.H.'s developmental regression began around October 11, 2013. *Id.* at 61.

Because there was some confusion with the timeline, Mrs. Heller then recounted what occurred from her September 13, 2013 phone call to the November 11, 2013 appointment with Dr. Hollis. Tr. at 63-66. Of note, Mrs. Heller stated that at some point after his vaccinations, H.H. ran a fever and on a Monday morning, they went to see Dr. Hollis; on a Tuesday, they had an appointment with Dr. Crawford; on Thursday, they went to Ms. Huling's house and went to the hospital. *Id.* at 65-66. Mrs. Heller also recalled having an argument with Mr. Heller the week of Halloween because other people had noticed H.H. having issues. *Id.* at 66. Mrs. Heller testified that all she could remember was H.H. slept throughout the weekend and "[b]y Halloween, he was

not running a fever anymore, because I wouldn't have let him around his little buddies, his friends." *Id.*at 68. Between Halloween and when he was seen by Dr. Hollis, H.H. must have only experienced leg dragging, otherwise she would have sought medical attention sooner. *Id.* at 68-69. Mrs. Heller's concern grew only when he was unable to sit up "that Monday morning." *Id.* at 69. There was a dramatic change between Monday and Thursday; H.H.'s legs were stiff, and his torso was hypotonic. *Id.* Mrs. Heller was unsure if his fever occurred the weekend after his October 17, 2013 vaccinations or after the October 23,2013 vaccination. *Id.* at 70-71. Mrs. Heller testified that around Halloween, H.H. could stand and he tried to play with his friends but he would fall over and it "presented more like maybe at that time a virus kind of thing." *Id.* at 72. The leg symptoms occurred in his right leg and transferred to his left, then torso, arms, grasping, and the mouth was last. *Id.* at 72-73. This progression lasted until the end of 2013, leaving H.H. nonverbal and unable to chew. *Id.* at 73.

Mrs. Heller testified that H.H. now sees seven therapists, once or twice per week, and regularly sees Drs. Marks and Hollis. Tr. at 87. H.H. has also had the same teacher for the past 2.5 years. *Id.* H.H. is able to communicate through his eyes, he can watch television, and he is happy most of time. *Id.* at 87-88. H.H. still cannot move independently but he can move his arms to grab people's faces. *Id.* at 89.

3. Sue Sewell

Ms. Sewell is Mrs. Heller's mother, grandmother to H.H. Tr. at 108-09. Ms. Sewell is now retired but was a registered nurse, and worked as the chief nursing officer at a hospital in Decatur. *Id.* at 109. Decatur is not far, so Ms. Sewell made almost weekly visits to the Hellers. *Id.* at 109-10. Ms. Sewell accompanied Mrs. Heller to the October 17, 2013 appointment with Dr. Hollis where H.H. received two vaccinations. *Id.* at 111. Ms. Sewell stated she remembered H.H. could walk about two to three steps unassisted. *Id.* at 112. She also stated she did not remember any conversation at the appointment regarding the turning inwards of H.H.'s right leg. *Id.*

Ms. Sewell testified that the weekend before Halloween, around October 26th, H.H. was sleeping for many hours and she thought it was strange. Tr. at 113. She brought it up to Mrs. Heller but they weren't sure if it was an issue they should be concerned about. *Id.* Ms. Sewell also noticed that H.H.'s legs did not really support him, and he kept falling over. *Id.* Ms. Sewell stated her daughter, Mrs. Heller, would call nearly every day expressing concern that H.H. was not standing anymore. *Id.* at 115. H.H. would try to feed himself but would end up biting his finger, demonstrating he couldn't coordinate his movements. *Id.*

On November 7, 2013,[14] Ms. Sewell recommended Mrs. Heller take H.H. to her sister, Sheri Huling, or Aunt Sheri, because she had been a pediatric physical therapist for 30 years. Tr. at 115-16. Aunt Sheri did some tests with H.H., including putting him on all fours and having him crawl to Mrs. Heller, but he couldn't do these things. H.H.'s arms would collapse and he couldn't move towards Mrs. Heller. *Id.* at 116. Aunt Sheri told them they needed to go Cook's (Hospital) immediately and Aunt Sheri drove them because they were in shock. *Id.* at 117. Ms. Sewell

[14] Again, this testimony shifted the visit to Cook's Hospital forward. It is documented in the medical records that H.H. did not visit the hospital on November 7, 2013.

accompanied Mrs. Heller to H.H.'s medical appointments when Mr. Heller could not. *Id.* The Hellers' lives have changed dramatically because of all the doctors they tried to take H.H. to, around the country. *Id.* at 118-19. H.H. has never been able to get a diagnosis from any doctor. *Id.* at 119.

4. Sheri Huling

Ms. Huling is H.H.'s great aunt, Mrs. Heller's aunt, and Ms. Sewell's sister. Tr. at 124. Ms. Huling was a physical therapist for 38 years. *Id.* at 125. She received her degree from the University of Texas Health Science Center. *Id.* Ms. Huling saw H.H. approximately every month during his first year of life. *Id.* at 126. Ms. Huling had no concerns with H.H.'s early development. *Id.* at 126-27.

Ms. Huling remembered Halloween very distinctly. Tr. at 128. The family was preparing to go on a hay ride, and H.H. was standing in the driveway and just fell over. *Id.* Ms. Huling examined him after he fell over and noticed his right ankle was tight. *Id.* Ms. Huling told Mrs. Heller to inform his pediatrician. *Id.*

Ms. Huling received a phone call from Mrs. Heller on November 7, 2013,[15] asking if she could bring H.H. over. Tr. at 129. Mrs. Heller stated on the phone that H.H. kept falling over and could not sit upright. *Id.* H.H. could not crawl and Ms. Huling told them to immediately go to Cook's hospital. *Id.* at 129. Ms. Huling's first impression was that H.H. was experiencing some type of encephalopathy because his problems appeared to be neurological. *Id.* at 130.

Ms. Huling testified about her affidavit (Ex. 91). Tr. at 130-34. Ms. Huling's affidavit stated she saw H.H. on November 14, 2021, but Ms. Huling stated she saw H.H. the same day he went to Cook's Hospital, and that her affidavit had an error. *Id.* at 134.

From a therapist's perspective, Ms. Huling stated H.H. would need constant care the rest of his life. *Id.* at 135. H.H. has made some improvements, as he has been able to feed without a tube and can play some games. *Id.* at 136. Ms. Huling testified that she did not remember if Mrs. Heller called her in September 2013 regarding the turning in of H.H.'s right leg.

Ms. Huling clarified that she saw H.H. after his October 17, 2013 vaccinations and noticed the right heel tightness then. *Id.* at 139. Ms. Huling stated it was specifically "the week before the 23rd… I think it was the week before the 23rd." *Id.* Ms. Huling was brought back to the stand to confirm that she observed H.H. have right heel cord tightness before the October 23, 2013 vaccination. *Id.* at 205. Ms. Huling wrote a letter to Petitioner's counsel to prepare her affidavit. *Id.* Ms. Huling noted that H.H. exhibited normal crawling, pulling and standing, cruising, and performed other physical acts prior to his October 17, 2013 vaccination and she had video footage of it. *Id.* at 206. After the pneumonia and flu vaccines, Mrs. Heller and Ms. Huling noticed some changes, and Ms. Huling instructed Mrs. Heller to bring up the right heel cord tightness when she

[15] Ms. Huling also shifted the date of this visit forward approximately one week from its occurrence.

returned on October 23, 2013. *Id.* at 207. Ms. Huling's letter to Petitioner's counsel was admitted into the record as Exhibit 97.[16]

## IV. Expert Opinions and Qualifications

### A. Petitioners' Expert: Dr. Leslie Hollis

#### 1. Qualifications

Dr. Hollis submitted a printout of her website's "about me" page as her CV, in conjunction with her affidavit. Ex. 66 at 4. Dr. Hollis received her medical degree from the University of Oklahoma and performed her pediatric residency at [Baylor] Scott & White [Medical Center]. *Id.*

#### 2. Affidavits

Dr. Hollis, H.H.'s treating pediatrician, filed two affidavits in this case. Exs. 66 (hereinafter "First Hollis Affidavit") and 90 (hereinafter "Second Hollis Affidavit"). In her first affidavit, Dr. Hollis stated she has been H.H.'s treating pediatrician since his birth on July 14, 2012. First Hollis Affidavit at 2. Dr. Hollis noted that H.H. was a healthy patient with no major issues; he had an abnormal newborn screen which was retested and came back normal. *Id.* Dr. Hollis examined H.H. on November 11, 2013, after he had been experiencing a fever of 101.5º. *Id.* She noted that at this appointment, H.H. had noticeably less energy and his development "had been regressing over the last month." *Id.* at 2. Dr. Hollis referred H.H. to Dr. Heather Crawford, a metabolic genetics specialist, and to an appointment with Dr. Brian Aalbers, a pediatric neurologist, for his developmental issues. *Id.* Dr. Hollis continued to treat H.H. along with his other doctors. *Id.* It is Dr. Hollis' opinion that H.H.'s "rapid decline can be attributed to receiving the vaccinations on October 17, 2013 and October 23, 2013." *Id.* at 3.

Dr. Hollis' second affidavit added a few more details regarding her history of treating H.H. *See generally* Second Hollis Affidavit. Dr. Hollis stated that "H.H. has dystonia and neurological impairment that manifested itself at 16 months of age." *Id.* at 2. Dr. Hollis noted that H.H. was assessed at 12 months of age and was within the normal developmental range for his age group. *Id.* At his 15-month wellness check, Dr. Hollis noted that

> he was taking a few steps independently between objects. His mom had noted his foot possibly turning in 1 week prior to his appointment. The child was observed to bear weight on both feet, and no significant intoeing was noted when he was trying to walk. In my medical opinion, H.H. was still well within the developmentally acceptable range for his age.

*Id.* Dr. Hollis next saw H.H. on November 11, 2013, where H.H.'s mother reported that his development had been regressing over the last month; he stopped crawling, playing with toys and eating table food. *Id.* Dr. Hollis immediately referred H.H. to neurology for evaluation of his

[16] Because Petitioners did not file this letter, I prompted them to do so after the hearing. *See* informal communication remark dated 3/15/2022; ECF No. 120. The letter was received as Ex. 102.

developmental regression. *Id.* Dr. Hollis further added that H.H.'s decline was severe and rapid after his 15 month vaccinations and it was her opinion that H.H. will have "neurological and physical suffering for the rest of his life." *Id.* at 3.

### B. Petitioners' Expert: Dr. Warren Marks

#### 1. Qualifications

Dr. Marks submitted a printout of his Cook Children's Hospital physician page as his CV. Ex. 67 at 6-7. Dr. Marks received his medical degree from Texas Tech University School of Medicine and completed his residency and fellowship at the University of Oklahoma College of Medicine. *Id.* at 6. Dr. Marks is board certified in neurology with a special qualification in child neurology. *Id.* Dr. Marks has published two papers and 10 abstracts. *Id.* at 6-7. I recognized Dr. Marks as an expert in pediatric neurology. Tr. at 146.

#### 2. Affidavit and Expert Report

Dr. Marks filed one affidavit and one expert report in this case. Exs. 67 (hereinafter "Marks Affidavit") and 94 (hereinafter "Marks Expert Report"). In his affidavit, Dr. Marks noted that his care of H.H. began on February 4, 2014, and that he had been treating H.H. for rapidly progressing dystonia with encephalopathy. Marks Affidavit at 2. H.H.'s other symptoms included: acute constipation, abnormal liver enzymes, encephalopathy, cough, dystonia, speech delay, and delayed milestones. *Id.* Dr. Marks has performed many work-ups over the years and has ruled out over 20 different possible causes of H.H.'s condition, to include AGS, GBS, lysosomal storage disease, Creutzfeldt-Jakob disease, heavy metal poisonings, Epstein-Barr virus, enteroviruses, and cytomegaloviruses. *Id.* Testing done on H.H. includes extensive lab work, exome sequencing and lumbar punctures. *Id.* Most testing was performed at Cook Children's Medical Center though testing for AGS was performed in England and France. *Id.* Dr. Marks opined that the start of H.H.'s symptoms began after the receipt of his fifteen month vaccinations.[17] *Id.* Dr. Marks further opined that there is no other explanation for why H.H. developed severe and rapidly progressing dystonia with encephalopathy at 15 months, other than his exposure to his 15 month vaccinations. *Id.* at 3-4. Dr. Marks provided a theory as to how H.H.'s exposure to his vaccines caused his condition:

> Essentially, H.H. was exposed to an antigen in the influenza or DTaP vaccines that triggered a neurological deterioration and an abnormal movement disorder, specifically dystonic posturing in his lower extremities which has rapidly progressed throughout his body. Unfortunately, this Influenza or DTaP antigen must have been similar to a "self" antigen in H.H.'s neurological structure, so that a neurological deterioration also occurred. H.H.'s lab results showed elevated levels of neopterin a marker of immune system activation, and tetrahydrobiopterin, an enzyme used to produce serotonin, dopamine and other neurotransmitters. Elevated levels of these enzymes have caused the interferonopathy, an up-

[17] It should be noted that Dr. Marks did not observe or treat H.H. until he was more than 18 months old.

> regulation of type-1 interferons, consequently resulting in his current symptomatic state. The increase in interferons creates a sense that the body is under attack from an outside source, but in H.H.'s case, there is no such source so the cause is only neurological in nature H.H.'s neurological status has since stabilized, but still has persistent increases in his interferon levels. This stabilization of his neurological status, which was hyperactive post-immunization is indicative of the cause being derived from the vaccinations…. Based on the timing of his vaccine inoculation and the development of his symptoms thereafter, this theory makes complete sense as a probable cause for his symptoms since there is no other explanation for the sudden development or rapidly progressive dystonia with encephalopathy due to the increased interferon levels in an otherwise previously healthy individual with no other environmental exposures.

*Id.* at 4-5. Dr. Marks also opined that H.H. will suffer from dystonia and encephalopathy for the remainder of his life and will require extensive continued medical treatment. *Id.* at 5.

