In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: August 31, 2017[1]

Refiled in Redacted Form: February 7, 2018

* * * * * * * * * * * * * *	PUBLISHED
MARIA L. TORRES, in her Own Right and as Best Friend of her Son, J.A.,	Chief Special Master Dorsey
Petitioner,	No. 15-561V
v.	Denial of Entitlement; Measles, Mumps & Rubella ("MMR") Vaccine; Hepatitis A ("Hep A") Vaccine; Varicella Vaccine; Autistic Disorder ("AD"); Residual Human DNA Fragments; HERV-K Fragments; Insertional Mutagenesis; Autoimmunity.
SECRETARY OF HEALTH AND HUMAN SERVICES,	
Respondent.	
* * * * * * * * * * * * * *	

John F. McHugh, Law Office of John McHugh, New York, NY, for petitioners.
Alexis B. Babcock, U.S. Department of Justice, Washington, DC, for respondent.

DECISION DISMISSING PETITION

On August 27, 2015, petitioner filed a status report in which she agreed to be bound by the ruling in the J.M. et al. (02-10V) case.

On September 1, 2017, I ruled against petitioners in J.M. et al. A copy of that decision is attached hereto as Appendix A and is incorporated herein.

Accordingly, petitioner is bound by that decision, and this case is **DISMISSED**. In the absence of a motion for review,[2] the Clerk of the Court **SHALL ENTER JUDGMENT** in accordance with this decision.

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[1] When this decision was originally filed, I advised the parties of my intent to post it on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002. 44 U.S.C. §3501 note (2012) (Federal management and Promotion of Electronic Government Services). Although the petitioner did not file a motion for redaction in her case, petitioners in the lead omnibus case, J.M. et al. (02-10V), filed a motion to have their names redacted to initials. This decision is being reissued to reflect that the names of the petitioners in the J.M. et al. case have been redacted to initials. Except for those changes and this footnote, no other substantive changes have been made.

[2] Pursuant to Vaccine Rule 11(a), entry of judgment is expedited by the parties' joint filing of notice renouncing the right to seek review.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Chief Special Master

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

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J.M. and V.M., in their Own Right and as Best Friends of their Son, V.J.M., Petitioners, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	PUBLISHED No. 02-10V Chief Special Master Dorsey Denial of Entitlement; Measles, Mumps & Rubella ("MMR") Vaccine; Hepatitis A ("Hep A") Vaccine; Varicella Vaccine; Autistic Disorder ("AD"); Residual Human DNA Fragments; HERV-K Fragments; Insertional Mutagenesis; Autoimmunity.

John F. McHugh, Law Office of John McHugh, New York, NY, for petitioners.
Ann Donohue Martin, U.S. Department of Justice, Washington, DC, for respondent.

DECISION

I. Introduction

On January 4, 2002, J.M. and V.M. ("petitioners") brought a claim pursuant to the National Vaccine Injury Compensation Program ("the Program")[2] on behalf of their son, V.J.M., in which they alleged that the measles, mumps and rubella ("MMR") vaccine that he received on January 19, 1999, caused his pervasive developmental disorder ("PDD"), not otherwise specified, autism. Amended Petition ("Am. Pet.") at ¶¶ 10, 12, 15. V.J.M. was one year old at

[1] When this decision was originally filed, I advised the parties of my intent to post it on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002. 44 U.S.C. §3501 note (2012) (Federal management and Promotion of Electronic Government Services). In accordance with Vaccine Rule 18(b), petitioners filed a motion to redact certain information. This decision is being reissued with minimal changes, including redaction of the petitioners' name in the case caption and text to initials and redaction of V.J.M.'s date and place of birth. Except for those changes and this footnote, no other substantive changes have been made.

[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, 42 U.S.C. §§ 300aa-10 et seq. [hereinafter "Vaccine Act" or "the Act"]. Hereafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

the time of the vaccination, and thereafter, petitioners allege he failed to either gain or maintain his verbal and social skills. Id. at ¶¶ 1, 6.

This case is the lead case for a mini-omnibus proceeding comprised of 23 cases.[3] Petitioners in each of these cases have agreed to be bound by the decision in this case, which will be filed in each of the cases in the mini-omnibus.

As their theory of causation, petitioners assert that V.J.M. had an adverse reaction to human DNA found in the rubella portion of the MMR[4] vaccine, which triggered his autism.[5] Am. Pet. at ¶¶ 15-16; Pet. Ex. 10 at ¶¶ 3, 17. Respondent argues against awarding compensation, stating that petitioners failed to provide adequate evidence that V.J.M.'s MMR vaccination, or any other vaccinations, caused him to suffer from autism.

After carefully analyzing and weighing all of the evidence and testimony filed and presented in this case in accordance with applicable legal standards, I find that petitioners have not met their legal burden under Prong One of Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005). Petitioners have not demonstrated preponderant evidence that the MMR or any other vaccinations that V.J.M., or the children in the other related proceedings, received can cause autism. Therefore, this case, and the other cases, must be dismissed.[6]

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[3] The 23 cases in the mini-omnibus include: J.M. et al. (02-010V), J.K.R. et al. (09-143V), Fuesel (02-095V), E.H. et al. (09-206V), Arranga (02-1616V), B.W. (14-375V), J.H.R. et al. (03-1156V), M.P. et al. (07-750V), Coiro-Lorusso (04-258V), S.O. et al. (08-125V), Young (05-207V), Graddy (08-416V), C.B. et al. (05-1168V), Eworonsky (04-992V), C.B. et al. (08-131V), King (05-717V), F.J.D. et al. (08-254V), P.R. et al. (10-096V), F.J.D. et al. (08-253V), Torres (15-561V), N.P. et al. (08-388V), M.J. et al. (16-434V), and A.E.R. (17-470V). This Decision applies to all of these cases.

[4] The MMR vaccine at issue is occasionally referenced as "MMR II" in petitioners' exhibits, expert reports, and medical literature, as this distinction is material to Dr. Deisher's theory. For purposes of this decision, the term "MMR vaccine" is used with no distinction drawn between MMR vaccine and MMR II vaccine, except when discussing Dr. Deisher's change point study. See section VIII(a).

[5] While the minor child in J.M. et al. received only the MMR vaccine, the petitioners in the other cases joined in this proceeding had one or more of the vaccines at issue: MMR, "Varivax, Vaqta, Havrix and Pentacel." See Pet. Prehearing Memorandum at n.1. This decision applies to these additional vaccines as well. Varivax is indicated for vaccination against varicella zoster virus in individuals 12 months of age and older. Vaqta (by Merck) and Havrix (by GlaxoSmithKline) vaccinate against hepatitis A. Pentacel is indicated for diphtheria, tetanus, pertussis, and polio (DTaP-IPV).

[6] A decision dismissing each of the mini-omnibus cases will issue following this decision.

II. Factual Background

a. Summary of Relevant Facts

V.J.M. was born at [redacted] on [redacted] Pet. Ex. A[7] at 12. His APGAR[8] scores were nine at one minute after birth and 10 at five minutes. Id. On January 31, 1998, V.J.M. had his first well-child visit with his pediatrician. Id. at 13. No developmental or behavioral concerns were noted, and he received the inactivated polio vaccine ("IPV"). Id. At his next well-child visit on March 18, 1998, V.J.M., age two months, was again assessed as a well-child, and he received the Haemophilus influenza type B ("Hib") and hepatitis B ("Hep B") vaccinations. Id. at 13-14. On May 20, 1998, V.J.M., age four months, received the IPV, Hib, and Hep B vaccinations. Id. at 14. At that visit, he was noted to be developing normally. Id. On August 3, 1998, V.J.M. presented to his primary care physician with a "single pustular lesion on [his] chin," and his skin was noted to have a "honey crusted vesicular rash." Id. at 20. He was prescribed a topical antibiotic. Id.

At his six month well-child visit on August 12, 1998, V.J.M. was eating cereal, fruit, and vegetables. No developmental or behavioral concerns were noted. Pet. Ex. A at 15. He received the diphtheria, pertussis, and tetanus ("DPT") vaccine at this visit. Id. On August 19, 1998, V.J.M. returned to his primary care physician and was noted to be "cranky, teething, [and] pulling on [his] ear." Id. at 20. He was diagnosed with bilateral otitis media and an upper respiratory infection and was given amoxicillin. Id. He returned to his doctor on September 4, 1998, to have his ears re-checked. Id. At that time, his doctor noted that V.J.M. showed signs of residual otitis media. Id.

At his one year old well-child visit on January 19, 1999, V.J.M. was again noted to be a well-child with no reported concerns. At this visit, he received the MMR[9] and Hib vaccines. Pet. Ex. A at 16. A few days later, on January 21, 1999, V.J.M. returned to his doctor with a chief complaint of a sore throat. No behavioral concerns were noted at this visit. Id. at 21. On February 13, 1999, V.J.M. presented to his primary care physician with a fever. He was diagnosed with an upper respiratory infection and bilateral otitis media and was prescribed amoxicillin. Id. He returned to his doctor on March 3, 1999, to have his ears re-checked, and both tympanic membranes were normal at that time. Id. At a well-child visit on April 19, 1999,

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[7] Petitioners organized their initial exhibits with the letters A through J. However, they later switched to numbers, beginning with Exhibit 10.