Dr. Marks' expert report was filed in response to Dr. Barañano's first expert report. Ex. 94 at 1. Dr. Marks clarified that H.H. had been tested for the IFIH1 gene and was negative. *Id.* He also confirmed that H.H. was negative for all known AGS genes and other non-genetic inflammatory disorders like Lyme disease. *Id.* Dr. Marks' report indicated that H.H.'s CSF neopterin levels were normal, indicating the immune activation process may be normalizing but extensive CNS damage has been done. *Id.* H.H.'s MRI in July 2017 also revealed no intracranial calcifications or injury to the basal ganglia consistent with AGS. *Id.* Dr. Marks' concluded that there are two realistic options for H.H. at this point: he is one of the very rare cases of AGS without a known genetic marker or he has an AGS-like interferonopathy triggered by "external immune stimulating condition such as immunization." *Id.* Given his normalizing neopterin levels, "I would favor the latter." *Id.*

2. Testimony

Dr. Marks testified at the January 22, 2020 entitlement hearing. Dr. Marks has practiced in the field of pediatric neurology for 40 years and specializes in movement disorders, rehabilitation, and neuromuscular disorders. Tr. at 140. Dr. Marks is H.H.'s treating pediatric neurologist. *Id.* at 141-42. Dr. Marks' first visit with H.H. was in February 2014. *Id.* at 142. When Dr. Marks saw H.H. on February 4, 2014, there was a presumptive diagnosis of Aicardi-Goutières syndrome based on elevated neopterin levels in his spinal fluid. *Id.* at 146.

Dr. Marks testified that AGS is "a disorder of interferon activity… it's an immune mediated disorder that typically result[s] in neurologic regression with dystonia, intracranial calcifications,… seizures… almost always have a skin rash of some kind." Tr. at 147-48. H.H. did not have a skin rash or calcifications on his neuroimaging. *Id.* at 148-49. AGS patients are also more likely to have seizures. *Id.*at 149. With a working diagnosis of AGS, Dr. Marks sent H.H.'s testing to be done by Medical Neurogenetics in Atlanta, which has a neurotransmitter gene panel test for AGS. *Id.* at 149-50. H.H. was tested against then six known genes for AGS. *Id.* at 150. A seventh gene was identified but H.H. tested negative for all seven genes. *Id.*

Dr. Marks had discussions with Dr. Yanick Crow, the world's expert in AGS. Tr. at 150. Samples were sent to France, where Dr. Crow's research lab was located. *Id.* Dr. Crow confirmed H.H.'s interferon levels were elevated. *Id.* H.H.'s entire genome was sequenced to find genes that would explain his dystonia, AGS, and other symptoms, but this testing did not provide an explanation for H.H.'s condition. *Id.* at 151. Dr. Marks gave H.H. a diagnosis of an "AGS-like" disease because H.H. has many of the clinical manifestations of AGS but no genetic markers. *Id.* Dr. Marks testified that he cannot prove H.H. does not have AGS, but noted that there is clinical evidence to suggest it is not AGS as well. *Id.* The most recent terminology he has used to describe H.H.'s condition is dystonia with interferonopathy. *Id.* at 153. An interferonopathy means H.H. has an elevated level of interferon. *Id.*

Dr. Marks stated vaccinations are meant to cause an immune response and H.H.'s symptoms began shortly after immunization. Tr. at 153-54. Dr. Marks additionally testified that "it's not unique for vaccine to cause immune responses that produce neurologic injury. Guillain-Barre has been well known to be associated with vaccines off and on." *Id.* at 154. Dr. Marks stated that H.H. has had elevated interferon levels for six years, with some fluctuation, but it otherwise indicates that there is a persistent immunologic response or a genetic defect. *Id.* at 155.

Dr. Marks also discussed H.H.'s case with Dr. Vanderver, the American expert on AGS, and had the Hellers see her while she was working at Children's National Hospital in Washington, DC. Tr. at 156-57. Dr. Marks testified that Dr. Vanderver was not convinced H.H. had AGS and H.H. could not participate in any trials because he did not have any genetic markers for the disease. *Id.* Regarding H.H.'s current condition, Dr. Marks opined that H.H. has stopped regressing and has been clinically stable for the last year because he has not lost any skills. *Id*. at 157.

Dr. Marks opined in favor of vaccine causation for several reasons. First, H.H. was a normally developing child prior to his 15-month vaccinations. Tr. at 158. Second, there is a temporal correlation between vaccination and H.H.'s deterioration. *Id.* at 159. Finally, H.H. has no known no genetic marker that would explain his condition. *Id.*

For the 5% subset of AGS patients who do not a known genetic marker for AGS, they are given the AGS diagnosis because they have other signs, like calcifications in the brain or skin rash. Tr. at 160-61. H.H.'s onset at 15-months of age is significant in that later onset cases of AGS tend to be milder. *Id.* at 161. Another difference in H.H.'s presentation is that he seems to have stabilized; if this were a "triggered reaction," it makes sense that it should wane over time. *Id.* Dr. Marks opined that he did not expect an AGS patient to make improvements; it is a "relentlessly progressive disorder." *Id.* at 164.

Dr. Marks examined H.H. one day prior to the entitlement hearing and observed that he was stable. Tr. at 166-67. Dr. Marks noted his condition had not changed; H.H. still has very severe dystonia but he has a communication device that helps him interact and he is much less irritable. *Id.* at 167. Dr. Marks confirmed his belief that either H.H. has a rare case of AGS without a known genetic marker or he has an AGS-like interferonopathy "triggered by external immune stimulating conditions such as immunization." *Id.* at 170. Dr. Marks also testified that he does not know why the vaccines were able to trigger such a sustained reaction, as he is not an immunologist. *Id.* at 170-71. Even in viral mediated diseases like Guillain Barré syndrome, the response is not sustained

over time. *Id.* Dr. Marks did not identify a specific vaccine he believed was more likely to be causal. *Id.* at 173. Dr. Marks used Guillain Barré syndrome as a model when discussing the medical appropriate time frame for when an immune mediate disease should develop, usually one to two weeks after immune stimulus. *Id.* at 175-76.

Dr. Marks communicated with Drs. Crow and Vanderver mostly at conference meetings or phone calls. Tr. at 177-78. Dr. Marks confirmed that Dr. Vanderver was unsure what condition H.H. had but she noted that she believed H.H. likely has an inherited interferonopathy. *Id.* at 179. Dr. Marks also confirmed that there was no literature submitted to support his proposed theory of molecular mimicry in this type of case. *Id.* at 187. But Dr. Marks stated his theory was not specific to molecular mimicry, just that an immune response was triggered as a result of the vaccinations H.H. received. *Id.* at 188. We know that vaccines trigger an immune response, and on occasion, "the immune system just goes wild." *Id.* at 193. Dr. Marks testified that in his conversations with Dr. Crow, Dr. Crow believed that AGS was the most logical diagnosis even though they could not identify which gene caused H.H.'s condition. *Id.* at 203-04.

Dr. Marks testified that H.H.'s condition started when H.H. had a fever and was irritable. Tr. at 195. I also asked Dr. Marks if I find onset of H.H.'s condition was prior to his 15-month vaccinations, would his theory change. *Id.* Dr. Marks opined that the vaccinations could cause a fever to develop which could be "enough to trigger an irreversible neurologic decline." *Id.* at 196-97.

### C. Petitioners' Expert: Dr. Lawrence Steinman

#### 1. Qualifications

Petitioner filed Dr. Steinman's CV on July 24, 2020. Ex. 101, Tab 1. Dr. Steinman received his medical degree from Harvard University and was a NIH Fellow in Chemical Neurobiology at Harvard Medical School. *Id.* at 1. Dr. Steinman completed his residency in pediatrics and pediatric and adult neurology at Stanford University Hospital. *Id.* Dr. Steinman is the GA Zimmermann Chair as Professor of Neurological Sciences, Neurology, and Pediatrics. *Id.* Dr. Steinman is board certified in neurology and is involved in the American Academy of Neurology as a fellow, the American Neurological Association, the American Association of Immunologists, and the Clinical Immunology Society. *Id.* at 2. Dr. Steinman has over 40 patents (not limited to U.S. patents). *Id.* at 2-3. Dr. Steinman has published nearly 600 articles. *Id.* at 5-48.

#### 1. Post-Hearing Expert Reports

Petitioners filed two reports from Dr. Lawrence Steinman. Exs. 101 (hereinafter "First Steinman Rep.") and 99 (hereinafter "Second Steinman Rep."). In his first report, Dr. Steinman stated that his theory focuses on "how the components of the [Pentacel] vaccine can drive an interferon response. It is *not* a theory based on molecular mimicry." First Steinman Rep. at 9. There are two types of interferons have different receptors but share common signaling pathways including JAK and STAT molecules. *Id.* Type 1 interferons break down into other subtypes, whereas Type 2 interferons are only broken down to gamma interferon. *Id.* The Pentacel vaccine consists of many different components, including DTaP-IPV, ActHIB, and H. influenzae type b

bound to tetanus toxoid. *Id.* at 11. The pertussis toxin "induces immune responses to both gamma-interferon and to type 1 interferon." *Id.* at 12.

The Pentacel vaccine also contains alum, which activates the NALRP3 inflammasome, "which plays a role in inducing interferonopathies." First Steinman Rep. at 12. There are a number of interferon responsive neuroinflammatory conditions such as multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE), and these conditions are tied to strong activation of innate immunity induced by the NLRP3 inflammasome. *Id.* Dr. Steinman also coauthored a paper about how Type 1 IFNs and type II IFN mediate both regulation and inflammation in MS, neuromyelitis optica, and EAE; however "the underlying mechanism for these Janus-like activities of type I and II IFNs in neuroinflammation remain unclear." *Id.* at 14. Dr. Steinman noted that "[a]lthough endogenous type I IFN signaling provides a protective response to neuroinflammation, we find that when IFFN-g signaling is ablated, type I IFNs drive inflammation, resulting in exacerbated EAE. *Id.*

Dr. Steinman stated that although H.H. does not have an ADAR-1 mutation, a vaccine could still trigger his interferonopathy. First Steinman Rep. at 14. Dr. Steinman cited to Dr. Crow's paper (Ref. 18) which states that:

> Indeed, considering a putative role of physical stressors, note should be made of the cold dependency of the skin lesions seen in the type I interferonopathies and of a striking temporal relationship between the onset of ADAR1-related bilateral striatal necrosis and preceding infection. Whether vaccination represents a disease trigger is an important, and currently unanswered, question. Meanwhile, the possibility of a "cumulative" genetic burden contributing to cellular pathology is notable in light of recently published data on the group of type I interferonopathies caused by loss-of-function mutations in proteasome subunits.

*Id.*; *see also* Rodero & Crow, *Type I interferon–mediated monogenic autoinflammation: The type I interferonopathies, a conceptual overview*, 213 J. EXP. MED. 12, 2527-38, 2351-52 (2016) (filed as Ex. 101, Tab 18) (hereinafter "Rodero & Crow"). Dr. Steinman opined that the onset of H.H.'s neuroinflammation within three weeks of the Pentacel vaccination is consistent with references 18 and 19. *Id.* at 15. Dr. Steinman further opined that the Pentacel vaccine significantly aggravated H.H.'s prior condition which included the mild intorsion of his foot prior to the vaccination. *Id.* at 16.

Dr. Steinman filed a second expert report in response to Dr. McGeady's report. Ex. 99. Dr. Steinman stated that both experts agree that the genetic basis for H.H.'s interferonopathy remains elusive, however the diagnosis of an interferonopathy is akin to AGS. *Id.* at 2. Where Drs. McGeady and Steinman disagree is whether the Pentacel vaccine can trigger a "physiologic amount of type I interferon." *Id.* Dr. Steinman clarified that he believes that the vaccine is merely a trigger for an interferon response. *Id.* The overproduction of interferon type 1 "can be explained by the references which show that there is a resistance in some forms of neuroinflammation to the normal beneficial response of interferon. So unchecked interferon production can drive neuroinflammation." *Id.*

Dr. Steinman added that if H.H. did have an underlying AGS condition, the Pentacel vaccine would have worsened his neuroinflammation. Second Steinman Rep. at 3. Dr. Steinman reiterated that it does not matter if H.H. had neurological symptoms prior to his 15-month vaccinations, just that the Pentacel vaccine on October 23, 2013 caused neuroinflammation, which could have significantly aggravated his condition, or caused his condition. *Id.* at 4.

**D. Respondent's Expert, Dr. Stephen McGeady:**

1. Qualifications

Respondent filed an updated curriculum vitae for Dr. McGeady on April 4, 2020. Ex. I. Dr. McGeady received his medical degree from Creighton University and completed his residency in pediatrics at St. Christopher's Hospital in Philadelphia, and his fellowship at Duke University in psychiatry and allergy. *Id.* Dr. McGeady is currently a professor of pediatrics at Jefferson Medical College and is the Emeritus Chief of the Allergy, Asthma & Immunology Division at duPont Hospital for Children. *Id.* Dr. McGeady is board certified in pediatrics and allergy/immunology. *Id.* Dr. McGeady has published at least 66 peer reviewed papers and 93 abstracts. *Id.* at 2-7, 7-13. I recognized Dr. McGeady as an expert in pediatric immunology and pediatrics. Tr. at 213.

2. Expert Reports

Dr. McGeady filed two expert reports in this case. Exs. D (hereinafter "First McGeady Rep.") and J (hereinafter "Second McGeady Rep."). In Dr. McGeady's first report, he noted that H.H. lacked some clinical features of AGS, such as calcification in the basal ganglia, chilblain-like skin lesions, and pleocytosis in the CSF. First McGeady Rep. at 4. However, AGS literature stated intracranial calcification should not be considered a prerequisite for an AGS diagnosis. *Id.* Dr. McGeady also disagreed with Drs. Hollis and Marks' assessment that H.H.'s normal development until 15-16 months is incongruous with AGS. *Id.* at 4-5. H.H.'s fever is also consistent with 405 of subjects in the Rice paper. *Id.* at 5. Markedly high neopterin and biopterin levels are typically only seen in two disorders, AGS and congenital HIV. *Id.* Dr. McGeady also noted that Dr. Vanderver believed H.H. has a "suspected heritable interferonopathy", which is consistent with AGS and inconsistent with an adverse vaccine reaction. *Id.* at 6; *see also* Ex. 81 at 10.