[8] Appearance, Pulse, Grimace, Activity, and Respiration ("APGAR") score is a method of evaluating newborns to determine their overall health at the time of birth. See NELSON TEXTBOOK OF PEDIATRICS (19th ed. 2011) at 536-37.

[9] It appears from the medical records that V.J.M. received only one dose of the MMR vaccine. See Pet. Ex. A. at 13-19. This MMR vaccine is alleged to be the cause of V.J.M.'s ASD. See Am. Pet. at 10, 12, 15.

no developmental or behavioral concerns were noted. The varicella vaccine was offered and refused. Id. at 17. V.J.M. presented to his physician for his 18 month well-child visit on July 20, 1999, at which time no behavioral or developmental concerns were noted. Id. at 17-18. During this visit, he received the DPT and the oral polio vaccine ("OPV") vaccinations. Id. at 18.

On April 6, 2000, V.J.M. visited his primary care doctor for an ear checkup, where residual otitis media was noted. Pet. Ex. A at 22. He had fluid in his left ear and his right ear was infected; he was prescribed Bactrim. Id. On June 21, 2000, a primary care note states that V.J.M. was pulling on both of his ears, and while he did not have a fever, he was cranky. Id. During that visit, he was referred to an early intervention program for a speech, hearing, and behavioral evaluation.[10] Id. At his next well-child visit on July 18, 2000, V.J.M. was noted to be a well-child with no developmental or behavioral concerns. Id. at 18. He received the Prevnar vaccination during this visit. Id. On September 26, 2000, he was given a neurological referral for "questionable pervasive developmental disorder ("PDD")." Id. at 23.

On July 21, 2000, when he was two and a half years old, V.J.M. underwent a psychological evaluation at the Programs for Special Children. Pet. Ex. B at 27. His evaluation indicated that he did not suffer from any significant medical problems at birth or thereafter, with the exception of repeated ear infections.[11] Id. at 28. The report further indicated that while his developmental milestones were within normal limits during his first year, his speech development did not progress as expected. Id.

Based on his psychological evaluation, it was recommended that V.J.M. receive an intensive early intervention program with an emphasis on developing his social and communication skills. Pet. Ex. B at 31. On September 5, 2000, V.J.M. began an intensive multi-modal therapeutic program at the New York City Early Intervention Program, which included 20 hours of behavioral therapy, one hour of daily speech and language therapy, and occupational therapy three times weekly. Pet. Ex. C at 33; Pet. Ex. F at 20. Notes from October 31, 2000, show that V.J.M. initially made great progress in therapy, though he continued to show speech and language delay. Pet. Ex. F at 20. Therapy notes reflect that his eye contact improved, he began responding to his name, and he was able to identify common objects. Id. at 19. While V.J.M.'s speech and language skills showed significant initial improvement, his progress plateaued, resulting in the need for neurological evaluation. Pet. Ex. C at 33. V.J.M. had no family history of neurological disorders, and his two month old sister had no behavioral abnormalities. Id.

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[10] The doctor's note from the visit on June 21, 2000, does not include an explanation as to why V.J.M. was referred to early intervention. See Pet. Ex. A at 22. However, this appears to be the first mention of any developmental issue in the medical records, which occurred approximately one year and five months after the January 19, 1999 MMR vaccination.

[11] V.J.M. went to the doctor for otitis media (recurrent ear infections) on the following dates: August 19, 1998, September 4, 1998, February 13, 1999, March 3, 1999, November 30, 1999, March 23, 2000, April 6, 2000, June 21, 2000, July 16, 2001, and December 4, 2001. Pet. Ex. A at 20-24.

On May 24, 2001, Dr. Arnold Gold, a neurologist, evaluated V.J.M. Pet. Ex. C at 32. During the evaluation, V.J.M. was irritable and fussy, apparently because he had been wakened from a nap. Id. at 33. Dr. Gold reported that V.J.M.'s one year milestones were considered age-appropriate by his parents. He was able to sit on his own at the age of six months and was able to walk unassisted by the age of 14 and a half months. V.J.M.'s parents did not express concern about his development until he was approximately 14 to 15 months old. Id. at 32. Although he uttered his first word, "car," at the age of 12 months, there was only limited improvement in his speech and language development. Id.

During Dr. Gold's evaluation, V.J.M. exhibited self-stimulatory behaviors such as spinning repetitively in a circle while seated. Pet. Ex. C at 32. The spinning eventually resolved, but V.J.M. then began jumping up and down and jumping across the room while grinding his teeth. Id. at 32-33. Additionally, he would frequently scatter and gather objects, such as blocks, and would at times rock in a repetitive manner. Id. at 33. He had no dysmorphic features or cutaneous lesions suggestive of a neurocutaneous disorder. His gait was normal and he had no difficulty walking, running, or jumping. Id. He did not like to have his head touched and could be occasionally physically aggressive by hitting. Id. Dr. Gold stated that V.J.M.'s behaviors were consistent with ASD. Id. An etiology could not be established, but Dr. Gold reported that he "would question any relationship to the MMR vaccination." Id. at 35. There was no evidence of a seizure disorder or progressive encephalopathy. Id. at 34.

b. Petitioners' Affidavit[12]

Along with their petition, petitioners also filed an affidavit from J.M., in which she averred that V.J.M. was healthy at birth and developed normally until his first birthday. Pet. Affidavit at 6. By his first birthday, he could stand up, say several words, and use words to identify the objects that he was holding. Id. On January 19, 1999, after receiving the MMR, Hib, and hepatitis B vaccinations, V.J.M. fell asleep in the car on the way home. Id. at 7. He did not wake up when being transferred from the car to his crib, which was unusual. Id. J.M. avers that V.J.M. awoke several hours later and was cranky and clingy, and when she put him on the floor, he began to spin himself around. Id. J.M. stated that sometimes he would fall silent and sit and stare for several minutes.[13] Id.

Two days after his vaccinations, J.M. took V.J.M. back to the doctor with a chief complaint of a sore throat. Pet. Affidavit at 8. Although she described V.J.M.'s symptoms to his pediatrician, J.M. stated that she did not alert his doctor to the spinning or staring because she did not know that either was a significant symptom. Id. V.J.M.'s pediatrician diagnosed him with an ear infection and a sore throat. Id.

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[12] Petitioners filed an affidavit from J.M. along with their petition. They did not attend or testify at the hearing in this matter.

[13] The medical records do not contain any mention of these behaviors after vaccination.

After January 21, 1999, J.M. stated that V.J.M.'s development halted, and he stopped attempting to use words. Pet. Affidavit at 8. He began repetitive activities and stopped sleeping through the night. Id. V.J.M. became more easily cranky, he stopped trying to speak, and when he resumed speaking, he was incessantly repetitive. Id. J.M. stated that she began reporting her observations of V.J.M. to his pediatrician beginning on January 21, 1999, but was told that there was nothing wrong. Id. at 9. Although she stated that her reports to his pediatrician became more frantic, the medical records do not reflect her concerns. Id. Specifically, she noted that when she took V.J.M. to his pediatrician on July 18, 2000, she reported her concerns about his lack of development, but her concerns were not recorded by the pediatrician. Id. She stated that V.J.M.'s health problems began immediately after he received his vaccinations on January 19, 1999, and that he is permanently disabled and in need of assistance. Id. at 10-11.

III. Procedural History

a. Omnibus Autism Proceeding

This case is one of more than 5,400 cases filed under the Program in which petitioners alleged that conditions known as "autism" or "autism spectrum disorders" ("ASD")[14] were caused by one or more vaccinations. A special proceeding known as the Omnibus Autism Proceeding ("OAP") was developed to manage these cases within the Office of Special Masters ("OSM"). A detailed history of the controversy regarding vaccines and autism, along with a history of the development of the OAP, was set forth in the six entitlement decisions issued as "test cases" for two theories of causation litigated in the OAP (see cases cited below), and will only be summarized here.

A group called the Petitioners' Steering Committee ("PSC") was formed in 2002 by the many attorneys who represented Vaccine Act petitioners who raised autism-related claims. About 180 attorneys, including petitioners' counsel, Mr. McHugh, participated in the PSC. Their responsibility was to develop any available evidence indicating that vaccines could contribute to causing autism, and eventually present that evidence in a series of "test cases," exploring the issue of whether vaccines could cause autism, and, if so, under what circumstances. Ultimately, the PSC selected groups of attorneys to present evidence in two different sets of "test cases" during many weeks of trial in 2007 and 2008. In the six test cases, the PSC presented two separate theories concerning the causation of ASDs. The first theory alleged that the measles portion of the MMR vaccine could cause ASDs. That theory was presented in three separate Program test cases during several weeks of trial in 2007. The second theory alleged that the mercury contained in thimerosal-containing vaccines could directly affect an infant's brain,

[14] ASD is a general classification, which as of 2010 included five different specific disorders: Autistic Disorder ("AD"), Childhood Disintegrative Disorder, Asperger's syndrome, Rett syndrome, and Pervasive Developmental Disorder Not Otherwise Specified ("PDD-NOS"). Pet. Ex. 27; Pet. Ex. 34 at 2; King v. Sec'y of Health & Human Servs., No. 03-584V, 2010 WL 892296, at *5 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). The term "autism" is often utilized to encompass all of the types of disorders falling within the autism spectrum. Id.

thereby substantially contributing to the causation of ASD. That theory was presented in three additional test cases during several weeks of trial in 2008.

Decisions in each of the three test cases pertaining to the PSC's first theory rejected the petitioners' causation theories. Cedillo v. Sec'y of Health & Human Servs., No. 98-916V, 2009 WL 331968 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), mot. for rev. denied, 89 Fed. Cl. 158 (2009), aff'd, 617 F.3d 1328 (Fed. Cir. 2010); Hazlehurst v. Sec'y of Health & Human Servs., No. 03-654V, 2009 WL 332306 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), mot. for rev. denied, 88 Fed. Cl. 473 (2009), aff'd, 604 F.3d 1343 (Fed. Cir. 2010); Snyder, 2009 WL 332044, mot. for rev. denied, 88 Fed. Cl. 706 (2009). Decisions in each of the three "test cases" pertaining to the PSC's second theory also rejected the petitioners' causation theories, and the petitioners in each of those three cases chose not to appeal. Dwyer v. Sec'y of Health & Human Servs., No. 03-1202V, 2010 WL 892250 (Fed. Cl. Spec. Mstr. Mar. 12, 2010); King, 2010 WL 892296; Mead v. Sec'y of Health & Human Servs., No. 03-215V, 2010 WL 892248 (Fed. Cl. Spec. Mstr. Mar. 12, 2010).

The "test case" decisions were comprehensive, analyzing in detail all of the evidence presented on both sides. The three test case decisions concerning the PSC's first theory totaled more than 600 pages of detailed analysis, and were solidly affirmed in many more pages of analysis in three different rulings by three different judges of the United States Court of Federal Claims, and in two rulings by two separate panels of the United States Court of Appeals for the Federal Circuit. The three special master decisions concerning the PSC's second theory were similarly comprehensive.

All told, the 11 lengthy written rulings by the special masters, the judges of the U.S. Court of Federal Claims, and the panels of the U.S. Court of Appeals for the Federal Circuit unanimously rejected the petitioners' claims, finding no persuasive evidence that either the MMR vaccine or thimerosal-containing vaccines could contribute in any way to the causation of autism.

The proceedings in the six "test cases" concluded in 2010. Thereafter, the petitioners in this case, and the petitioners in other cases within the OAP, were instructed to decide how to proceed with their own claims. The vast majority of those autism petitioners elected either to withdraw their claims or to request that the special master file a decision denying their claim on the written record, resulting in a decision rejecting the petitioner's claim for lack of support. However, a small minority of the autism petitioners elected to continue to pursue their cases, seeking other causation theories and/or other expert witnesses. A few such cases have gone to trial before a special master, and in the cases of this type decided thus far, all have resulted in rejection of petitioners' claims that vaccines played a role in causing their child's autism. See, e.g., Henderson v. Sec'y of Health & Human Servs., No. 09-616V, 2012 WL 5194060 (Fed. Cl. Spec. Mstr. Sept. 28, 2012) (autism not caused by pneumococcal vaccination); Franklin v. Sec'y of Health & Human Servs., No. 99-855V, 2013 WL 3755954 (Fed. Cl. Spec. Mstr. May 16, 2013) (MMR and other vaccines found not to contribute to autism); Coombs v. Sec'y of Health & Human Servs., No. 08-818V, 2014 WL 1677584 (Fed. Cl. Spec. Mstr. Apr. 8, 2014) (autism not caused by MMR or Varivax vaccines); Blake v. Sec'y of Health & Human Servs., No. 03-31V, 2014 WL 2769979 (Fed. Cl. Spec. Mstr. May 21, 2014) (autism not caused by MMR

vaccination); Long v. Sec'y of Health & Human Servs., No. 08-792V, 2015 WL 1011740 (Fed. Cl. Spec. Mstr. Feb. 19, 2015) (autism not caused by influenza vaccine); Brook v. Sec'y of Health & Human Servs., No. 04-405V, 2015 WL 3799646 (Fed. Cl. Spec. Mstr. May 14, 2015) (autism not caused by MMR or Varivax vaccines); Holt v. Sec'y of Health & Human Servs., No. 05-136V, 2015 WL 4381588 (Fed. Cl. Spec. Mstr. June 24, 2015) (autism not caused by hepatitis B vaccine); Lehner v. Sec'y of Health & Human Servs., No. 08-554V, 2015 WL 5443461 (Fed. Cl. Spec. Mstr. July 22, 2015) (autism not caused by influenza vaccine); Miller v. Sec'y of Health & Human Servs., No. 02-235V, 2015 WL 5456093 (Fed. Cl. Spec. Mstr. Aug. 18, 2015) (ASD not caused by combination of vaccines); Allen v Sec'y of Health & Human Servs., No. 02-1237V, 2015 WL 6160215 (Fed. Cl. Spec. Mstr. Sept. 26, 2015) (autism not caused by MMR vaccination); R.K. v. Sec'y of Health & Human Servs., No. 03-632V, 2015 WL 10911950 (Fed. Cl. Spec. Mstr. Sept. 28, 2015) (autism not caused by influenza vaccine), mot. for rev. denied, 125 Fed. Cl. 57 (2016); Hardy v. Sec'y of Health & Human Servs., No. 08-108V, 2015 WL 7732603 (Fed. Cl. Spec. Mstr. Nov. 3, 2015) (autism not caused by several vaccines); Sturdivant v. Sec'y of Health & Human Servs., No. 07-788V, 2016 WL 552529 (Fed. Cl. Spec. Mstr. Jan. 21, 2016) (autism not caused by Hib and Prevnar vaccines); R.V. v. Sec'y of Health & Human Servs., No. 08-504V, 2016 WL 3882519 (Fed. Cl. Spec. Mstr. Feb. 19, 2016) (autism not caused by influenza vaccine), mot. for rev. denied, 127 Fed. Cl. 136 (2016); Murphy v. Sec'y of Health & Human Servs., No. 05-1063V, 2016 WL 3034047 (Fed. Cl. Spec. Mstr. Apr. 25, 2016) (autism not caused by DTaP or MMR vaccines).

In addition, some autism causation claims have been rejected without trial, at times over the petitioner's objection, in light of the failure of the petitioner to file plausible proof of vaccine-causation. See, e.g., Waddell v. Sec'y of Health & Human Servs., No. 10-316V, 2012 WL 4829291 (Fed. Cl. Spec. Mstr. Sept. 19, 2012) (autism not caused by MMR vaccination); Fester v. Sec'y of Health & Human Servs., No. 10-243V, 2016 WL 1745436 (Fed. Cl. Spec. Mstr. Apr. 7, 2016) (autism not caused by measles, mumps, rubella, and varicella ("MMRV") vaccine); Fresco v. Sec'y of Health & Human Servs., No. 06-469V, 2013 WL 364723 (Fed. Cl. Spec. Mstr. Jan. 7, 2013) (autism not caused by multiple vaccines); Fesanco v. Sec'y of Health & Human Servs., No. 02-1770V, 2010 WL 4955721 (Fed. Cl. Spec. Mstr. Nov. 9, 2010) (autism not caused by multiple vaccines); Miller v. Sec'y of Health & Human Servs., No. 06-753V, 2012 WL 12507077 (Fed. Cl. Spec. Mstr. Sept. 25, 2012) (autism not caused by DTaP or MMR vaccines); Pietrucha v. Sec'y of Health & Human Servs., No. 00-269V, 2014 WL 4538058 (Fed. Cl. Spec. Mstr. Aug. 22, 2014) (autism not caused by multiple vaccines); Bushnell v. Sec'y of Health & Human Servs., No. 02-1648V, 2015 WL 4099824 (Fed. Cl. Spec. Mstr. June 12, 2015) (autism not caused by multiple vaccines); Bokmuller v. Sec'y of Health & Human Servs., No. 08-573V, 2015 WL 4467162 (Fed. Cl. Spec. Mstr. June 26, 2015) (autism not caused by multiple vaccines); Canuto v. Sec'y of Health & Human Servs., No. 04-1128V, 2015 WL 9854939 (Fed. Cl. Spec. Mstr. Dec. 18, 2015) (autism not caused by DTP and DTaP vaccines); Valle v. Sec'y of Health & Human Servs., No. 02-220V, 2016 WL 2604782 (Fed. Cl. Spec. Mstr. Apr. 13, 2016) (autism not caused by DTaP vaccine). Judges of this court have affirmed the practice of dismissal without trial in such cases. E.g., Fesanco v. Sec'y of Health & Human Servs., 99 Fed. Cl. 28 (2011) (Chief Judge Braden affirming).