Dr. McGeady also opined regarding Dr. Marks' proposed causal theory. First McGeady Rep. at 7-10. Dr. McGeady stated that there are six possible metabolic lesions that have been proposed to account for the excess production and/or accumulation of interferon alpha and none of these mechanisms is "dependent upon immune activation alone." *Id.* at 8. Dr. McGeady also noted that H.H.'s medical history does not include any localized reaction to any of the vaccines he received, which indicates no excessive reaction was produced. *Id.* at 9. Additionally, H.H. had elevated transaminase levels, which are associated with AGS but have not been associated in cases of patients who developed encephalopathies after vaccination. *Id.*

Dr. McGeady also pointed out Mrs. Heller's 9/13/2013 phone call regarding H.H.'s inturning of his right foot and inability to walk; he opined this may have been the first mention of H.H. losing skills. *Id.* at 10. Dr. McGeady also addressed Dr. Hollis' affidavit which broadly stated

she had never seen a similar loss of skills in a previously normal child, and based on the timing, believed that H.H.'s condition was caused by his immunizations. *Id.* at 11. Dr. McGeady reiterated that H.H.'s lack of genetic markers does not rule out AGS, considering his clinical and laboratory findings. *Id.*

3. Testimony

Dr. McGeady provided testimony on molecular mimicry and testified that it is "intuitively appealing" but in reality, almost never happens. Tr. at 214-15. There are many mimics widespread in nature but there are not many autoimmune diseases linked to molecular mimicry in a frequency one expects if molecular mimicry were real. *Id.* at 215-16. There are two accepted examples of molecular mimicry, which include GBS and campylobacteria and more recently, narcolepsy with the 2010 H1N1 flu. *Id.* at 216. There is no literature or case reports linking the flu and/or DTaP vaccine to a Type 1 interferonopathy. *Id.* at 217. Nor are the viruses of these vaccines known to cause a Type 1 interferonopathy. *Id.* at 218. Dr. McGeady testified that the only know causes of a Type 1 interferonopathy are a genetic predisposition or intrauterine viral infections. *Id.* at 218-19.

In the case of an intrauterine viral infection, a Type 1 interferonopathy is caused when a viral infection is "particularly persistent" like the HIV virus in a pregnant woman. Tr. at 220. The fetus become infected as well and starts to produce large quantities of Type 1 interferon; the fetus is extremely susceptible to the adverse effects of Type 1 interferonopathy and becomes badly damaged as a result. *Id.* Both viral causation and genetically predisposed babies look similar even when different etiologies exist. *Id.* Dr. McGeady testified that even if molecular mimicry were a viable theory, he does not believe vaccinations could have triggered this kind of response. *Id.* at 223. Any triggered reaction could have an intense activation however "it gets damped down quickly." *Id.* Only in hereditary interferonopathies are there no breaks. *Id.* H.H.'s neopterin levels have fluctuated over the years but there are no active organisms in the vaccines he's received that could cause this kind of neopterin production. *Id.* at 223-224. Molecular mimicry cannot explain "something that perpetuates over six years." *Id.* at 224. Molecular mimicry also pertains to the adaptive immune system and there was no evidence of H.H. having an adaptive immune response, or localized reaction, to the vaccinations. *Id.* at 224-25.

Dr. McGeady testified that he believed that H.H.'s lack of genetic markers does not mean he does not have AGS; he noted that new genes and sub mutations are still being identified. Tr. at 228-29. Dr. McGeady opined that AGS is the condition most consistent with H.H.'s presentation. *Id.* at 233. Dr. McGeady also testified that H.H.'s improvement is not inconsistent with AGS; some patients have normal intellectual capacity and have courses that stabilize. *Id.* at 234.

4. Post-Hearing Report

Dr. McGeady's second report was filed in response to Dr. Steinman's first expert report (Ex. 101). Dr. McGeady opined that Dr. Steinman's proposed mechanism regarding how the Pentacel vaccine caused H.H.'s condition is not consistent with what is known regarding type I interferonopathies. Second McGeady Rep. at 1.

Dr. Steinman proposed that the Pentacel vaccine activated H.H.'s innate immune system and the subsequent production of type I interferon and other inflammatory cytokines caused damage to H.H.'s central nervous system. Second McGeady Rep. at 1. Dr. McGeady argued that Dr. Steinman's theory does not explain how this reaction caused elevation in interferon levels for the past six years. *Id.* Vaccines are meant to trigger an immune reaction however, to trigger a cytokine storm that is perpetuated over a number of years is unpersuasive. *Id.* at 2. Only in an inherited interferonopathy are interferon levels elevated for the length of time seen in H.H. *Id.*

Dr. McGeady addressed Dr. Steinman's second theory, that the Pentacel vaccine significantly aggravated a pre-existing condition. Second McGeady Rep. at 1. Type I interferons are produced by the innate immune system and are present in measurable quantities within 12 hours following a viral exposure. *Id.* Interferon production promptly decreases following a non-progressive provocation, thus "it would be expected that an acute injury to the CNS due to excessive type I interferon would appear sooner than several weeks following the immunization if vaccines are to be suspected as the initiating event." *Id.* H.H. suffered from many febrile illnesses (on 12/10/2012, 5/20/2013, 7/29/2013, and 11/11/2013); these would have been suspected initiating events as well. *Id.*

Dr. McGeady opined that the persistent elevations of interferon alpha and other markers of type I interferonopathy cannot be the result of H.H.'s October 17 and 23, 2013 vaccinations. Second McGeady Rep. at 3. Dr. McGeady reiterated that Dr. Steinman's theory does not account for the chronic overproduction of type I interferon. *Id.* Congenital type I interferonopathies do produce enduring excess amounts of cytokines, as seen in H.H. *Id.*

### E. Respondent's Expert, Dr. Kristin Barañano

#### 1. Qualifications

Respondent filed an updated curriculum vitae for Dr. Barañano on April 14, 2020. Ex. H. Dr. Barañano received her medical degree and a Ph.D. in neuroscience from Johns Hopkins University School of Medicine. *Id.* at 1. Dr. Barañano completed residencies in pediatrics and pediatric neurology at Johns Hopkins University School of Medicine and was a research and clinical fellow in neurogenetics at the Kennedy Krieger Institute. *Id.* Dr. Barañano is currently an Assistant Professor of Neurology at Johns Hopkins School of Medicine and is Medical Staff at the Kennedy Krieger Institute. *Id.* Dr. Barañano has published papers, case reports, book chapters and editorials. *Id.* at 2-3. Dr. Barañano is board certified in neurology, with special qualification in child neurology. *Id.* at 4. I recognized Dr. Barañano as an expert in pediatric neurology and neurogenetics. Tr. at 252.

#### 2. Expert Reports

Dr. Barañano filed two reports in this case. Exs. A (hereinafter "First Barañano Rep.") and C (hereinafter "Second Barañano Rep."). In Dr. Barañano's first report, she provided a typical presentation of AGS but cited to AGS case studies that demonstrated a wide spectrum on onset and presentations. First Barañano Rep. at 3. In Dr. Crow's 2015 paper, 8.6% of patients presented after one year of age, and this occurrence was more common with certain AGS-associated genes.

*Id.* at 3-4. Dr. Barañano also identified Mrs. Heller's 9/13/2013 phone call as onset of neurological symptoms with the in-turning of H.H.'s right foot and right heel cord tightness. *Id.* at 5. Dr. Barañano testified that H.H. had a fever in between his vaccinations; onset of AGS symptoms is often described in association with a febrile illness. *Id.* According to Dr. Barañano, H.H.'s clinical presentation is entirely consistent with AGS and it is more likely that a genetic disorder like AGS explains H.H.'s neurologic condition, rather than a molecular mimicry-like process triggered by the vaccination. *Id.* It is Dr. Barañano's opinion that H.H.'s clinical picture is consistent with AGS, with his elevated liver enzymes, high CSF neopterin and biopterin levels, elevated interferon-alpha levels in blood and CSF. *Id.* at 5-6.

In Dr. Barañano's second report, she opined that normalized neopterin levels are reported in 25% of AGS cases. Second Barañano Rep. at 1. The normalization of H.H.'s neopterin levels does not provide support that this was a vaccine-mediated process. *Id.* It remains Dr. Barañano's opinion that H.H. falls into the 5% of AGS cases where a genetic marker has not been identified. *Id.*

3. Testimony

Dr. Barañano provided a summary of AGS. Tr. at 253-54. When cells break down in our body and release DNA products, such as nucleotides, the immune system is activated to clean up the nucleotides. *Id.* at 253. In AGS, patients with the known AGS genes sense aberrant nucleotides and attack its own body and nucleotides. *Id.* at 254. There are classical traits in AGS patients, namely calcifications in the brain, white matter abnormalities, and skin lesions, however over time, a greater spectrum of AGS phenotypes have been discovered, including children with later onset and even some adult patients. *Id.* at 254-55. Dr. Barañano treats a number of AGS patients, including one with a later onset. *Id.* at 255. AGS is generally an autosomal recessive gene; if H.H.'s parents were carriers, there would be a 25% chance with each pregnancy of having an affected child. *Id.* at 256.

Interferon alpha is not tested in the United States, so other doctors, like Dr. Crow, will run the tests. Tr. at 261-62. Dr. Barañano's understanding is that interferon alpha is "essentially thought to be pathognomonic for AGS" meaning it goes hand in hand with the diagnosis of AGS. *Id.* at 262. With more patients who are confirmed with the genetic markers for AGS, we have seen more and more AGS phenotypes, thus calcifications are not considered mandatory for an AGS diagnosis. *Id.* at 262-63.

Dr. Barañano discussed exhibit 83, a case study of children who have the confirmed gene for AGS but do not have calcifications. *Id.* at 263. Dr. Barañano stated that a definite genetic diagnosis only happens in 25-40% of cases. *Id.* at 264. Whole genome sequencing is a breakthrough but "not the end all, be all." *Id.* at 264. Dr. Barañano opined that she has not yet seen a report regarding testing for the seventh AGS gene, and would have also recommended a chromosomal microarray. *Id.* at 264-65. Dr. Barañano also stated that Dr. Vanderver's research program offers whole genome sequencing so her diagnostic rate is around 85%. *Id.* at 266. There are improvements in genetic testing but there are still limitations. *Id.* Of 20,000 genes, only 5,000 are in the online Mendelian Inheritance in Man database. *Id.* at 267.

Dr. Barañano reiterated that H.H.'s onset at 15-16 months of age did not affect her opinion that AGS is still the best clinical diagnosis at this time. Tr. at 268. H.H.'s irritability is consistent with the onset of neurological symptoms. *Id.* The clinical course for AGS involves acute neurologic symptoms followed by a period of stabilization. Dr. Barañano disagreed with Dr. Marks' assessment that AGS is a relentlessly progressive neurodegenerative disorder. *Id.* at 270. Dr. Barañano added that the nervous system's normal programming is to make developmental progress, so if you superimpose a neurodegenerative process on that, a child plateaus and starts losing skills, but if the disease has stabilized, a child's underlying developmental process can continue forward even though he remains severely impaired; thus improvement is not inconsistent with AGS. *Id.* at 271.

Dr. Barañano confirmed that to the best of her knowledge there is no literature that discusses the flu or Pentacel vaccines causing a Type 1 interferonopathy. *Id.* at 271-72. Dr. Barañano also testified that other interferonopathies exist but AGS presents in the central nervous system, affecting the brain, whereas other interferonopathies are more systemic. *Id.* at 273-74. Dr. Barañano also stated that skin rashes were seen in 40% of AGS cases so it is not a universal finding. *Id.* at 277. In short, there is nothing in H.H.'s presentation that is inconsistent with AGS. *Id.* at 293. However, without a genetic confirmation, Dr. Barañano cannot say definitively that H.H. has AGS, just that it is the most likely diagnosis. *Id.* at 296.

## V. Applicable Law

### A. Petitioner's Burden in Vaccine Program Cases

Under the Vaccine Act, when a petitioner suffers an alleged injury that is not listed in the Vaccine Injury Table, a petitioner may demonstrate that he suffered an "off-Table" injury. § 11(c)(1)(C)(ii).

In attempting to establish entitlement to a Vaccine Program award of compensation for a off-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioner establish by preponderant evidence that the vaccination he received caused his injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278.

Under the first prong of *Althen*, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford,* 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Proof that the proffered medical theory is reasonable, plausible, or possible does not satisfy a petitioner's burden. *Boatmon v. Sec'y of Health & Hum. Servs*., 941 F.3d 1351, 1359-60 (Fed. Cir. Nov. 7, 2019).

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical

theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006). However, special masters are "entitled to require some indicia of reliability to support the assertion of the expert witness." *Boatmon*, 941 F.3d at 1360, *quoting Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010). Special Masters, despite their expertise, are not empowered by statute to conclusively resolve what are complex scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Hum. Servs*., 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017); *see also Hock v. Sec'y of Health & Hum. Servs*., No. 17-168V, 2020 U.S. Claims LEXIS 2202 at *52 (Fed. Cl. Spec. Mstr. Sept. 30, 2020).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause-and-effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record. *Hibbard v. Sec'y of Health & Hum. Servs*., 100 Fed. Cl. 742, 749 (2011), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Hum. Servs*., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs*., 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem*., 503 F. App'x 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs*., No. 11-

355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). In *Loving*, the United States Court of Federal Claims established the governing six-part test for off-Table significant aggravations. Petitioner must prove by a preponderance of the evidence:

> (1) The person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

*Loving v. Sec'y of Health & Hum. Servs.*, 86 Fed. Cl. 135, 144 (2009); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (adopting this as the proper legal standard for significant aggravation claims brought under the Vaccine Act). *Loving* prongs four, five, and six are derived from the Federal Circuit's test for off-Table actual causation cases. *Althen v. Sec'y of Health & Hum. Servs.*, 17 F.3d 374 (Fed. Cir. 1994).