In none of the rulings since the test cases has a special master or judge found any merit in an allegation that any vaccine can cause autism.[15]

b. Procedural History Specific to This Case

Petitioners filed their petition on January 4, 2002. The initial status conference was held on February 6, 2002, and respondent filed a Rule 4(b) Report on June 3, 2002.[16] Respondent requested additional medical records, and petitioners were ordered to file those records. Resp. R. 4(b) Rept. at 2-3. A Rule 5 conference was held on June 20, 2002.

Petitioners filed additional exhibits on November 27, 2002, including an expert report from Dr. Harold Buttram and additional medical records. Notice of Filing dated November 27, 2002 (ECF No. 17). On December 16, 2002, respondent filed an expert report from Dr. Arnold Gale, and petitioners filed a supplemental expert report from Dr. Buttram on February 19, 2003. Respondent filed a supplemental expert report from Dr. Gale on April 1, 2003.[17] During a status

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[15] I note that during the years since the "test cases" were decided, Vaccine Act compensation was granted in only two cases involving vaccinees suffering from ASDs. But in neither of those cases did respondent concede, nor did a special master find, that there was any causation-in-fact connection between a vaccination and the vaccinee's ASD. Instead, in both cases it was conceded or found that the vaccinee displayed the symptoms of a Table Injury within the Table time frame after vaccination and causation under the Act was presumed.

In Poling, the presiding special master clarified that the family was compensated because the respondent conceded that the Poling child had suffered a Table Injury – not because respondent or the special master had concluded that any vaccination had contributed to causing or aggravating the child's ASD. See Poling v. Sec'y of Health & Human Servs., No. 02-1466V, 2011 WL 678559, at *1 (Fed. Cl. Spec. Mstr. Jan. 28, 2011) (a fees decision noting specifically that the case was compensated as a Table Injury).

Second, in Wright v. Sec'y of Health & Human Servs., No. 12-423V, 2015 WL 6665600 (Fed. Cl. Spec. Mstr. Sept. 21, 2015), Special Master Vowell concluded that a child, later diagnosed with ASD, suffered a Table Injury after a vaccination. However, she stressed that she was not finding that the vaccinee's ASD in that case was caused-in-fact by the vaccination – to the contrary, she specifically found that the evidence in that case did not support a causation-in-fact claim, going so far as to remark that the petitioners' causation-in-fact theory in that case was "absurd." Id. at *2. The compensation of these two cases thus does not afford any support to the notion that vaccinations can contribute to the causation of autism.

[16] Respondent stated in her Rule 4(b) Report that because the medical records were not complete, she could not provide a full evaluation of the merits of petitioners' case. Resp. R. 4(b) Rept. dated June 3, 2002 (ECF No. 8) at 9, 12.

[17] The reports of Drs. Buttram and Gale were superseded when petitioners later introduced and pursued a theory by Dr. Theresa Deisher. In their Joint Prehearing Submission, the parties

conference on March 27, 2003, petitioners requested that the case be stayed pending the completion of the OAP.[18] See Order dated April 15, 2003 (ECF No. 25) at 1. On May 16, 2003, a formal notice was filed to inform the parties that the statutory time period for the special master's issuance of a decision in the case had expired. Petitioners filed a response to the formal notice on June 24, 2003, stating that they wished to remain in the Program. Resp. to Formal Notice dated June 24, 2003 (ECF No. 27). Petitioners further stated that they wished for their case to be "consolidated with the omnibus autism litigation for initial determination of causation." Id. at 2.

After June 24, 2003, no filings were made in the case until January 15, 2008, on which date petitioners were ordered to file the remainder of the medical records and a statement of whether their claim should proceed in an omnibus proceeding. Order dated January 15, 2008 (ECF No. 29). The order provided an overview of the OAP to date, and petitioners were ordered to file completed records in anticipation of the forthcoming OAP rulings. Id. at 1-2. The Order also explained the two-stage approach for filing medical records. First, petitioners were required to provide evidence that the "first symptom or manifestation of onset" occurred within 36 months of the vaccine. Id. at 3; see also 42 U.S.C. § 300aa-16(a)(2). Assuming this first requirement could be met, petitioners would then proceed to gather and file all medical records from V.J.M.'s birth through either the date of the petition's filing or the date of V.J.M.'s initial diagnosis of autism, whichever was later. Order dated Jan. 15, 2008 (ECF No. 29) at 5.

On March 17, 2008, respondent filed a Statement Regarding Jurisdiction and Appropriateness of Proceeding within the Court's OAP. Resp. Statement dated Mar. 17, 2008 (ECF No. 31). Respondent stated that after an initial review of the record, petitioners' claims appeared to have met the 36 month onset requirement. Id. at 2. On April 21, 2009, petitioners filed a Notice of Compliance that phase one medical records production was complete. Notice of Compliance dated Apr. 21, 2009 (ECF No. 35). Petitioners also filed a statement that "[V.J.M.'s] claim is that he became autistic following an MMR vaccination. This action belongs in the Omnibus Autism Proceeding." Statement dated Apr. 27, 2009 (ECF No. 36). This case was converted to electronic case filing ("ECF") on March 24, 2011.

Petitioners filed an amended petition on June 10, 2011, which included additional details regarding V.J.M.'s medical history and diagnosis. Am. Pet. dated June 10, 2011 (ECF No. 42). The petition states that V.J.M. was diagnosed with PDD by Dr. Ruben Rosenblatt on July 20, 2000. Id. at 3. Petitioners claimed that V.J.M. had an adverse reaction to one or more of the vaccines he received on January 19, 1999, which caused him to develop autism. Id. at 4. They also alleged that the MMR and varicella vaccines contained human embryonic tissue. Id. at 5. Petitioners claimed that the human DNA contained in these vaccines played a role in V.J.M.'s

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confirmed that "[t]he parties agree that the sole issue to be resolved through the upcoming hearing is whether Dr. Deisher's theory of vaccine-caused autism meets petitioners' burden under [P]rong [O]ne of Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005)." See Joint Prehearing Submission (ECF No. 223) at 1.

[18] For a full explanation of the OAP, see supra Omnibus Autism Proceeding at 6-9.

development of ASD. Id. Petitioners filed a status report on October 26, 2011, which listed several other Program cases alleging the same medical theory of causation. Status Report dated Oct. 26, 2011 (ECF No. 44) at 1.

On January 3, 2012, petitioners filed an expert report and supporting materials by Theresa Ann Deisher, Ph.D.[19] On February 3, 2012, petitioners filed their first motion to compel access to the Vaccine Safety Datalink ("VSD"). Pet. Mot. to Compel dated Feb. 3, 2012 (ECF No. 46). Petitioners sought access to data contained in the VSD in order to perform research related to their medical theory of causation. Petitioners argued that access to the VSD would allow their expert witness to independently corroborate her statistical data. Id. at 3. Dr. Deisher testified that she made several unsuccessful attempts to gain access to the VSD, and some of her efforts pre-dated her involvement in this case. Tr. 245. After she became involved in the case, in 2011, she made another unsuccessful attempt to access the VSD. Id. Further, her team applied for an NIH grant to help fund her research on the VSD, but the application was denied. Id. She also stated that she applied for access to government maintained databases on ASD in two European countries but that her team was denied access to these databases as well. Tr. 97.

Petitioners filed a second motion to compel on March 2, 2012, further seeking "documents in the custody and control of the respond [sic] which are reasonable and necessary to a fair and informed determination on the merits of this matter." Mot. to Compel dated Mar. 2, 2012 (ECF No. 50) at 1. Respondent and other non-party managed care organizations ("MCOs") filed responses opposing petitioners' motions on March 30, 2012. Resp. to Mot. to Compel dated Mar. 30, 2012 (ECF No. 58); Resp. to Mot. to Compel dated March 30, 2012 (ECF No. 60). Respondent and the non-party MCOs made three essential arguments against petitioners' motions to compel. First, they argued that the proposed research investigation for which the data was requested was a litigation-driven and results-oriented study. Next, they argued that Dr. Deisher was not an independent and disinterested researcher, because her hypothesis was informed by an anti-stem cell research agenda. Third, respondent stated that Dr. Deisher's proposed study did not meet criteria for institutional board review and thus would not be reliable. Scheduling Order dated Feb. 24, 2012 (ECF No. 49) at 2. Petitioners filed a reply to respondent and the MCOs' responses on April 13, 2012. Pet. Reply dated Apr. 13, 2012 (ECF No. 63).

Respondent filed a response to petitioners' second motion to compel on June 14, 2012. Resp. to Mot. to Compel dated June 14, 2012 (ECF No. 65). Respondent argued that petitioners' requests were not reasonable or necessary, in accordance with the standards of the Program. Id. at 3. Respondent further argued that the discovery was irrelevant to petitioners' medical theory. Id. at 5. Petitioners filed a reply on July 14, 2012. Pet. Reply dated July 14, 2012 (ECF No. 69). The litigation over petitioners' motions to compel continued throughout the remainder of 2012 and 2013. The presiding special master denied petitioners' motion to compel access to the VSD, their motion for authority to issue subpoenae to the MCOs, and their motion to compel production of Food and Drug Administration ("FDA") documents. [redacted] v. Sec'y of Health & Human Servs., No. 02-10V, 2013 WL 3368236 (Fed. Cl. Spec. Mstr. June 12, 2013).

[19] Petitioners' Notice of Intent to File on CD was previously filed on December 20, 2011. See ECF No. 45.

Petitioners' motion for reconsideration of the special master's Order was also denied. [redacted], 2013 WL 6038670 (Fed. Cl. Oct. 24, 2013).

Petitioners filed a supplemental report from Dr. Deisher on December 20, 2013. Notice of Filing dated Dec. 20, 2013 (ECF No. 95). On March 14, 2014, petitioners filed a status report in which they identified 13 other Program cases which alleged the same medical theory of causation. Status Rept. dated Mar. 14, 2014 (ECF No. 106). Petitioners filed an expert report from Dr. William Toffler on March 31, 2014, and a supplemental letter from Dr. Toffler on May 9, 2014.[20] Notice of Compliance dated Mar. 31, 2014 (ECF No. 110); Notice of Filing dated May 9, 2014 (ECF No. 113). I held a status conference in the case on February 9, 2015, during which petitioners identified J.M. et al. as the lead case in the mini-omnibus. Scheduling Order dated Feb. 10, 2015 (ECF No. 130) at 2. Due to conflicts in Dr. Deisher's schedule, the hearing originally scheduled for late 2015 was rescheduled for March 2016. Status Rept. dated May 15, 2015 (ECF No. 134). Petitioners filed a number of medical records and additional medical literature throughout the remainder of 2015. Petitioners also filed an expert report from Dr. Karin Burkhard on January 15, 2016. Petitioners also filed a motion for interim fees, and I issued a decision partially granting that request. [redacted] v. Sec'y of Health & Human Servs., No. 02-10V, 2016 WL 720969 (Fed. Cl. Spec. Mstr. Feb. 4, 2016).

Petitioners filed their prehearing submissions on January 15, 2016. Pet. Prehearing Brief ("Prehrg Br.") dated Jan. 15, 2016 (ECF No. 202). Respondent filed her prehearing submissions on February 8, 2016. Prehrg Submissions dated Feb. 8, 2016 (ECF No. 222). An entitlement hearing was held on March 7-8, 2016, in Seattle, Washington. The hearing continued in Washington, D.C. on March 10-11, 2016. I heard rebuttal testimony from Dr. Deisher and Dr. Burkhard in Washington, D.C. on May 6, 2016.

On May 5, 2016, the day before the hearing on May 6, 2016, petitioners filed a motion to issue subpoena to obtain the testimony of Dr. William Thompson, an epidemiologist employed by the CDC, and to recall Dr. Fallin, one of respondent's expert witnesses. Pet. Mot. dated May 5, 2016 (ECF No. 261). Respondent filed a response opposing the motion on June 16, 2016, arguing that such testimony was unnecessary and irrelevant to the determination of vaccine causation. Resp. Res. dated June 16, 2016 (ECF No. 264). Petitioners filed a reply on July 7, 2016. Pet. Reply dated July 7, 2016 (ECF No. 268). On August 30, 2016, I issued an Order denying petitioners' motion to issue subpoena but granting petitioners' motion to file documentation. [redacted], 2016 WL 5362878 (Fed. Cl. Aug. 30, 2016).

On August 1, 2016, respondent filed a supplemental expert report from Dr. Arking in response to the rebuttal testimony presented by Dr. Deisher and Dr. Burkhard. Notice of Filing dated Aug. 1, 2016 (ECF No. 270). Petitioners then filed a reply to Dr. Arking's supplemental report on September 9, 2016. The parties agreed that post hearing briefs were not necessary, and the evidentiary record was closed on September 9, 2016.

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[20] Petitioners did not call Dr. Toffler to testify at the hearing in this case. See Order dated March 28, 2016 (ECF No. 254). Although not discussed herein, I have nonetheless reviewed his written opinion, and I do not find it to offer support to petitioners' causation theories. See Pet. Ex. 263.

The case is now ripe for adjudication.

IV. Issue to be Decided

The sole issue to be decided in this mini-omnibus proceeding is whether Dr. Deisher's theory of vaccine-caused autism meets petitioners' burden under Prong One of Althen, 418 F.3d at 1278. Joint Prhrg Submission dated Feb. 8, 2016 (ECF No. 223), at 1. This Decision is therefore limited to an evaluation of whether petitioners have met their burden under Althen Prong One.

V. Standards for Adjudication

The Vaccine Act established the Program to compensate vaccine-related injuries and deaths. 42 U.S.C. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Human Servs. 35 Fed. Cl. 1, 7 (1996) (quoting H.R. REP. No. 99-908, at 3 (1986), as reprinted in 1986 U.S.C.C.A.N. 6287, 6344).

To receive compensation under the Program, petitioners must prove either: (1) that V.J.M. suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that he received,[21] or (2) that V.J.M. suffered an injury that was actually caused by the vaccine (or vaccines) he received. See §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006).

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[21] Although petitioners have not contended that V.J.M. suffered a Table encephalopathy, out of an abundance of caution, I have thoroughly analyzed the issue and concluded that V.J.M.'s symptoms cannot properly be classified as a Table encephalopathy. As explained in Waddell, 2012 WL 4829291, "[t]he scope of the medical term 'encephalopathy' is more expansive than the narrower, statutory definition set forth in the Table." Id.*12 (referencing Hazelhurst, 2009 WL 332306, at *26-29). The Qualifications and Aids to Interpretation ("QAI") definition of acute encephalopathy simply does not encompass every type of brain dysfunction to which the broader meaning of "encephalopathy" applies.

To establish an MMR-Table encephalopathy, petitioners would have to demonstrate that V.J.M. suffered an "encephalopathy" as defined by the QAI section to the Vaccine Injury Table within five to 15 days of his MMR vaccination. 42 C.F.R. § 100.3(b). According to the QAI, a vaccinee is considered to have suffered a Table encephalopathy if the vaccine manifests an injury encompassed in the definition of an acute encephalopathy within the appropriate time period, and if a chronic encephalopathy is present for more than six months after the immunization. 42 C.F.R. § 100.3(b)(2). I note that V.J.M.'s medical records fail to demonstrate evidence of such an encephalopathy.

Because petitioners cannot show that V.J.M. suffered a Table injury, they must prove that a vaccine that he received caused his injury. To do so, petitioners must establish, by preponderant evidence, a medical theory causally connecting a vaccine and V.J.M.'s injury ("Althen Prong One"). Althen, 418 F.3d at1278; § 300aa–13(a)(1) (requiring proof by a preponderance of the evidence).

VI. Expert Opinions

a. Experts' Education, Background, and Experience

i. Petitioners' Experts

1. Dr. Theresa Deisher, Ph.D.

Dr. Theresa Deisher holds a Bachelor of Arts in Human Biology and a Ph.D. in Molecular and Cellular Physiology, both from Stanford University. Pet. Ex. 12 at 2. She also completed a post-doctoral fellowship in Pathology/Hematology at the University of Washington. Id.

Dr. Deisher's career has been predominantly focused on commercial biotechnology, and her research has led to the development of 22 patents. Pet. Ex. 12 at 2. From 1988 to 1990, she worked as a research associate for Genentech, Inc., in the area of cardiovascular pharmacology. Id. at 4. From 1993 to 1995, she worked as a research scientist for Repligen Corporation in the Inflammation Department. Id. From 1995 to 1998, Dr. Deisher worked as a scientist and project leader for ZymoGenetics, Inc., where she directed a research program focused on the discovery of cardioprotective compounds for ischemic or cytotoxic damage. Id. at 3.[22] From October 2000 to July 2002, Dr. Deisher worked as a senior staff scientist in the Vascular Biology Department at Immunex Corporation, where she acted as a project leader on anti-thrombotics and inflammation/myocardial repair. In July 2002, after Amgen, Inc. acquired Immunex, she began working as a principal scientist in the Inflammation Department of Amgen, where part of her work focused on the use of stem cell therapies for myocardial regeneration. Id. While there, Dr. Deisher was the lead inventor on a patent for the use of stem cells in cardiac repair. Id. From September 2006 to October 2007, she served as the Vice President of Research and Development for CellCyte Genetics Corporation. Id.

Dr. Deisher is currently the President of Sound Choice Pharmaceutical Institute ("Sound Choice"), which she founded in January 2008. Pet. Ex. 12 at 2. She is also the CEO, Founder, and Research and Development Director of AVM Biotechnology, LLC ("AVM").[23] Id. The

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[22] Dr. Deisher's work with ZymoGenetics in the areas of catecholamine or anthracycline administration led "to the discovery of a novel regenerative growth factor (licensed to Serono for development) and to the identification of adult cardiac stem cells." Pet. Ex. 12 at 3.