In *Sharpe,* the Federal Circuit clarified the *Loving* prongs and what is required by petitioners to successfully demonstrate a causation-in-fact significant aggravation claim. *Sharpe v. Sec'y of Health & Hum. Servs.,* 964 F.3d 1072 (Fed. Cir. 2020). *Loving* prong three only requires a comparison of a petitioner's current, post-vaccination condition with his pre-existing pre-vaccination condition. *Sharpe* at 1082; *Whitecotton v. Sec'y of Health & Hum. Servs.,* 81 F.3d 1099 (Fed. Cir. 1996). A petitioner is not required to demonstrate an expected outcome or that his post-vaccination condition was worse than such an expected outcome. *Sharpe* at 1081. Further, a petitioner is not required "to disprove that a pre-existing genetic mutation caused [his] significant aggravation." *Sharpe* at 1087.

Under *Loving* prong four, a petitioner need only provide a "medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination." *Sharpe* at 1083; *see also Loving*, 86 Fed. Cl. at 144. In other words, petitioner is required to present a medically reliable theory demonstrating that a vaccine "can cause a significant worsening" of the condition. *Sharpe* at 1083 (citing to *Pafford ex. rel. Pafford v. Sec'y of Health & Hum. Servs.,* 451 F.3d 1352, 1356-57 (Fed. Cir. 2006). A petitioner may be able to establish a prima facie case under *Loving* prong four without eliminating a pre-existing condition as the cause of her significantly aggravated injury. *Id.*; citing *Walther v. Sec'y of Health & Hum. Servs.,* 485 F. 3d 1146, 1151 (Fed. Cir. 2007) (noting that "the government bears the burden of establishing alterative causation. . . . once petitioner has established a prima facie case").

*Loving* prong five requires a petitioner to show "a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation." *Loving*, 86 Fed. Cl. at 144. In other words, petitioner must show that the vaccinations "did" cause a worsening of [petitioner's underlying disorder]. *Id.*

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any *Althen* prong. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met their burden of proof. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009); *see also Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992).

**B. Law Governing Analysis of Fact Evidence**

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs.*, 3 F.3d 413, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records created contemporaneously with the events they describe are generally trustworthy because they "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions," where "accuracy has an extra premium." *Kirby v. Sec'y of Health & Hum. Servs.*, 997 F.3d 1378 (Fed. Cir. 2021) citing *Cucuras*, 993 F.2d at 1528. This presumption is based on the linked proposition that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11-685V, 2013 WL 1880825 at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) *mot. for rev. denied*, 142 Fed. Cl. 247, 251-52 (2019), *vacated on other grounds and remanded*, 809 Fed. Appx. 843 (Fed. Cir. Apr. 7, 2020).

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs.*, No. 03-1585V, 2005 WL 6117475 at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony -- especially

where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; see also *Murphy v. Sec'y of Health & Hum. Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs.*, 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475 at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent and compelling." *Sanchez*, 2013 WL 1880825 at *3 (citing *Blutstein v. Sec'y of Health & Hum. Servs.*, No. 90-2808V, 1998 WL 408611 at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *LaLonde v. Sec'y of Health & Hum. Servs.*, 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

### C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires petitioners to present expert testimony in support of their claim. *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (*citing Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora. *Daubert* factors are employed by judges to exclude evidence that is unreliable and potentially confusing to a jury. In Vaccine Program cases, these factors are used in the weighing of the reliability of scientific evidence. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted").

Respondent frequently offers one or more experts of his own in order to rebut petitioners' case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). 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. Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Id.* at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations").

### D. Consideration of Medical Literature

Although this decision discusses some but not all of the medical literature in detail, I reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Hum. Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

## VI. Analysis

### A. Diagnosis

In *Broekelschen v. Sec'y of Health and Human Servs.*, 618 F.3d 1339, 1346 (Fed. Cir. 2010), the Federal Circuit recognized that in some circumstances, the special master may "first determine which injury was best supported by the evidence presented in the record before applying the *Althen* test."

1. <u>There is Preponderant Evidence that H.H. has Aicardi Goutières syndrome or a Similar Type I Interferonopathy due to a Congenital Abnormality in an Unidentified Gene</u>

Aicardi-Goutières syndrome is a "rare genetic disorder most consistently affecting the brain and the skin." Crow et al., *Characterization of Human Disease Phenotypes Associated with Mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR, and IFIH1,* AM J MED GENET Part A 167A:296–312 (2014) (filed as Ex. A4) (hereinafter "Crow 2014"). Dr. Marks described AGS as "a disorder of interferon activity, so … it's an immune mediated disorder that typically result[s] in neurologic regression with dystonia, intracranial calcifications." Tr. at 147. There are currently seven gene mutations known to cause AGS. La Piana et al., *Neuroradiologic patterns and novel imagining findings in Aicardi-Goutières syndrome,* 86 NEUROLOGY 28-35 (2015) (filed as Ex. D, Tab 3) (hereinafter "La Piana"). Rice noted that "Some individuals with AGS do not harbor mutations in any of these … genes." Rice et al., *Gain-of-function mutations in IFIH1 cause a spectrum of human disease phenotypes associated with upregulated type I interferon signaling,* 46 NATURE GENETICS 5, 503-10 (2014) (filed as Ex. A, Tab 5) (hereinafter "Rice 2014"). La Piana noted that "[b]rain calcification, leukoencephalopathy,[18] and cerebral atrophy are the classic hallmarks of the disease and have suggested the diagnosis of AGS in the majority of cases." La Piana at 28.

The condition was first recognized in 1984 by French pediatric neurologists, Jean Aicardi and Françoise Goutières. Rice et al., *Clinical and Molecular Phenotype of Aicardi-Goutières Syndrome*, 81 AMERICAN JOURNAL OF HUMAN GENETICS 713-25 (2007) (filed as Ex. C, Tab 1) (hereinafter "Rice 2007"). However, since 1984, "the spectrum of disease resulting from mutations in the AGS-related genes has broadened, in part due to the advent of the new sequencing technologies." Crow 2014 at 300. Dr. Crow noted that AGS patients consistently demonstrated "increased levels of interferon activity in the cerebrospinal fluid and serum and an increased expression of interferon-stimulated genes (ISGs) in peripheral blood." *Id.* at 301. Dr. Crow goes on to note that "[t]hese observations are important in identifying AGS as an inflammatory disorder associated with the induction of a type I interferon mediated innate immune response, likely driven by endogenously-derived nucleic acids." *Id.*

Several factors suggest that H.H. more likely than not, has AGS or a similar genetic disorder.

a. *H.H.'s Clinical Presentation*

H.H. presented with the rapid onset of encephalopathy with the development of spasticity[19]

[18] Leukoencephalopathy is "any of a group of diseases affecting the white matter of the brain, especially of the cerebral hemispheres, and occurring as a rule in infants and children." *Leukoencephalopathy*, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=28070&searchterm=leukoencephalopathy (last accessed March 12, 2022).

[19] Spasticity is "the state of being spastic." Spastic is defined as "hypertonic, so that the muscles are stiff and the movements awkward." *Spastic*, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=46356&searchterm=spasticity (last accessed March 14, 2022).

and dystonia,[20] which Dr. Barañano described as "entirely consistent with a clinical diagnosis of AGS." First Barañano Rep. at 5. Dr. Barañano further opined that "clinically, [H.H.] has behaved like an AGS patient with stabilization of [his] irritability." Tr. at 292.

Dr. McGeady opined that H.H. had "evidence of leukodystrophy[21] and thinning of the corpus callosum, which are described in AGS." First McGeady Rep. at 4. *See* Ex. 95 at 135, 147. In support of this point, Rice et al. noted that "[c]ortical atrophy was a common feature in later scans, and a number of children demonstrated significant brain-stem and cerebellar atrophy. Thinning and, in one subject, complete absence of the corpus callosum were also observed." Rice 2007 at 719.

Several of H.H.'s treating physicians also agreed that H.H.'s clinical presentation was suggestive of or consistent with AGS. Dr. Aalbers, one of H.H.'s treating neurologists, noted that H.H.'s progressive encephalopathy, dystonia, and spasticity were all consistent with AGS. Ex. 52 at 28.

Dr. Heather Crawford, a metabolic geneticist, saw H.H. on February 4, 2014. She noted in the medical records that H.H. presented "with developmental regression and developed progressive dystonia that is characteristic of [AGS]." Ex. 50 at 24. Dr. Crawford further stated that H.H. "appears to … have a later-onset presentation for AGS as he presented after a long period of normal development." *Id.* In discussing the natural history of AGS with Petitioners, Dr. Crawford told them that:

> Typically, these children have a regression phase, followed by irritability, then a slow progressive encephalopathy phase. These children typically develop peripheral spasticity, truncal hypotonia, dystonic posturing [of the] upper limbs and poor head control, all of which [H.H.] is currently displaying. … Seizures are also observed in up to 50% of affected [children].

*Id.* The progression of H.H.'s disease was consistent with Dr. Crawford's description. Although H.H. had not developed seizures at the time of this conversation, he had his first seizure on July 9, 2017. *See* Ex. 95 at 130.

Dr. Vanderver assessed H.H. in March of 2015 upon referral from Dr. Marks. *See* Ex. 81 at 1-10. Dr Marks described Dr. Vanderver stating, "she's probably the United States' expert on … AGS." Tr. at 156.

Dr. Vanderver noted in her final report:

---

[20] Dystonia is "[a] syndrome of abnormal muscle contraction that produces repetitive involuntary twisting movements and abnormal posturing of the neck, trunk, face, and extremities." Stedman's Medical Dictionary, 28th ed. 2006 (p. 602).

[21] Leukodystrophy is "any of various types of neurodegeneration involving disturbance of the white matter of the brain. See also adrenoleukodystrophy and leukoencephalopathy." *Leukodystrophy*, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=28066&searchterm=leukodystrophy (last accessed March 14, 2022).

> [H.H.] is seen in the context of developmental delay, dystonia, abnormal MRI and elevated CSF interferon/neopterin/tetrahydrobiopterin with clinical diagnosis of Aicardi Goutieres Syndrome but negative genetic testing and no evidence of visible intracranial calcifications on an early CT scan.

Ex. 81 at 1. In the "diagnostic and treatment plan" section, Dr. Vanderver indicated an intent to collaborate with Dr. Crow "to facilitate genetic resolution of [H.H.]'s suspected heritable interferonopathy." *Id.* at 6.

b. *Elevated Liver Enzymes*

Several of H.H.'s treating physicians noted that H.H. had elevated liver enzymes, which is also consistent with a diagnosis of AGS.

H.H. visited Dr. Crawford on November 12, 2013. During this visit, Dr. Crawford noted that some of H.H.'s lab values were high. Specifically, his AST (aspartate transaminase) was 353, his ALT (alanine transaminase) was 400, and his AP (alkaline phosphatase) was 232. Ex. 50 at 4. Dr. Crawford noted that H.H.'s transaminases (liver enzymes) were elevated. *Id.* at 6.

On December 17, 2013, Dr. Aalbers stated in the medical record that "[o]f concern the patient had previously unexplained transient elevations of liver enzymes which is consistent with AGS…" Ex. 52 at 28.

During H.H.'s hospital admission to address his tethered cord on December 18, 2013, Dr. Richard Roberts remarked that his liver enzymes were as follows: AST, 325; ALT, 472, "raising the concern for possible Aicardi-Goutieres syndrome, a very rare and progressive encephalitic disease of childhood." Ex. 55 at 1.

On May 23, 2014, H.H. visited Dr. Jane Keng, who noted that his AST was elevated at 119 and his ALT was elevated at 125. Ex. 63 at 2.

The concerns regarding H.H.'s elevated transaminases noted by several of his treating physicians are also supported by the medical literature. Rice et al. collected clinical data from 123 patients with a confirmed AGS gene mutation. The authors noted that 15 of the 123 AGS patients "demonstrated liver involvement, with hepatosplenomegaly and/or raised transaminase levels." Rice 2007 at 718. Livingston & Crow similarly noted liver dysfunction in a subset of AGS children. Livingston & Crow at 3.

The fact that H.H. had intermittently elevated liver enzyme levels is certainly not diagnostic of AGS, but these levels do provide support for his diagnosis with that condition.

c. *Elevated Interferon Alpha/Neopterin Levels*

In examining H.H.'s presentation and evolving clinical picture, one of the most striking aspects of it is his high neopterin and interferon alpha levels. As early as 2003, Dr. Crow stated

that "an increase of CSF IFN-[alpha] in the absence of infection is currently considered a marker for the condition." Crow et al., *Cree encephalitis is allelic with Aicardi-Goutières syndrome: implications for the pathogenesis of disorders of interferon alpha metabolism*, 40 JOURNAL OF MEDICAL GENETICS 3, 183-87, 184 (2003) (filed as Ex. D, Tab 5) (hereinafter "Crow 2003"). In 2014, Crow et al. noted that "[p]atients with AGS consistently demonstrate increased levels of interferon activity in the cerebrospinal fluid and serum … and an increased expression of interferon-stimulated genes (ISGs) in peripheral blood … a so-called interferon signature." Crow 2014 at 301.

Livingston & Crow additionally support the importance of this "interferon signature"; they describe that

> [t]he detection of elevated levels of interferon α in the CSF and blood of patients with AGS was recognized soon after the disorder was described. More recently, evidence for abnormal interferon activity in AGS has been demonstrated by identifying an "interferon signature" in peripheral blood. The interferon signature measures the expression of interferon stimulated genes and has been identified in almost 100% of patients with mutations in TREX1, RNASEH2A, RNASEH2C, SAMHD1, ADAR1, and IFIH1.

Livingston & Crow at 5.

H.H.'s neopterin levels were high on 11/14/2013, (Ex. 96 at 7), 12/19/2013 (Ex. 96 at 7), 11/14/2014 (Ex. 56 at 94), 4/17/2014 (Ex. 56 at 323). In fact, Dr. Richard Roberts assessed H.H. in December of 2013. He noted that H.H.'s lumbar puncture "showed remarkably high elevations of biopterin and neopterin: **the highest neopterin levels we have ever seen.**" Ex. 55 at 1 (emphasis added). H.H.'s levels remained elevated through 2017 when they returned to the normal range only to become elevated again when they were tested in 2019.

On February 4, 2014, Dr. Heather Crawford noted that H.H.'s elevated neopterin levels are "**only seen** in Aicardi-Goutieres syndrome (AGS) and HIV infection." Ex. 50 at 24 (emphasis added). H.H. tested negative for HIV. Ex. 52 at 75. H.H.'s blood was sent to England and his CSF was sent to France for interferon alpha testing. Dr. Crawford noted that "[b]oth CSF and blood showed elevated levels of INF-alpha which is **diagnostic for AGS**." Ex. 50 at 24 (emphasis added).

During the entitlement hearing, I asked whether you could see elevated neopterin levels in a viral infection other than HIV. Dr. Barañano testified as follows:

> You could. So … for example, they looked at patients who had encephalitis and, meningoencephalitis, and with herpes virus infections, they would see elevated neopterin. There's a very terrible brain stem encephalitis that can be caused by an enterovirus, and so it's been reported in that situation. But these are clinical settings where patients would have fever. They would have lot of white cells in their spinal fluid. They would … have very different imaging abnormalities on their MRI that would point to some kind of infectious picture going on.

Tr. at 293-94.

H.H. also had his interferon alpha levels in both the blood and CSF tested in England and France. The French results revealed elevated levels of interferon alpha in the serum on two different dates: January 15, 2014 and March 25, 2014; the levels were 18 and 9, respectively, with < 2 being normal. Ex. 56 at 357.

After the extensive testing performed in this case, there was no explanation for H.H.'s elevated neopterin and interferon alpha levels other than AGS. Ultimately, Dr. Barañano opined that "based on his clinical course and his biochemical abnormalities, the most leading, the most likely diagnosis right now is suspected AGS." Tr. at 279.

Petitioners argue that H.H. does not have AGS because his clinical presentation is lacking "five major characteristics" that should be present in order to render an AGS diagnosis. See Pet'rs' Post-Hearing Brief at 13. Petitioners note that H.H. does not have one of the seven genetic mutations known to cause AGS; he did not have calcifications on MRI; he had no known damage to his basal ganglia; his neopterin levels did not normalize; and his rapid decline occurred after 12 months of age. *Id.* I will discuss each of these points, in turn.

d. *Genetic Mutation*

Because H.H. does not have one of the seven identified genes known to cause AGS, diagnosis in this case has been challenging. Livingston and Crow have noted that "[m]utations in these [seven] genes account for around 95% of patients with classical AGS." Livingston & Crow at 2. This means that five percent of AGS cases are associated with an unidentified genetic mutation. Second Barañano Rep. at 1. Dr. McGeady agreed, noting that the "identification of genetic mutations causing AGS is a work in progress." First McGeady Rep. at 6.

The fact that H.H. does not have a gene currently identified with AGS is Petitioners' strongest argument that he does not have the disease.

Petitioners also argue that H.H. did not exhibit four other "major characteristics" that have been observed in other patients with AGS. At the outset, I note that our understanding of AGS has evolved as physician-scientists have conducted additional research. This additional research has led those who study the disease to recognize that "the range of phenotypes associated with mutations" of AGS genes "is much broader than previously realized." Crow & Manel, *Aicardi-Goutières syndrome and the type I interferonopathies*, 15 NATURE REVIEWS IMMUNOLOGY 429-40, 429 (2015) (filed as Ex. D1) (hereinafter "Crow & Manel"). Crow & Manel recognized that "patients with mutations in the AGS-associated genes frequently lack one or more, **sometimes even all**, of the original diagnostic criteria outlined by Aicardi and Goutières in their 1984 paper." *Id.* at 430 (emphasis added). Similarly, Livingston & Crow noted that "[a]s more patients harboring mutations in these genes have been described, in particular facilitated by the advent of whole exome sequencing, a remarkably broad spectrum of associated neurologic phenotypes has been revealed." Livingston & Crow, *Neurologic Phenotypes Associated with Mutations in TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1, and IFIH1: Aicardi–Goutières*

*Syndrome and Beyond*, NEUROPEDIATRICS, DOI http://dx.doi.org/10.1055/s-0036-1592307 ISSN 0174-304X, 1-6 (2016) (filed as Ex. A, Tab 1) (hereinafter "Livingston & Crow"). Finally, Crow and Manel noted that

> although the AGS diagnostic label still has a useful clinical purpose, there are many patients who do not fit this paradigm as initially delineated. Hence, we are now tending towards the use of the generic term 'type I interferonopathy' to refer to this group of monogenic diseases in which a constitutive upregulation of type I IFN production is considered directly relevant to pathogenesis.

Crow & Manel at 430. It is important to consider this expanded understanding of the AGS phenotype in analyzing H.H.'s presentation.

e. *Calcifications*

Brain calcifications are consistently recognized as a feature usually present in children with AGS. The fact that H.H. did not have brain calcifications supports Petitioners' position that AGS is not his proper diagnosis. As Dr. Barañano noted in her testimony, "if he had calcifications, we would not be having this hearing." Tr. at 280.

Although brain calcifications are typical of most AGS patients, some do not have them. Dr. McGeady opined that "[w]hile calcification of the CNS are not described in HH's MRI studies, the authors of the 2007 report of Rice et al. state "this feature (i.e. intracranial calcification) should not be considered prerequisite for the diagnosis of AGS" since it is variably present. *Id.*; *See* Rice at 721.

Similarly, Dr. Barañano noted that "it's become well established that calcifications are not required for … a definitive genetic diagnosis of AGS." Tr. at 279.

f. *Basal Ganglia Damage*

In his letter submitted on August 25, 2017, Dr. Marks stated that "On his most recent July 2017 MRI scan, there is diffuse atrophy but there are no intracranial calcifications or physical injury to the basal ganglia damage, two of the common findings in AGS." Second Marks Rep. at 1.

It is not clear that damage to the basal ganglia is a "major characteristic" of an AGS diagnosis. Petitioners did not cite to any authority for this proposition except for the opinion of Dr. Marks. In examining the medical literature, Crow & Manel provide a chart that summarizes the "major clinical features associated with genetically distinct type I interferonopathies". Crow & Manel at 434. Under "neurological phenotypes", Crow & Manel list, "developmental delay", "intracranial calcification", "white matter disease", "cerebral atrophy", and "spastic paraparesis". *Id.*

La Piana et al. note that "[b]asal ganglia atrophy was documented in cases with bilateral striatal necrosis." La Piana at 30. It is unclear if this is the damage to which Dr. Marks referred. If so, it does not appear to be a common feature of the disease.

Additionally, Dr. Barañano briefly discussed this issue at the entitlement hearing; she testified that "the basal ganglia damage is seen in a subset of patients especially those with a particular mutation in something called ADAR." Tr. at 280. She noted that it is not universally seen in all cases of AGS. *Id.* Of note, mutations on the ADAR gene account for approximately 7% of AGS cases, according to Dr. Crow's data. *See* Crow 2014 at 301. Based on the above, I do not find that basal ganglia damage is a major characteristic of AGS, as argued by Petitioners in their post hearing brief.

g. *Normalization of Neopterin Levels*

In his letter filed into the record on August 25, 2017, Dr. Marks stated that "HH has had persistently biomarkers for intrathecal interferon production until his most recent testing performed in July 2017 which revealed normal levels of CSF neopterin, a marker for interferon production." Marks Expert Report at 1. Dr. Marks cited this normalization of neopterin as a basis to opine that he favored vaccine causation over AGS because of H.H.'s "waning immune response." *Id.*

However, H.H.'s neopterin levels changed by the time of the entitlement hearing. While it is true that his levels were in the normal range on August 7, 2017 (Ex. 95 at 78), they were again elevated on January 23, 2019. Ex. 96 at 14; Ex. 96 at 115.

In their post-hearing brief, Petitioners argue that "H.H.'s presentation showed … 3) no normalization of neopterin levels". Pet'rs' Post-Hearing Brief at 13. Petitioners further argued that a normalization of neopterin constitutes one of the five major characteristics of an AGS diagnosis. *Id.* It is unclear whether Petitioners misstated their position, as they later argue in their brief that H.H.'s neopterin levels normalized in July 2017. They stated that "H.H. has persistently shown biomarkers for intrthecal [sic] interferon production until his most recent testing performed in July 2017, which revealed normal levels of CFS neopterin, a marker for interferon production." Pet'rs' Post-Hearing Brief at 16.

Dr. Marks testified at hearing with respect to H.H.'s neopterin levels. He stated, "So in 2017, the levels had dropped down some, and then … with the last one, they actually went back up again. Now … admittedly, that's known to happen in AGS. The … interferon levels can fluctuate some over time." Tr. at 176. Dr. Marks' testimony does not ascribe great significance to H.H.'s drop in neopterin levels in 2017 and subsequent re-elevation in 2019. Although he did not mention it at hearing, apparently he no longer believes that H.H.'s neopterin normalization suggests vaccine causation, as that level is again elevated.

Further, the medical literature filed in this case does not provide compelling support for the point that it is characteristic for AGS patients to experience normalization in neopterin levels. In fact, Crow et al. note that their data "clearly demonstrate that an interferon signature persists long term in most patients, indicative of an ongoing inflammatory process." Crow 2014 at 309.

Accordingly, I do not credit Petitioners' position that normalization of neopterin is characteristic of AGS. In fact, the persistent elevation of H.H.'s neopterin levels lends support for an AGS diagnosis.

h. *Onset of AGS after 12 Months of Age*

Petitioners correctly note that most children who develop AGS do so within the first year of life. They go on to argue that because H.H. developed normally until he was approximately 15 months-old, this suggests that AGS is not his correct diagnosis.

Both Dr. McGeady and Dr. Barañano opined that there is variability in AGS presentation which includes onset after the first year of life. Dr. McGeady specifically opined that "a period of normal development before the onset of symptoms in AGS is described in some cases and should not be considered as a finding implicating the vaccines." First McGeady Rep. at 4-5.

The medical literature supports the fact that while onset of "typical" cases of AGS occurs in the first year of life, it is well recognized that children can develop onset after this time. *See e.g.*, Orcesi et al., *Aicardi–Goutières syndrome presenting atypically as a sub-acute leukoencephalopathy*, 12 EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY, 408-11 (2008) (filed as Ex. A2) (describing a case of Aicardi–Goutières syndrome in a 16-month-old child with previously normal development); *see also* D'Arrigo (same). Livingston & Crow also described a case of later onset AGS. They discussed a child

> who showed completely normal development until the age of 15 months, at which time he could walk and had 6 to 10 words. After this point, he developed intermittent posturing and rigidity of his legs, and then of the upper extremities. He also developed exaggerated startle. He subsequently experienced a relentless loss of motor and intellectual skills, and by the age of 24 months, he was unable to sit unsupported and had lost the ability to swallow. Between 15 months and 4 years of age, he demonstrated a fluctuating pattern of poor sleep, with persistent whining and crying.

Livingston & Crow at 3.

Finally, Crow et al. studied 325 children with AGS and observed that "[t]wenty-eight patients (8.6%) presented after the age of 1 year, with 35% and 30% of patients with mutations in ADAR and IFIH1, respectively, demonstrating the onset of disease after this age." Crow 2014 at 303. Crow's data suggest that later onset is associated primarily with mutations in two specific AGS genes.

Ultimately, the fact that H.H. developed symptoms consistent with AGS at 15 months does show his clinical course is not a typical presentation of the disease. At the same time, this point does not provide persuasive evidence that H.H. does not have AGS, as cases of later onset are reported in the medical literature.

i. *Neurologic Stabilization/Improvement*

Although not specifically alleged by Petitioners in their post hearing brief, Dr. Marks discussed H.H.'s neurologic stabilization and improvement as support for the fact that he does not have AGS.

In his affidavit, Dr. Marks opined as follows: "H.H.'s neurological status has since stabilized, but [he] still has persistent increases in his interferon levels. This stabilization of his neurological status, which was hyperactive post-immunization is indicative of the cause being derived from the vaccinations." Marks Affidavit at 4-5. At hearing, Dr. Marks described AGS as a "relentlessly progressive disorder." Tr. at 164. He opined that H.H.'s improvement in function is not expected in an AGS patient. *Id.*

Dr. Barañano disagreed with Dr. Marks on this point. She testified that "based on [her] clinical experience and understanding of the literature, what is the most common clinical course is to have the acute neurologic symptoms followed by a period of stabilization." Tr. at 270. "it's well established that AGS is not necessarily a relentlessly progressive neurodegenerative disorder. So I would respectfully disagree with Dr. Marks in his assessment … of that." *Id.*

Dr. McGeady disagreed with Dr. Marks as well. He opined that "stabilization of the neurologic status of AGS patients is a characteristic of the disease, and should not be considered evidence against that diagnosis." First McGeady Rep. at 7.

The medical literature supports the opinions of Drs. Barañano and McGeady. For example, Crow et al. noted that "[b]eyond an initial encephalopathic phase, generally lasting several months, continued neurological deterioration was not obvious in most patients; indeed, some parents reported a slow but steady acquisition of new skills over time." Crow 2014 at 309. Rice et al. similarly observed that the majority of children presented with "subacute onset of a severe encephalopathy, characterized by irritability, inconsolable crying, intermittent sterile pyrexias … and a loss of skills. These episodes usually lasted several months, beyond which time the condition stabilized. Thereafter no further disease progression was generally observed." Rice 2007 at 718.

Finally, Livingston & Crow noted that

> Although initially considered a neurodegenerative, progressive disease, as more patients have been studied longitudinally, this point has come into question. In our opinion, the most classical clinical course is of a period of several months of neurologic regression in infancy associated with progressive radiological changes. For most patients, the disease then stabilizes, leaving the child with profound disabilities.

Livingston & Crow at 4-5. The fact that H.H.'s condition stabilized and even showed some improvement is consistent with a diagnosis of AGS.

Dr. Barañano testified at the entitlement hearing regarding the question of diagnosis. She opined that "[H.H.] has something like AGS that in my experience we will eventually find the genetic underpinnings of his disorder." Tr. at 296. Dr. Steinman agreed. He opined that "the

diagnosis is an interferonopathy akin to AGS" and noted that "the genetic basis of the disease has not been shown at the time I wrote Ex 101." Second Steinman Rep. at 2. Dr. Vanderver, one of the nations' leading authorities on AGS, treated H.H. in March of 2015. Dr. Vanderver noted that H.H. had a "suspected heritable interferonopathy." Ex. 81 at 6. Ultimately, in considering the evidence presented on this issue, I find the opinions of Dr. Barañano, Dr. McGeady, Dr. Vanderver, and Dr. Steinman to be persuasive. H.H., more likely than not, has AGS or a similar genetic interferonopathy.