[23] According to Dr. Deisher, AVM is "[d]edicated to safe, effective, affordable and ethical human therapeutics, focusing initially on regenerative medicine and vaccinations." Pet. Ex. 12 at

initial focus of AVM "was to develop drugs that optimized the activity of stem cells outside of the blood-forming cells."[24] Tr. 34. According to Dr. Deisher, Amgen was already selling stem cell optimization drugs at that time, but AMV was formed to create drugs that would improve stem cell effectiveness for heart, pancreatic, or liver repairs. Id. at 35. AMV's future business plan also included developing an alternative to vaccines that use human cell lines.[25] Id. The company's mission statement is focused on doing research "that would not exploit or harm another human being," including human fetuses.

Sound Choice Pharmaceuticals is a non-profit organization "whose purpose is to inform … pediatricians about the human exploitation that goes on in biomedical research and in the name of biomedical progress, and to conduct research into the autism human-fetal-manufactured contaminants in vaccines link." Tr. 45.[26] Dr. Deisher decided to form Sound Choice due to the "compelling association" between autism and vaccines. Id. She states, "The association was so compelling, and the known biology of the potential dangers accumulated over decades from different scientific fields was so well established that it would be unconscionable to ignore this association." Id.

Dr. Deisher testified, "The publication of the articles we pursued largely at your [John McHugh's] insistence. You … definitely wanted that data to be published, and so we did pursue that." Id. Dr. Deisher has written papers focused on various aspects of stem cell treatments and research.[27] Pet. Ex. 12 at 5-8. She has also given speeches and lectures to religious, political,

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[24] Dr. Deisher testified that while she was working at ZymoGenetics, she was involved in a research project to develop heart muscle cell lines that could be continuously cultured. Tr. 23. At that time, researchers at ZymoGenetics were using mice to try to develop these cell lines. Dr. Deisher testified that she was the first to isolate pluripotent stem cells from adult mouse hearts – something which had previously been thought as impossible. Id. at 25-26. She further defined pluripotent stem cells as "a stem cell that can give rise to any type of cell in the body." Id. Dr. Deisher stated that her discovery resulted in a "huge controversy," because scientists previously believed that adult stem cells did not exist outside of the blood-forming cells. Id.

[25] To date, AVM has not produced any such alternative vaccines. Tr. 312. AVM was unsuccessful in developing vaccines that did not use human cell lines, and thus this goal was dropped from its business plan by 2011. Id. at 229; 312.

[26] Sound Choice Pharmaceutical Institute is "[c]ommitted to providing education, scientific research, development and resources to encourage safe and moral medicines and therapeutics." Pet. Ex. 12 at 2.

[27] Dr. Deisher did not disclose a conflict of interest in her 2015 article in the Journal of Public Health regarding the potential for vaccines derived from human fetal stem cell lines to cause ASD. Tr. 225. Dr. Deisher testified that at the time the article was published, she was attending to urgent personal family business and that the potential conflict of interest between her research

and student-led organizations regarding the use of stem cells in scientific manufacturing and research. Id.

2. Dr. Karin Burkhard, M.D.

Dr. Karin Burkhard testified on behalf of petitioners during the hearing in Washington, D.C., on March 10-11, 2016, and she also offered rebuttal testimony on May 6, 2016. Dr. Burkhard has a Bachelor of Arts from the New School for Social Research in New York, New York, and a M.D. from Dartmouth Medical School in Hanover, New Hampshire. Pet. Ex. 475 at 1.[28] She completed her post graduate adult psychiatry residency at Beth Israel Medical Center from 1984-1987, and afterward completed a Child Psychiatry Fellowship from 1987-1989 at the Long Island Jewish Medical Center.

From 1988-1990, Dr. Burkhard worked as a staff psychiatrist and consultant at Pride of Judea Mental Health Center in Douglaston, New York. Pet. Ex. 475 at 1. In 1989, she began working as a staff psychiatrist and consultant at St. Mary's Children and Family Services in Syosset, New York, where she worked until 1993. Id. In 1989, she also entered private practice in child, adolescent, and adult psychiatry, where she has worked ever since. Id.

ii. Respondent's Experts

1. Dr. M. Daniele Fallin, Ph.D.

Dr. M. Daniele Fallin testified on behalf of respondent during the hearing in Washington, D.C., on March 11, 2016, as an expert in autism epidemiology. Dr. Fallin received her Bachelor of Science in Zoology at the University of Florida, and she was also a doctoral student in the genetic epidemiology of Alzheimer's disease at the University of South Florida from 1995-1998. Resp. Ex. K at 1. She received her Ph.D. in Genetic Epidemiology from Case Western Reserve University in Cleveland, Ohio. Id.

Dr. Fallin is a professor at Johns Hopkins University in both the School of Medicine and the Bloomberg School of Public Health. She holds a joint appointment in the Departments of Medicine, Biostatistics, and Epidemiology, and she is the Director of the Wendy Klag Center for Autism and Developmental Disabilities. Resp. Ex. K at 1-2. She also serves on the advisory board for Autism Speaks and as a committee co-chair for the International Society for Autism Research. Id. at 3. She co-organized the Autism Speaks Conference on Epigenetics in Autism in 2011, and she has spoken on a number of panels on autism and genetics. Id. at 3-4.

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on alternatives to fetal cell manufactured vaccines and her ownership of AVM pharmaceuticals was not apparent to her or her research team. She stated that the team pursued the research independent of any legal claims. Id. However, Dr. Deisher further stated that "theoretically, [there] is a potential conflict of interest [that] probably should have been disclosed." Id. at 226.

[28] Dr. Burkhard's CV was filed on December 29, 2015, at CM/ECF No. 198-1.

Dr. Fallin is an editor for numerous medical journals, including Epidemiology, Genetic Epidemiology, and the American Journal of Human Genetics. Id. at 4. She has published over 160 articles in the areas of genetics, epigenetics, Alzheimer's disease, and autism, and she has co-authored several book chapters. Id. at 4-24. Dr. Fallin also has extensive teaching experience and serves as an advisor for Ph.D. students, public health masters' students, and post-doctoral fellows. Id. at 25-27. She has taught courses on Public Mental Health, Autism Spectrum Disorder and Public Health, Introduction to Genetic Epidemiology, and Genetic Epidemiology in Populations, just to name a few. Id. at 33. Dr. Fallin has received a number of grants to do genetic research on autism. She has received awards to do research as part of the Study to Explore Early Development ("SEED"), as well as the Early Autism Risk Longitudinal Investigation ("EARLI") network. Resp. Ex. K at 37-41.

Dr. Fallin described two autism epidemiology studies for which she is the main investigator, which are funded by the Centers for Disease Control ("CDC") and the National Institutes of Health ("NIH"), respectively. Tr. 652. The first study is called SEED, which is a national case control study. Dr. Fallin explained, "There are six sites nationally that go out and recruit children between ages two and five who have autism, and then also recruit children who have a non-autistic developmental disability, as well as children from the same birth cohorts and geographic regions who are typically developing." Id. at 652-53. Researchers collect bio samples from parents and children in an effort to understand both environmental as well as genetic components of autism. Id. at 653.

The second autism study which Dr. Fallin leads is EARLI, which is a pregnancy cohort[29] study. Tr. 653. The study follows pregnant women and fetuses in four different sites around the country in an effort to look at the interplay between genetics and the environment in a child's risk for developing autism. Id.

2. Dr. Neal Halsey, M.D.

Dr. Neal Halsey testified on behalf of respondent during the hearing in Washington, D.C., on March 10, 2016. Dr. Halsey received his Bachelor of Science and a Doctor of Medicine from the University of Wisconsin. Resp. Ex. M at 1. He completed an internship in pediatrics at the Center for Health Sciences in Madison, Wisconsin, and he completed a residency in pediatrics at the University of Colorado Medical Center in Denver, Colorado. Id. From 1975 – 1978, he worked at the CDC in Atlanta, Georgia, first as an epidemic intelligence service officer and then as a preventive medicine resident. Id. Dr. Halsey also completed a fellowship at the University of Colorado Medical Center in pediatric infectious diseases from 1978-1980. He is licensed to practice medicine in the State of Maryland, and he was licensed by the National Board of Medical Examiners in 1972. Id. He is board certified by the American Board of Pediatrics and a Diplomat in Pediatric Infectious Diseases. Id.

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[29] In epidemiology, a "cohort" is a "group of individuals who share a common characteristic, e.g., all of the individuals born in one year (a birth cohort) …. The term [ ] indicates observation of the individuals over time." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 382 (32d ed. 2012).

Dr. Halsey is a professor in the Department of International Health at Johns Hopkins University, Bloomberg School of Public Health, in Baltimore, Maryland, and the Director of the Institute for Vaccine Safety at the Bloomberg School of Public Health. Resp. Ex. M at 1. From 1999 to 2011, he served as the Co-Director for the Center for Disease Studies and Control in Guatemala City, Guatemala, and he was the Director of the Division of Disease Control at Johns Hopkins from 1985-2002. Id. at 2. He has served on a number of advisory panels and committees, including the Advisory Board of the Albert B. Sabin Vaccine Foundation, the Scientific Advisory Committee at the Johns Hopkins Autoimmune Disease Center, and the Advisory Board for the Immunization Action Coalition. Id. at 3. Dr. Halsey has served as editor, advisor, and committee chair for five books, he has been on the editorial board of four medical journals, and he has participated in a number of manuscript reviews since 1981. Id. at 5-6. In 2015, he received the Stanley A. Plotkin Lecture in Vaccinology Award from the Pediatric Infectious Disease Society. Id. at 6. He has also published over 230 articles in the areas of pediatrics, immunization, and infectious diseases. Id. at 8-28. Dr. Halsey was admitted as an expert in the fields of pediatric medicine, pediatric infectious disease, medical epidemiology, and vaccine safety. Tr. 431.