2. H.H.'s Aicardi Goutières Syndrome/Genetic Type I Interferonopathy Manifested around the Time of his October 17, 2013 Vaccinations and before his October 23, 2013 Vaccination

On September 13, 2013, Mrs. Heller called Wise Pediatrics. The note from this phone call reads as follows: "mom concerned with pt not walking and rt foot turned inward has appt in one month, questions if needs to be seen earlier than scheduled appt, discussed development per Dr. Hollis, will wait till scheduled to be seen." Ex. 49 at 37. There is no mention of this issue in the notes from the 15-month well visit on October 17, 2013. *Id.* at 39. At the entitlement hearing, Mrs. Heller testified that H.H. had appeared "pigeon-toed" when she called Wise Pediatrics, but that his feet were not turned in during the 15-month appointment. Tr. at 13-14. Dr. Hollis assessed him as a well child.[22] *Id.*

The experts did not provide a persuasive opinion regarding this evidence. Dr. Barañano opined "there is evidence that his onset of symptoms began prior to the vaccine administration." Second Barañano Rep. at 1. Dr. McGeady stated that "It is not possible to know with certainty why the concerns expressed in the phone contact of 9/13/2013 were not addressed in the office visit of 10/17/2013, if only to dismiss them." Second McGeady Rep. at 2. Dr. Steinman opined: "I personally do not think that H.H. had pre-existing evidence of a neurologic problem, unless the turning of the right foot inward was the earliest manifestation of dystonia. Whether or not there was a subtle form of an underlying problem prior to October 17, 2013 is a point that cannot easily be resolved." First Steinman Rep. at 5.

Although there may be a relation between this documented concern in September involving H.H.'s right foot, and the onset of his type I interferonopathy (which also first manifested in his right foot/leg), I do not find there is sufficient evidence to draw this connection. In particular, none of the experts explained why or how H.H. would begin to demonstrate signs of his genetic disorder and then improve. This point is especially confounding given H.H.'s rapid and relentless decline once his disease process started. As such, I find there is not preponderant evidence that the inturning of H.H.'s right foot in September of 2013 constituted the onset of his condition.

[22] Dr. Hollis filed a supplemental affidavit on August 26, 2016. Ex. 90. In it, she stated that she examined H.H. on October 17, 2013, and noted that he was "taking a few steps independently between objects." *Id.* at 2. Dr. Hollis then wrote that "His mom had noted his foot possibly turning in 1 week prior to his appointment." *Id.* I assume that "one week" is a typo and Dr. Hollis meant to write one month. In making this assumption, I have credited the contemporaneously created medical records over an affidavit created years after the fact.

On November 11, 2013, Mrs. Heller brought H.H. to visit Dr. Hollis. In the history of present illness section of the record, Dr. Hollis noted that "Pt has been fussy for the last week. He has run fever to 101.5. His energy level is decreased. Pts development has regressed in the last month." Ex. 49 at 41. This record is the medical record most contemporaneous to the onset of H.H.'s condition; it suggests that H.H. had regressed in the last month, or since mid-October of 2013.

The fact witnesses consistently testified at the entitlement hearing that H.H. was not himself on Halloween. Mrs. Heller testified that he began dragging his right foot that week. Tr. at 19. Mrs. Heller also testified that he fell on Halloween. *Id.* at 19-20. Ms. Sewell testified that H.H. began falling around October 26, 2013. *Id.* at 113-14. Ms. Huling also saw H.H. fall on Halloween. *Id.* at 128.

On March 14, 2014, H.H. was evaluated at an infectious diseases consultation. Dr. Kenneth Colina noted as follows:

> [H.H.] is a 20-month-old … who has developed progressive developmental delay over the last 5 months, relatively acutely. His mother reports that she breastfed him constantly until 10/9. Within a day or 2 of stopping breastfeeding he seemed to trip and fall when he was crawling. She reports that he was completely normal at his 15-month checkup, walking and talking, and very active and playful. She then stopped breastfeeding, and within a week he was falling. About 8 days later after stopping breastfeeding, he got his 15-month shots.

Ex. 57 at 1. The "review of systems" section noted that "after he started falling in mid-October his parents noticed that he had a fever for about a week, with a red throat that resolved." *Id.*

This record does contain some inconsistencies. For instance, it is not clear whether H.H. was falling before his 15 month appointment or not. Mrs. Heller testified that H.H. did not trip and fall within one or two days of the date she stopped breastfeeding. Tr. at 39. However, several points in this record are accurate. First, Mrs. Heller did stop breastfeeding on approximately October 9, 2013. She discussed this matter at the entitlement hearing, testifying that, "I wanted my kids two years apart, so I decided to wean him at the beginning of October so I could start trying again…" Tr. at 37. Mrs. Heller testified that she wanted H.H. to be completely weaned by 15 months. *Id.* at 37-38. She additionally stated, "there's probably no question that I quit breast-feeding the week before vaccines …" *Id.* at 60. It is also true that eight days after October 9 is October 17, 2013, the date H.H. received his flu and Prevnar vaccines. Ultimately, this record does support that H.H. started falling in mid-October, although the term "mid-October" is not precise.

Mrs. Heller took H.H. to see her aunt, Sheri Huling, early in the week of October 20, 2013. As of the date she drafted her letter, Ms. Huling had been a practicing pediatric physical therapist for 35 years. Ex. 102 at 1.[23] According to Ms. Huling, H.H.

[23] Ms. Huling testified at the entitlement hearing that her affidavit (Ex. 91) was not entirely accurate. The affidavit noted that "[a] few weeks prior to H.H.'s 10-23-13 visit with his pediatrician, I noted some

> had the pneumonia and flu vaccine[s] on 10-17-13, and I saw him the following week. His mom had noticed that over the last few days he was having some trouble cruising around furniture and taking steps and she asked me to take a look at him from a therapist perspective. I noted some tightness in his right heel [] cord that was alarming. I advised her of some stretches to do and then told her to make sure and call this to the attention of her physician on his next visit which was to be 10-23-13.

Ex. 102 at 1. This visit with Ms. Huling took place either Sunday, October 20, 2013, Monday the 21st, or Tuesday the 22nd, as it was the "next week" after the October 17 vaccinations and before H.H.'s visit on October 23rd. This places onset of H.H.'s difficulty walking to a few days before this visit, or around the date the first two vaccines were administered. Ms. Huling went on to note that when she saw H.H. on Halloween, she noted "worsening in his tightness in [the] right heel [] cord." *Id.* Ms. Huling stated that she observed H.H. fall once while seated and once while standing on October 31, 2013. *Id.*

The right heel cord tightness that Ms. Huling observed is also documented in the medical records. Dr. Crawford evaluated H.H. on November 12, 2013. During this visit, she noted that H.H.'s "heel cords appear somewhat tight and he may require AFOs [ankle-foot orthosis][24] at some point in the future." Ex. 50 at 2. The physical exam section of this record indicates that H.H. had "hypertonicity (noted in lower extremities especially at the ankles)." *Id.* at 5. Dr. Crawford recommended that H.H. attend physical therapy. *Id.* at 6.

H.H.'s clinical picture worsened by the time of his next visit with Dr. Crawford on December 3, 2013. Dr. Crawford noted that H.H. had "hypertonicity (noted in lower extremities especially at the ankles, feet held inward position). Pt now holds hand in a fist when trying to reach for objects and when crawling…" Ex. 50 at 11.

During a physical therapy session on June 26, 2014, the physical therapist noted that H.H. had several abnormal exam findings, to include "bilateral Achilles contractures". Ex. 95 at 145.

Ultimately, Ms. Huling noted that H.H. had a tight right heel cord – an observation that she described as "alarming." She noticed this tightness sometime in the days after H.H. received his October 17, 2013 vaccinations, and before he received the Pentacel vaccine on October 23, 2013. The medical records also document this finding, and associate the tightness with his disease

---

tightness in his right heel [] cord that I suggested should be mentioned to his pediatrician." Ex. 91 at 2 (emphasis added). Ms. Huling testified that before signing her affidavit, she had prepared a letter (filed as Ex. 102) outlining her memory of the events surrounding the onset of H.H.'s condition. Tr. at 205-07. Ms. Huling specifically referenced H.H.'s heel cord tightness and testified that she noticed it a few days before the October 23, 2013 vaccination. *See* Tr. at 206-07.

[24] An ankle-foot orthosis is "any orthotic device for the lower limb that encloses the ankle and foot and does not extend above the knee; often there is a cuff or other device in the region of the knee or upper calf to take weight off the limb." *Ankle-foot orthosis*, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=95032 (last accessed March 28, 2022).

progression. I find Ms. Huling's description to be compelling evidence that is also supported by other medical records. *See* Ex. 49 at 41 (medical record from November 11, 2013, noting that H.H.'s development had regressed in the last month); Ex. 57 at 1 (stating that H.H. began falling in mid-October). Accordingly, I find there is preponderant evidence that the onset of H.H.'s condition began close-in-time to his October 17, 2013 vaccinations and before he received the Pentacel vaccine.

In sum, I have found the evidence preponderantly supports the fact that H.H. has a genetic type I interferonopathy that is either AGS or is AGS-like. Although I am unable to make a specific finding as to whether H.H. began to develop signs of his type I interferonopathy before or after the flu and pneumonia vaccines, I have not analyzed whether these vaccines either caused or significantly aggravated H.H.'s condition because Dr. Steinman only offered an opinion with respect to the Pentacel vaccine. My finding that H.H. began to show signs of his type I interferonopathy *before* he received the Pentacel vaccine makes the analysis more pointed. It means that the Pentacel vaccine did not cause H.H.'s condition, but instead, raises the question as to whether the Pentacel vaccine caused the significant aggravation of H.H.'s genetic condition that had already begun to manifest. *See Locane v. Sec'y of Health & Hum. Servs.*, 685 F.3d 1375, 1381 (Fed. Cir. 2012) (stating that if "the illness was present before the vaccine was administered, logically, the vaccine could not have caused the illness.").

### B. *Loving* Prong One: H.H.'s Condition prior to the October 23, 2013 Vaccination with Pentacel

H.H. developed normally up until the time surrounding his October 17, 2013 vaccinations. Right around this time, he began to have difficulty cruising around furniture and walking. His right heel cord was tight. Ms. Huling observed this tightness before H.H. received his October 23, 2013 Pentacel vaccine.

### C. *Loving* Prong Two: H.H.'s Condition after the October 23, 2013 Vaccination with Pentacel

After the October 23, 2013 vaccination, H.H.'s walking/cruising continued to deteriorate. He began dragging his right foot, and then falling. He lost the ability to bear weight on his legs and to crawl. H.H. developed rapid and progressively worsening encephalopathy, spasticity, and dystonia. His neopterin levels were dramatically elevated and have remained elevated through 2019, with a return to normal levels for a period of time in 2017. Although H.H.'s condition stabilized, he cannot sit unassisted, cannot eat without a G-tube, and requires 24 hour medical care.

### D. *Loving* Prong Three: Did H.H. Experience a Significant Aggravation of his Condition?

H.H.'s deterioration is consistent with the Vaccine Act's definition of significant aggravation resulting in markedly greater disability, pain, or illness accompanied by substantial deterioration of health. § 33(4). Therefore, this leaves the question of whether the significant aggravation of H.H.'s condition was vaccine-related.

### E. *Loving* Prong Four/*Althen* Prong One: Petitioners have not Established a Reliable and Reputable Theory Concerning How the Vaccinations H.H. Received Can Cause a Significant Aggravation of AGS/a type I Interferonopathy

Under *Loving* prong four/*Althen* prong one, the causation theory must relate to the injury alleged. Thus, Petitioners must provide a "reputable" medical or scientific explanation, demonstrating that the vaccines received can cause the type of injury alleged. *Pafford,* 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id*. at 549.

Dr. Steinman emphasized that the Pentacel vaccine was causative and did not provide a theory involving either the flu or pneumonia vaccines (*See* First Steinman Rep. at 8, where Dr. Steinman noted that "Petitioner herein provides a theory on how the components of the October 2013 vaccine induced activation of both type 1 interferon and type II interferon, known as gamma interferon. I shall focus on the Pentacel vaccine…"; First Steinman Rep. at 11, Dr. Steinman stated, "I shall show that Pentacel causes increases in both type 1 interferons and in the type 2 interferon, known as gamma-interferon."; First Steinman Rep. at 12, Dr. Steinman discussed the importance of alum in Pentacel; First Steinman Rep. at 13, Dr. Steinman noted that "Induction of type 1 and type 2 interferon by Pentacel could worsen neuroinflammation and this more likely than not occurred in H.H."; First Steinman Rep. at 14, Dr. Steinman stated that "I have provided a mechanistic basis for how Pentacel can trigger a type 1 and type 2 interferon response and how the NALRP3 inflamm[a]some can be triggered by the components of Pentacel."; *See* First Steinman Rep. at 15-16 for more examples). Because I have found that H.H. developed signs of his interferonopathy before he received the Pentacel vaccine, I will analyze whether the Pentacel vaccine can cause a significant aggravation of H.H.'s interferonopathy.

Dr. Barañano defined an interferonopathy as a "class of disorders where there is dysregulation of the control of the levels of interferon alpha in the immune system." Tr. at 272. They are thought to occur "as a result of the failure to appropriately regulate the metabolism of nucleic acids." Tr. at 221. This gives continued stimulation to type I interferons. *Id.* Dr. McGeady testified that "in the hereditary interferonopathies, there [are] no breaks. The … interferon just keeps getting produced more and more over … an extended period of time." *Id.* at 223. He further opined that, "In the case of HH, the control mechanisms failed, apparently from a genetically determined dysregulation of nucleic acid metabolism, and exceedingly large amounts of interferon alpha were produced and allowed to persist for an extended period of time." Second McGeady Rep. at 2. This explains both the elevated levels and the persistence of these elevated levels. *Id.*

Type I interferonopathies are inherited genetic disorders. Tr. at 272, 287. This point is supported by the medical literature filed in this case. *See e.g.*, Rodero & Crow, describing "the grouping of Mendelian disorders associated with an up-regulation of type I interferon signaling as a novel set of human inborn errors of immunity." Rodero & Crow at 2527.

Dr. Steinman opined that the Pentacel vaccine activated H.H.'s immune system resulting in the production of type 1 and type 2 interferons, which led to the worsening of his neuroinflammation. First Steinman Rep. at 11-13.[25]

In support of this theory, Dr. Steinman discussed literature describing the production of type 1 and type 2 interferons in response to components of the Pentacel vaccine.

He cited Fadugba et al., *Immune Responses to Pertussis Antigens in Infants and Toddlers after Immunization with Multicomponent Acellular Pertussis Vaccine*, 21 CLINICAL AND VACCINE IMMUNOLOGY 12 (2014) 1613-19 (filed as Ex. 101, Tab 12) (hereinafter "Fadugba"). Fadugba studied the antibody, cell-mediated, and cytokine responses to *B. pertussis* antigens in children who received a primary DTaP vaccination at two, four, and six months, and a booster vaccination at 15 to 18 months. The authors noted that: "One month after booster vaccination, … our study revealed significant increase in gamma interferon (IFN-gamma) production in response to the [pertussis toxin] and [fimbriae] antigens, a significant increase in IL-2 production with the [pertussis toxin], [filamentous hemagglutinin], and [pertactin] antigens, and a lack of significant interleukin-4 (IL-4) secretion with any of the antigen." Fadugba at 1613. Fadugba does stand for the proposition that DTaP vaccination results in an increase in gamma interferon, albeit these levels were not measured until one month after the booster vaccination.

Dr. Steinman also cited to the Kooijman article. *See* Kooijman et al., *Vaccine antigens modulate the innate response of monocytes to Al(OH)3*, PLOS ONE, https://doi.org/10.1371/journal.pone.0197885, 1-22 (2018) (filed as Ex. 101, Tab 13) (hereinafter "Kooijman"). Kooijman "compared the innate immune responses induced by Al(OH)3 [aluminum hydroxide] alone *versus* that of a licensed combination DTaP vaccine containing Al(OH)3, using cytokine analysis, transcriptomics and proteomics, to determine unique, shared and potential synergistic or antagonistic effects of adjuvant and antigen components." Kooijman at 2. Kooijman noted that "After 24 hours of stimulation, both Al(OH)3 and DTaP-stimulated monocytes showed a trend towards increased gene expression of the type I interferon *IFN*β." *Id.* at 13.

Dr. Steinman also discussed "the importance of alum in Pentacel in activating []the NALRP3 inflamm[a]some, which plays a key role in inducing interferonopathies." First Steinman Rep. at 12. Dr. Steinman cited to the Li article. Li et al., *Cutting Edge: Inflammasome Activation by Alum and Alum's Adjuvant Effect Are Mediated by NLRP3,* 181 J IMMUNOL 17-21 (2008) (filed as Ex. 101, Tab 14) (hereinafter "Li"). In this study, mice were vaccinated with one-tenth of a human dose of the DT/TT vaccine, and then boosted two weeks later. On days 14, 28, and 56, blood samples were collected. Li at 18. Li described that "inflammasome activation by alum and alum's adjuvanticity are mediated by NLRP3 and ASC." Li at 18. In concluding, the authors noted that "[o]ur results identified for the first time NLRP3 as an important player in alum's adjuvant

[25] Although at hearing Dr. Marks opined that H.H.'s vaccines caused him to develop an interferonopathy via molecular mimicry, Petitioners appear to have abandoned that theory in their post hearing brief. *See* Petr's' Post-Hearing Brief at 12-13, 15-16. Indeed, as discussed in section VI F, Dr. Marks was unable to provide a persuasive causation opinion. Although not analyzed in this decision, I do not find that Dr. Marks' opinion on molecular mimicry constitutes a sound and reliable theory in this case.

effect and indicate an important role for the inflammasome in the development of adaptive immunity. The ability to activate the inflammasome must be one of the properties to be considered during the development of new generation vaccines." *Id.* at 20-21.

While vaccines may activate the inflammasome, Dr. Steinman has not presented a link between such activation and the development of AGS or a similar type I interferonopathy. Indeed, Crow & Manel noted that "to our knowledge, a possible engagement of the inflammasome in patients with AGS has not been investigated." Crow & Manel at 431.

Dr. Steinman also cited to two articles discussing Experimental Autoimmune Encephalitis (EAE) and Multiple Sclerosis for the proposition that inflammasome activation can worsen neuroinflammation. Inoue et al., *Mechanism to develop inflammasome-independent and interferon-β-resistant EAE with neuronal damages*, 19 NAT NEUROSCI. 12, 1599-1609 (2016) (filed as Ex. 101, Tab 15); Axtell et al., *Type I Interferons: Beneficial in Th1 and Detrimental in Th17 Autoimmunity*, 44 CLIN REV ALLERGY IMMUNOL. 2, 114-20 (2013) (filed as Ex. 101, Tab 16).

Dr. McGeady disagreed with Petitioners' causation theory, noting that the vaccines "are not related to the central nervous system (CNS) pathology which occurred in the child." Second McGeady Rep. at 1. He cited two main reasons for this opinion. First, Petitioners' theory does not explain how vaccination caused H.H.'s innate immune response to be so "massively exaggerated as demonstrated by the elevated levels of interferon alpha in the blood and cerebrospinal fluid (CSF) of HH." *Id.* Second, Dr. Steinman did not explain how H.H.'s interferon alpha levels remained elevated for years after vaccination. *Id.*

Dr. McGeady agreed that vaccination "would be expected to generate a physiologic amount of type I interferon and other pro-inflammatory cytokines". Second McGeady Rep. at 2. However, he noted that interferon production "promptly decreases" after a non-progressive provocation such as vaccination. *Id.* In further substantiation of this opinion, Dr. McGeady noted that interferons are "biologically potent molecules excessive amounts of which can cause the acute illness called "cytokine storm", and their production and metabolism are regulated closely in achieving homeostasis." *Id.* Dr. Marks and Dr. Barañano were similarly unable to identify any medical literature that suggests that vaccination can caused substantially elevated levels of interferon alpha. Tr. at 193, 289.

Dr. McGeady is persuasive with respect to this point. While the literature cited by Dr. Steinman does demonstrate that vaccination causes the production of some amount of interferon, it does not suggest that these levels are excessive. In fact, both Fadugba and Kooijman discuss normal innate immune responses after vaccination. Neither article suggests that interferon production post-DTaP vaccination is anything resembling H.H.'s interferon alpha levels, which one provider described as "the highest neopterin levels we have ever seen."[26] Ex. 55 at 1.

[26] As Dr. Marks noted at the entitlement heating: "neopterin is a marker for interferon activity." Tr. at 194.

Petitioners' theory is equally unpersuasive in preponderantly establishing that vaccination can cause persistently elevated levels of interferon alpha. With respect to this point, Dr. McGeady testified as follows:

> here you have a youngster who in 2013 has high levels of neopterin in his spinal fluid. In 2017, he's back to normal again, and in 2019, he's way up again. So it's that constant up and down. There's no living organism in any of the vaccines that he received. So what could possibly keep that process going on for that long a period of time?

Tr. at 223-24. Dr. Steinman claimed that the continuous production of type I interferon can be explained by the medical literature, which shows "that there is a resistance in some forms of neuroinflammation to the normal beneficial response of interferon." First Steinman Rep. at 14. Dr. Steinman's opinion seems to be that the beneficial type of interferon that would normally modulate an interferon response was absent or deficient in H.H., and as a result, his immune system continuously produced type I interferon, which resulted in disease. *Id.*

Naves et al. discusses the interplay between type I and type II interferons. Naves et al., *The Interdependent, Overlapping, and Differential Roles of Type I and II IFNs in the Pathogenesis of Experimental Autoimmune Encephalomyelitis*, 191 J IMMUNOL, 2967-77 (2013) (filed as Ex. 101, Tab 17) (hereinafter "Naves"). The authors state, "In summary, our data reveal that cooperative signaling from type I and II IFNs is necessary to restrain the pathogenesis in EAE. Loss and perhaps imbalance of either IFN signal aggravates inflammation and results in exacerbated disease." Naves at 2975. This article does support the principle that imbalance in interferon signaling aggravates disease in EAE. EAE is the animal model for MS; it is not an interferonopathy. It is difficult to see how this point is persuasive in the case at bar when it involves an entirely different disease. I find that Petitioners have not provided a sound and reliable medical theory explaining how vaccination causes the chronic overproduction of interferon.

I also note that there appears to be no published medical literature (to include case reports) indicating that the flu, pneumonia, or Pentacel vaccines can cause or exacerbate a type I interferonopathy. *See* Tr. at 217, 272. Dr. McGeady testified that there is also no literature suggesting the live viruses associated with these vaccines could cause one of these conditions. *Id.* at 218.

Dr. Steinman pointed to the Rodero & Crow article as providing support for his theory. In discussing type I interferonopathies and the ADAR-1 mutation, Rodero & Crow stated that "[w]hether vaccination represents a disease trigger is an important, and currently unanswered, question." Rodero & Crow at 2532. This statement suggests that vaccination as a potential trigger for a type I interferonopathy involving an ADAR-1 mutation could be an area of study at some point in the future. This statement does not provide persuasive evidence in support of Petitioners' theory in this case.

Petitioners are not required to present medical literature or epidemiological evidence to establish the first *Althen* prong. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009). However, as the Federal Circuit noted in Andreu, "a claimant's theory of

causation must be supported by a 'reputable medical or scientific explanation.'" *Andreu*, 569 F.3d at 1379 (quoting *Althen*, 418 F.3d at 1278). Petitioners have not presented such a reputable explanation in this case; as such, they have failed to present preponderant evidence in support of *Loving* prong four/Althen prong one.

### F. *Loving* Prong Five/*Althen* Prong Two: Petitioners have not Established a Logical Sequence of Cause and Effect between H.H.'s Vaccinations and the Significant Aggravation of his Condition

*Loving* prong five/*Althen* prong two requires the Petitioners to provide a logical sequence of cause and effect demonstrating that vaccination did cause a worsening of H.H.'s pre-existing condition. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Grant*, 956 F.2d at 1148. *Althen's* second prong is not without meaning. *Capizzano*, 440 F.3d at 1327.

#### 1. Petitioners have not Presented Evidence in Support of Vaccine Causation

Petitioners have not presented evidence demonstrating that H.H. experienced a vaccine-associated significant aggravation of his interferonopathy, signs of which had already begun to manifest by the time he received his Pentacel vaccine. They do not point to any testing or clinical signs that suggest vaccine causation. Instead, they assert that because H.H.'s deterioration occurred close-in-time to his vaccinations, and because no alternate explanation exists, then the vaccines "did cause" a significant aggravation of H.H.'s condition. This showing is insufficient. *See Moberly*, 592 F.3d at 1323 (citing *Althen*, 418 F.3d at 1278) (stating that "neither a mere showing of a proximate temporal relationship between vaccine and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation.").

#### 2. The Medical Record Evidence Indicates the Vaccines did not Cause or Significantly Aggravate H.H.'s Condition

Not only have Petitioners failed to present evidence from H.H.'s medical records which supports vaccine causation, but the records contain evidence supporting the opposite position – that the vaccines H.H. received did not affect his condition.

Dr. McGeady noted that H.H.'s clinical history does not indicate that he experienced a severe local reaction at the vaccine injection sites. Dr. McGeady opined that "[w]hile interferon alpha is principally produced by the plasmacytoid dendritic cells and monocytes/macrophages that might migrate to regional lymphoid tissue, the absence of local reaction after several prior immunizations suggests that no excessive or untoward reaction was produced." First McGeady Rep. at 9. He further opined that this exaggerated interferon release could cause a cytokine storm. There is certainly no evidence in the record that H.H. experienced this type of reaction.[27]

[27] There is medical record evidence indicating that H.H. had a fever at his November 11, 2013 visit with Dr. Hollis. *See* Ex. 49 at 41 (noting that "Pt has been fussy for the last week. He has run fever to 101.5."). This record places onset of fever one week prior to this appointment, or on approximately November 4,

Petitioners' causation theory also does not explain how the vaccines caused an elevation in H.H.'s transaminases. Several of H.H.'s treating physicians noted that H.H. had elevated liver enzymes. During his visit with Dr. Crawford on November 12, 2013, H.H.'s AST was 353, and his ALT was 400. Ex. 50 at 4. On December 18, 2013, H.H.'s liver enzymes were again elevated. His AST was 325, and his ALT was 472. Ex. 55 at 1. On May 23, 2014, H.H.'s was 119 and his ALT was 125. Ex. 63 at 2. H.H.'s treating physicians have drawn a connection between the abnormally elevated levels and the onset of his disease process, indicating these levels were suggestive of AGS. While elevated liver enzymes are consistent with AGS, there has been no evidence presented in this case that they are consistent with a vaccine reaction. In short, Petitioners have not explained how this finding fits into their causation theory. Dr. McGeady opined that there is no medical literature supporting such a connection. First McGeady Rep. at 9. Dr. Barañano agreed. Tr. at 294. The fact that a vaccine reaction does not explain H.H.'s elevated liver enzymes suggests that the vaccines did not cause or significantly aggravate his condition.

3. Treating Physicians

Several of H.H.'s treating doctors opined that the vaccines he received caused his condition. In weighing evidence, special masters are expected to consider the views of treating doctors. *Capizzano*, 440 F.3d at 1326. The views of treating doctors about the appropriate diagnosis are often persuasive because the doctors have direct experience with the patient whom they are diagnosing. *See McCulloch v. Sec'y of Health & Hum. Servs.*, No. 09-293V, 2015 WL 3640610, at *20 (Fed. Cl. Spec. Mstr. May 22, 2015). However, the opinions of treating physicians are not sacrosanct. *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed.Cl. 706, 745 n.67 (2009). These opinions are only as trustworthy as the reasonableness of their suppositions or bases.