3. Dr. Dan Arking, Ph.D.

Dr. Dan Arking testified on behalf of respondent during the hearing in Washington, D.C., on March 10-11, 2016. Dr. Arking has a Bachelor of Science in Molecular Biology and Genetics from the University of Maryland in College Park, Maryland. Resp. Ex. I at 1. He holds a Ph.D. in Human Genetics from the Johns Hopkins University School of Medicine in Baltimore, Maryland, and he completed a post-doctoral fellowship in complex disease genetics in the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins. Id.

From 2007-2011, Dr. Arking served as an assistant professor at the McKusick-Nathans Institute of Genetic Medicine and Department of Medicine, Institute of Cardiology at Johns Hopkins. Resp. Ex. I at 1. He is currently an associate professor at the McKusick-Nathans Institute, and he also serves as affiliated faculty for the Johns Hopkins Institute for Data-Intensive Engineering and Science. Id. He is a faculty member of the Wendy Klag Center for Autism and Developmental Disabilities at the Johns Hopkins Bloomberg School of Public Health. Id. Dr. Arking has published over 100 articles in the areas of genetics, genetic variation, and autism, and he has made contributions to several patents and copyrights. Id. at 1-14. He has received a number of research grants for various studies, including grants from the Autism Center of Excellence, the American Heart Association, and the Simons Foundation Autism Research Initiative. Id. at 14-15. Dr. Arking serves as the Co-Director of the Johns Hopkins Claude D. Pepper Older Americans Independence Center Biological Mechanisms Core, and he has served as a member of a number of institutional committees. Id. at 16-18. He also currently serves as an editor for two academic journals and participates in a number of advisory committees, including the Simons Foundation Autism Research Initiative Gene Advisory Board and the Scientific Review Board. Id. at 18-19.

Dr. Arking conducts large-scale genetic studies to identify and distinguish particular genetic traits for autism. Tr. 563. His research team at Johns Hopkins focused on mapping the

entire genome[30] of autistic patients to look at gene variances. Id. He testified, "When I started up my own lab, I wanted to incorporate more than just genetics, so one of the things we focused on is getting access to brains from autistic individuals and match controls." Id. The lab he began at Johns Hopkins in 2005 focuses on combining "traditional genetics" with the study of the brain, including gene expression. Id. at 563-64.[31]

VII. Autism Spectrum Disorders

The terms "autism" and "autism spectrum disorders" are used to describe a set of "complex neurodevelopmental disorders characterized by a combination of deficits in communication and social interaction and repetitive, stereotyped behavior and interest." Pet. Ex. 14 at 2;[32] Pet. Ex. 27;[33] Pet. Ex. 34 at 2.[34] There is no definitive diagnostic test, and thus, diagnosis is based on behavior, using the various criteria, tests,[35] and the Diagnostic and Statistical Manual of Mental Disorders ("DSM").[36] See, e.g. Snyder, 2009 WL 332044, at *39

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[30] The genome is defined as "the entirety of the genetic information encoded by the nucleotide sequence of an organism, cell, organelle, or virus; it is DNA in eukaryotes and prokaryotes, and DNA or RNA in viruses. In a human being, the genome size is approximately [three] billion base pairs of DNA and approximately 25,000 genes." DORLAND'S at 771.

[31] Dr. Arking's lab performs research on ASD as well as in the areas of cardiovascular genetics and frailty in aging. Tr. 564.

[32] Hjoris O. Alottodir, Association of Family History of Autoimmune Disease and ASDs, 124 PEDIATRICS 687-94 (2009) [Pet. Ex. 14].

[33] Michael E. McDonald & John F. Paul, Timing of Increased Autistic Disorder Cumulative Incidence, 44 ENVIRON. SCI. TECHNOL. 2112 (2010) [Pet. Ex. 27, 432].

[34] Helen V. Ratajczak, Theoretical Aspects of Autism: Causes – A Review, 8 J. IMMUNOTOXICOLOGY 68-79 (2011) [Pet. Ex. 34].

[35] Such tests include the Childhood Autism Rating Scale ("CARS"), a tool used to identify autism in children that includes classifying their symptoms on a numbered scale. See, e.g. Emanuela Rellini et al., Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) Correspondence and Conflicts with DSM-IV Criteria in Diagnosis of Autism, 34 J. AUTISM AND DEV. DISORDERS 703 (Dec. 2004) [Pet Ex. 461]; But cf. Synder, 2009 WL 332044, at *39 (noting that CARS "has been used for many years," but also noting more recent rating systems such as the Autism Diagnostic Interview-Revised ("ADI-R") and the Autism Diagnostic Observational Schedule–Generic ("ADOS-G")).

[36] The DSM is published by the American Psychiatric Association. It comprises "a classification of mental disorders with associated criteria designed to facilitate more reliable diagnoses of these disorders." AMERICAN PSYCHIATRIC ASSOCIATION, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS xli (5th ed. 2013). First published in 1952, the DSM "has become a

(noting that "specialized checklists and interview instruments are used to evaluate ASD" and that "most autism specialists use one or more of the checklists in making a diagnosis."); Hazlehurst, 2009 WL 332306, at *29 (noting that "[a]n evaluating clinician may select the method of assessing a child's symptoms, choosing either a clinical examination or one of the standardized checklists that afford a more standardized observation or measure, or a developmental interview that guides the clinician in the collection of informative symptoms and then can be used to apply DSM–IV criteria in an algorithmic manner to reach a diagnostic conclusion. The diagnosis of an ASD is based entirely on abnormalities in behavior and development observed by clinicians and reported by parents. There are no biological markers or medical tests that are diagnostic of an ASD." (internal citations omitted).)

Despite extensive investigation, the causes of autism remain elusive. Generally, autism[37] is thought to be a "disruption of brain development caused by a combination of genes and environment." Pet. Ex. 15 at 2.[38] Well-funded, large scale and highly technical studies have revealed considerable information on the genetic causes. Id. Current research suggests that 1,000 genes, or more, may contribute to the cause of ASDs. Resp. Ex. J47 at 9.[39] Approximately 50-56 percent of ASDs are due to inherited genetics, five to 10 percent are due to de novo genetic mutations,[40] and the other 40 percent of cases have unknown causes. Tr. 572, 613.

As for environmental causes, research in neuroanatomy based on autopsies and imaging studies suggest that the prenatal time frame is the "window of susceptibility" for causation. Tr. 660-61. See also Resp.'s Ex. J3 at 1.[41] Environmental factors are believed to affect the fetus during the prenatal period. Tr. 661. In addition to neuroanatomical evidence, genetic research supports the prenatal period as important with regard to causation. Id. at 663.

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standard of reference for clinical practice in the mental health field." Id.

[37] Petitioner's expert, Dr. Deisher, characterizes autism as "an encephalopathy." See Pet Ex. 10 at 3; Pet Ex. 76 at 41. V.J.M. received the MMR vaccine at issue on January 19, 1999, and his medical records do not reveal any signs or symptoms consistent with any brain injury after vaccination. The first mention of any developmental issue was not until June 21, 2000. Pet. Ex. B at 27, 30-31. There is no evidence to support a finding that V.J.M. suffered either a Table or non-Table encephalopathy.

[38] Nature Publishing Group, The Mind's Tangled Web, 479 NATURE 1 (2011) [Pet. Ex. 15].

[39] Jeremy A. Willsey et al., Coexpression Networks Implicate Human Midfetal Deep Cortical Projection Neurons in the Pathogenesis of Autism, 155 CELL 997 (2013) [Resp. Ex. J47].

[40] De novo mutations are defined as "a mutation observed in a child that is not observed in the parent." Tr. 573.

[41] Margaret L. Bauman, & Thomas L. Kemper, Neuroanatomic Observations of the Brain in Autism: A Review and Future Directions, 23 INT. J. DEVL. NEUROSCIENCE 183 (2005) [Resp. Ex. J3].

VIII. Petitioners' Theory of Causation[42]

Petitioners posit that residual human DNA[43] and/or retroviral fragments[44] found in three vaccines, MMR II, varicella, and hepatitis A, serve as environmental triggers, and that exposure to these vaccines accounts for the increase in the prevalence of autism. To develop her theory, Dr. Deisher performed a study in which she purports to identify change points[45] as to autism

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[42] Though this decision does not discuss every medical article that petitioners filed, I have carefully reviewed and considered all of petitioners' medical literature, as well as all other documents filed in this case. See § 300aa-13(a)(1) (stating that the special master should consider the "record as a whole").