Dr. Hollis is H.H.'s pediatrician. She opined as follows: "It seems to me that [H.H.'s] rapid decline can be attributed to receiving the vaccinations on October 17, 2013 and October 23, 2013." Ex. 66 at 3. Dr. Hollis based her opinion on the fact that H.H. was previously healthy, and because of that, a "severe and rapid developmental regression is unusual" in these circumstances, and that many diagnoses have been ruled out by his medical team. *Id.* Dr. Hollis did not provide any additional information to support her opinion. She did not articulate a theory of causation. Under these circumstances, although I have considered Dr. Hollis' opinion, I have not given it great weight.

Dr. Marks is H.H.'s treating neurologist. Dr. Marks opined that the vaccines H.H. received caused his condition. He stated that

> It is also my opinion that considering the commencement of H.H.'s symptoms occurred after the receipt of his fifteen (15) month vaccinations, the fact that his symptoms have persisted, and the lack of any other explanation for why he has developed severe and rapidly progressing dystonia with encephalopathy at this age, I have concluded that H.H.'s exposure to the fifteen (15) month vaccines was within

2013. This is 18 days after the flu and pneumonia vaccines and 12 days after Pentacel vaccine, too long for a fever associated with vaccination.

> a reasonable medical probability, the most likely trigger for him to develop rapidly progressing dystonia with encephalopathy to this degree.

Ex. 67 at 3-4. Dr. Marks' theory of causation is that H.H.'s vaccines caused him to develop a type I interferonopathy via molecular mimicry between a component of one of the vaccines and a self antigen. *Id.* at 4-5. Dr. Marks was unable to provide persuasive testimony at the entitlement hearing in support of this opinion.

> Q. And in your first report, which is Exhibit 67, and I will just quote it from Page 4, Paragraph 8 for the paraphrase, you propose an antigen in the influenza or DTaP vaccine must have been similar to a self-antigen in HH's neurological structure. Can you be any more specific what in the vaccine you think was involved?
>
> A. No. I'm – I'm not – I'm not an expert in -- in vaccines. I'm not an expert in vaccine manufacture. This was -- this was the hypothesis of a clinical neurologist looking for some way to explain what was going on. Okay.

Tr. at 172. When asked whether he could identify anything beyond his opinion that supports a vaccine-caused AGS-like disease, he testified:

> No. And, again, it doesn't even -- it doesn't even really have to be mimicry. It just has to be something that triggers an immune response, so mimicry was my way of explaining it as much to me and -- and to the family. But that doesn't necessarily have to be the theory. It's – it's one idea.

*Id.* at 187. Dr. Marks testified concerning his causation theory by addressing several of my questions:

> THE COURT: So you just testified that the theory in this case doesn't have to be one of molecular mimicry but is something that triggers an immune response. I do need to hear a theory as to how either the Pentacel or the flu vaccine caused the issues that HH has experienced. … And so … what is your most succinct way … of articulating that … theory?
>
> THE WITNESS: So if you think of molecular mimicry as an antigen which is -- which is what's presented to the body, okay -- being similar to something that the body doesn't recognize. Then you might -- it might be a little more specific.
>
> And I still think it's – it's a logical theory that there's something in the vaccine that -- that clearly the body has recognized as foreign. That's the whole -- to give a vaccine is -- is to do that.
>
> So you are -- vaccines, in general, basically, work by mimicry or by -- or by introducing something real to the body that the body should recognize as a[] foreign substance. And in this case, basically, the immune system has gone wild to -- in response to the immune presentation. So it's – it's -- it is a foreign antigen to the

> body. Okay. Whether -- whether it -- regardless of which vaccine it is, the -- the goal of the vaccine is -- is to introduce this -- this negative antigen, this foreign substance to the body, so create an immune response to it.
>
> And on occasion, the immune system just goes wild. That – that's known to happen. And in this case, it's the interferon system that seems to have gotten out of control.
>
> THE COURT: But what specifically about Pentacel or flu caused that to happen?
>
> THE WITNESS: Well, again, it -- it -- it is the -- it is whatever -- it -- it could be antigen. It could be the binding agent. The – I'm -- I – I'm not an expert on vaccines and -- and how they're made and all the things that go into them.

Tr. at 188-90. Dr Marks' inability to persuasively articulate a theory of causation caused me to afford his opinion less weight.[28]

In support of his causation opinion, Dr. Marks highlighted the fact that H.H.'s neurologic status stabilized after his rapid decline. He stated that "[t]his stabilization … which was hyperactive post-immunization is indicative of the cause being derived from the vaccinations." Ex. 67 at 4-5. After analyzing this issue earlier in the decision, I concluded that H.H.'s stabilization is consistent with a diagnosis of AGS. Indeed the medical literature makes this point clear. The fact that Dr. Marks based his opinion, in part, on an incorrect premise, has further reduced the value of this opinion in supporting Petitioners' case.

Dr. Marks additionally pointed to H.H.'s normalization of neopterin levels in July of 2017 as a reason to tip the scales in favor of vaccine causation. He stated,

> With 95% of patients having a known genetic marker, we are left with two essentially equal possibilities for H.H.'s condition. Either he is one of the very rare cases of AGS without a known genetic marker or an AGS-like interferonopathy triggered by external immune stimulating condition such as immunization. Given the waning immune response based on his most recent neopterin levels, I would favor the latter.

Ex. 94 at 1. At the time Dr. Marks drafted this opinion it was true that H.H.'s neopterin levels had normalized. However, by the time of the entitlement hearing, they were again elevated. Dr. Marks never reconciled his opinion expressed in exhibit 94, that the waning immune response tipped the scales in favor of vaccine causation where there were "essentially equal possibilities for H.H.'s condition", with this new information available at trial.

I also note that neither Dr. Hollis nor Dr. Marks considered that onset of H.H.'s interferonopathy took place around the time of the flu and pneumonia vaccines and before H.H. received the Pentacel vaccine. While I do not fault either doctor on this point as my findings are

[28] I additionally note that Petitioners have since abandoned this molecular mimicry theory in place of the one proposed by Dr. Steinman.

articulated for the first time in this decision, I do find that it diminishes the persuasive value of their opinions. *See Mosley v. Sec'y of Health & Hum. Servs.*, No. 08-724V, 2015 WL 2354316, at *18-19 (Fed. Cl. Spec. Mstr. Apr. 27, 2015) (affording the opinions of treating physicians less weight because they either did not consider how onset of TM one day after vaccination impacted their opinion or did not explain the basis for their opinion).

Ultimately, I have considered the opinions of Dr. Marks and Dr. Hollis, two of H.H.'s treating physicians, in arriving at my determination that there is not preponderant evidence that H.H.'s vaccinations did cause or significantly aggravate his condition. For the reasons articulated in this decision, I am not persuaded by these opinions, and instead have credited the opinions of Dr. Barañano and Dr. McGeady, who have opined that H.H. suffers from a genetic type I interferonopathy the onset of which was unrelated to and unaffected by vaccination. *See Locane*, 685 F.3d 1375. Petitioners have failed to meet their burden under *Loving* prong five/*Althen* prong two.

### G. *Loving* Prong Six/*Althen* Prong Three: Petitioners have not Established an Appropriate Temporal Relationship between H.H.'s Vaccinations and the Significant Aggravation of his Condition

The final *Loving* prong requires Petitioners to establish a "proximate temporal relationship" between the significant aggravation of A.S.'s condition and the vaccines he received. *Loving* at 144; *see also Althen*, 418 F.3d at 1281. Petitioners must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

The timing prong contains two parts. First, Petitioners must establish the "timeframe for which it is medically acceptable to infer causation" and second, they must demonstrate that the onset of the disease occurred in this period. *Shapiro v. Sec'y of Health & Hum. Servs.*, 101 Fed. Cl. 532, 542-43 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x 952 (Fed. Cir. 2013). I will address the question of onset first.

#### 1. The Onset of H.H.'s Interferonopathy

Dr. Steinman opined that H.H.'s disease course began three weeks after his receipt of the Pentacel vaccine. He stated that "[n]ot until three weeks after the Pentacel immunization on October 23, 2013 was there any symptomatology related to an interferonopathy." First Steinman Rep. at 16. This forms the premise for his opinion regarding the appropriateness of the onset interval. However, my determination in this case is contrary to Dr. Steinman's; I found that H.H. began to develop heel cord tightness around the time he received his October 17, 2013 vaccinations, and before he received the Pentacel vaccine, and further, that this heel cord tightness constituted a physical sign of his type I interferonopathy.

#### 2. Medically-Acceptable Timeframe

With respect to the medically-acceptable onset interval, Dr. Steinman opined that "[t]he onset of neuroinflammation within 3 weeks of the October 23, 2013 immunizations with Pentacel is consistent with references 18 and 19, which cover related neuroinflammatory conditions of the peripheral (19) and central nervous systems (20). H.H. has a condition involving the central nervous system primarily." First Steinman Rep. at 15. He then went on to state "A showing of a proximate temporal relationship between vaccination and injury" is met from similar studies on other neuroinflammatory conditions linking neuroinflammation and immunization, with onset at approximately 3 weeks post-Pentacel vaccine. *See* References 17–18." *Id.* at 16. Although it appears that Dr. Steinman is relying on references 19 and 20 in support of his timing position (and not 17 and 18), I have examined references 17-20 in an abundance of caution.

Reference 17, Naves et al., discussed earlier in this decision, does not support the position that an interferonopathy would begin or become significantly aggravated either the same day or within one or two days after a trigger.

Reference 18 is an article by Rodero & Crow. This article does not discuss the onset timeframe of a type I interferonopathy.

Reference 19 is a paper by Schonberger that is oft-cited in the Vaccine Program. Schonberger et al., *Guillain Barre Syndrome following vaccination in the National Influenza Immunization Program, United States, 1976-1977*, 110 AMERICAN JOURNAL OF EPIDEMIOLOGY 2, 105-23, (1979) (filed as Ex. 101, Tab 19) (hereinafter "Schonberger"). Schonberger demonstrates that the swine flu vaccine can cause Guillain Barré syndrome (GBS), a demyelinating disease of the peripheral nervous system. The increased risk for developing GBS after swine flu vaccination was concentrated within the five weeks after vaccination. Schonberger at 105.

Through his reference to this article, Dr. Steinman appears to opine that the findings from Schonberger regarding onset of GBS after swine flu vaccination are analogous to the onset of a type I interferonopathy after Pentacel vaccine. I do not find this position to be persuasive.

Chief Special Master Corcoran addressed Dr. Steinman's reliance on Schonberger in a different case. *See Rowan v. Sec'y of Health & Hum. Servs.*, No. 17-760V, 2020 WL 2954954, at *16 (Fed. Cl. Spec. Mstr. Apr. 28, 2020). The Chief Special Master noted that Schonberger "loses persuasive heft when offered in disparate contexts, such as when invoked to prove a CNS injury (rather than peripheral nerve injury) was vaccine-caused." *See, e.g., L.Z. v. Sec'y of Health & Hum. Servs.*, No. 14-920V, 2018 WL 5784525, at *18 n.18 (Fed. Cl. Spec. Mstr. Aug. 24, 2018) ("[p]etitioner's evidentiary showing regarding the timing prong is similarly deficient based on the scientific literature submitted" because it relied on the Schonberger study on GBS, which was "distinguishable from MS"); *see also Jones v. Sec'y of Health & Hum. Servs.*, No. 15-1239V, 2018 WL 7139212, at *16 (Fed. Cl. Spec. Mstr. Dec. 21, 2018) ("Schonberger's timeframe [ ] is much less persuasive when used by way of analogy to a different condition that purportedly resulted from different vaccines").

Not only is a type I interferonopathy a different condition than GBS, but the underlying theory of causation in GBS generally implicates molecular mimicry, a causation theory involving the adaptive immune system that has been eschewed by Dr. Steinman in this case. ("The theory

here focuses on how the components of the vaccine can drive an interferon response. It is *not* a theory based on molecular mimicry…") First Steinman Rep. at 9. Accordingly, the fact that swine flu vaccine can cause GBS via molecular mimicry in three weeks does not advance Petitioners' position that the Pentacel vaccine significantly aggravated H.H.'s type I interferonopathy.

Finally, reference 20 is a paper by Bennetto and Scolding. *See* Bennetto & Scolding, *Inflammatory/Post-Infectious Encephalomyelitis*, 75 J NEUROL NEUROSURG PSYCHIATRY, i22-i28, doi: 10.1136/jnnp.2003.034256 (2004) (filed as Ex. 101, Tab 20) (hereinafter "Bennetto & Scolding"). In this article, the authors discuss acute disseminated encephalomyelitis (ADEM) and its link to various infections and immunizations. Bennetto & Scolding state that "[t]he timing of the first symptoms varies slightly with the precipitant: typically 1–14 days after non-neural vaccines, … and 1–3 weeks (or more) after rabies inoculation." *Id.* at 3. The authors further note that "[i]n the case of post-infectious ADEM, molecular mimicry between virus and myelin antigens may be responsible for initiating disease…" Bennetto & Scolding at 6. ADEM is a demyelinating disease of the central nervous system. It is an entirely different condition than a type I interferonopathy. Bennetto & Scolding briefly discuss the mechanism of molecular mimicry, which is not at play in this case. In short, this article does not advance Petitioners' position in articulating a timeframe after vaccination for which it is medically acceptable to infer that H.H.'s vaccines caused the significant aggravation of his inherited type I interferonopathy.

In sum, I do not find that H.H.'s type I interferonopathy either began or was significantly aggravated three weeks after the Pentacel vaccine, or that Petitioners have preponderantly established that three weeks post vaccination is a medically acceptable onset interval. For these reasons, Petitioners have not met their burden to provide preponderant evidence with respect to *Loving* prong six/*Althen* prong three.

## VII. CONCLUSION

Petitioners have experienced great suffering as a result of H.H.'s condition. However, in order to find they are entitled to compensation they must preponderantly demonstrate that the vaccines caused or significantly aggravated H.H.'s condition. Based on the evidence presented in this case, I conclude that Petitioners have not made such a showing. **Their petition is therefore DISMISSED. The clerk shall enter judgment accordingly.**[29]

**IT IS SO ORDERED.**

**s/ Katherine E. Oler**
Katherine E. Oler
Special Master

[29] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by each filing (either jointly or separately) a notice renouncing their right to seek review.