[43] Most biologicals, including vaccines, are produced within living cells in cell substrates, typically resulting in final products that contain some residual cellular constituents. Ivana Knezevic, et al., WHO Study Group on Cell Substrates for Production of Biologicals, Geneva, Switzerland, 11-12 June 2007, 36 BIOLOGICALS 203 (2008) [Pet Ex. 136]. These residual constituents include DNA from the substrate, which may be referred to variously as "residual cellular DNA," "cell contaminating residual DNA," "anomalous DNA," or simply as "cellular," or "residual" DNA. See, e.g., Pet Ex. 136 at 2; Pet. Ex. 34 at 1; Resp. Ex. L at 2; Pet. Ex. 42 at 3; Pet Ex. 10 at 13. Cell substrates can be used from a number of different sources. Cell substrates commonly used in U.S. vaccine manufacturing include primary cells of avian or monkey origin as well as primate diploid cell strains and a continuous cell line called the Vero cell line. Pet Ex. 34 at 1. "Residual human fetal DNA," refers to petitioner's specific contention that certain vaccines manufactured using human cell lines contain residual DNA originating from human fetal material. See Pet Ex. 10 at 13; Tr. 239-40. At various points in her testimony Dr. Deisher also referenced "human-fetal-manufactured contaminants," (Tr. 45) "residual fetal cellular debris," (Tr. 79) "contaminating human fetal DNA," (Tr. 80) "fetal DNA contaminants," (Tr. 102) and "fetal DNA fragments" (Tr. 121).

[44] A retrovirus is any virus belonging to the retroviridae family of viruses, which are a family of single strand RNA viruses. DORLAND'S at 1636. A human endogenous retrovirus ("HERV") is a retrovirus-like sequence found in the human genome and believed to be the remains of true retroviruses previously absorbed through evolution. Id. HERVs, which make up at least eight percent of the human genome, have been associated with several human diseases, including HIV infection, autoimmune diseases and malignancies. Derek Dube, et al., Genomic Flexibility of Human Endogenous Retrovirus Type K, 88 J. VIROLOGY 9673 (2014) [Resp. Ex. L4]. Human endogenous retrovirus type K ("HERV-K") is the most recent family of HERVs to be incorporated into the human genome, integration having occurred as recently as 200,000 years ago. Id. In her expert reports, Dr. Deisher cites HERV-K fragments as a vaccine contaminant. See, e.g., Pet. Ex. 10 at 20-21; Pet. Ex. 76 at 5.

[45] According to Dr. Deisher, a change point indicates that "autism was rising at a lower rate in children" prior to the date of the change point, than after it. Pet. Ex. 26 at 8. For example, with regard to the change point in 1988, "this means that autism was rising at a lower rate in children born prior to 1988 than in children born after 1988." Id.

prevalence. The change points relevant to the United States are 1980.9, 1988.4, and 1996.[46] Dr. Deisher opines that these change points correspond to "the introduction of or increased doses of" the three vaccines manufactured using human DNA. Pet. Ex. 265 at 1. Dr. Deisher offers two broad causal mechanisms as to how these vaccines cause ASD: insertional mutagenesis and autoimmunity.

Petitioners' theory of causation is discussed in two parts. Dr. Deisher's change point research and the criticisms brought against it are discussed first, followed by a discussion of petitioners' two causal mechanisms: insertional mutagenesis and autoimmunity.

a. Dr. Deisher's Change Point Study[47]

The goal of Dr. Deisher's change point study was to "investigate a previously overlooked, universally introduced environmental factor, fetal and retroviral contaminants in childhood vaccines, absent prior to change points in autistic disorder prevalence…and known pathologic mechanisms of action." Pet. Ex. 265 at 1. Data was obtained from the United States, Australia, United Kingdom, and Denmark. Vaccines included MMR II, varicella and hepatitis A, given to children ages 19 to 35 months of age at the time of vaccination. Dr. Deisher identified birth year change points 1980.9, 1988.4 and 1996 for the United States ("U.S.") data. In the United Kingdom, one change point, 1987, was identified. Change points of 1990.4, for Australia, and 1987.5 for Denmark were also identified. Dr. Deisher asserts that these change points "corresponded to introduction of or increased doses of human fetal cell line-manufactured vaccines." Pet. Ex. 265 at 1. She opined that the change points were not due to other factors such as paternal age or to changes in diagnostic criteria due to revisions of the DSM. She concluded that "rising autistic disorder prevalence is directly related to vaccines manufactured utilizing human fetal cells."[48] Id.

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[46] Dr. Deisher referred to the second change point as occurring between "approximately 1988 to 1989." Tr. 67. Dr. Deisher's valuation of the third change point is not entirely clear. She occasionally referred to this change point as occurring in 1995, but later, she testified that it occurred in 1996. Compare Tr. 67 with Tr. 817.

[47] Dr. Deisher's change point study, "Impact of environmental factors on the prevalence of autistic disorder after 1979," was published in the Journal of Public Health and Epidemiology in 2014. Theresa A. Deisher et al., Impact of Environmental Factors on the Prevalence of Autistic Disorders After 1979, 6 J. PUBLIC HEALTH & EPIDEMIOLOGY 9, 271 (. 2014) [Pet. Ex. 265]. Follow-up articles were published in Issues in Law & Medicine at Mr. McHugh's behest (Tr. 227) in November of 2015. See Theresa Deisher & Ngoc Doan, Sociological Environmental Causes are Insufficient to Explain Autism Change Points of Incidence, 30 ISSUES IN LAW & MEDICINE 1, 25 (2015) [Pet Ex. 419]; and Theresa A. Deisher et al., Epidemiologic and Molecular Relationship Between Vaccine Manufacture and Autism Spectrum Disorder, 30 ISSUES IN LAW & MEDICINE 47 (2015) [Pet Ex. 675].

[48] In an earlier draft of the study, Dr. Deisher is much more restrained and circumspect in stating the conclusions. She does not conclude that an increase in autism prevalence is related to

Prior to Dr. Deisher's study, in 2010, McDonald and Paul ("McDonald") co-authored a study in which they calculated a change point in 1988-1989 associated with the increased incidence of AD. Pet. Ex. 27 at 2112. The purpose of their study was to identify one or more change points so as to focus the time frame required for researching possible environmental exposures associated with autism. Id. Using data from California and Denmark, McDonald identified a change point, or increase in the cumulative incidence of AD, occurring in 1987.5. Id. Based on a worldwide data set, the change point was estimated to be 1988.7. Id. The McDonald study, and the use of change points relative to researching environmental factors that may contribute to autism, provided a model and frame of reference for Dr. Deisher's change point study. However, McDonald did not identify any environmental causes associated with their change point of 1988-1989. In fact, McDonald specifically stated that "studies on MMR vaccine…did not support a relationship with autism." Pet. Ex. 27 at 2. Further, McDonald did not identify the additional two change points noted by Dr. Deisher for 1980.0 and 1996 (US). Id. No other researcher or publication has referenced the two additional change points found in Deisher's study for 1980.9 and 1996. Tr. 236-37. Moreover, there is no evidence suggesting that any other researcher or publication has associated any autistic disorder change points as being associated with vaccines.

Like the change point in McDonald, Dr. Deisher's autism prevalence change points are reported based on birth year cohorts. Tr. 62. Data on autism prevalence are also typically reported by birth year, rather than the year symptoms become evident or the year of diagnosis, because children are diagnosed with autism at different stages of life. Id. Dr. Deisher "focused on autistic disorder…the more severe form of autism," because of its "relatively constant diagnostic criteria over the past [five] decades."[49] Id. at 48-49. Dr. Deisher used the print dates for DSM editions, and its revisions, to "indicate the rapidity with which changes in diagnostic criteria were disseminated to the professional community." Id. Autistic disorder data was obtained from a number of sources, including the California Department of Developmental Services and Individuals with Disabilities Educations Act program. Birth data were obtained from the CDC, the U.S. Census Bureau and similar agencies.[50] Linear regression and R statistical software were used for analysis. Id. at 75.

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vaccines. Instead she states, "our results…place emphasis on identifying environmental or other factors that are temporally associated with specific AD [birth year] change points of 1981, 1988, and 1996. Further research on other environmental factors is clearly warranted." Pet. Ex. 26 at 20.

[49] The terms "autism" and "autism spectrum disorder" are used interchangeably to refer to the entire group of disorders within the broad PDD category. The specific term "autistic disorder," ("AD") on the other hand, refers to the subcategory of PDD, consistent with Dr. Deisher's use described above.

[50] For a full discussion of methodology and data sources, see Pet. Ex. 265 at 2.

Vaccines manufactured from human cell lines referenced in Dr. Deisher's study included Meruvax (Rubella), the rubella component of MMR II,[51] and HAVRIX (hepatitis A). Meruvax and MMR II are manufactured using fetal cell line WI-38 and were approved for use in 1979. Pet. Ex. 265 at 9; Pet. Ex. 30. Varivax vaccine is manufactured using fetal cell line MRC-5, and was licensed for use in 1995. Pet. Ex. 265 at 9. Havrix is also manufactured using cell line MRC-5, and while it was initially approved for use in 1995, it was not made part of the immunization schedule for children at that time. Pet. Ex. 29 at 3. In 2005, it was included in the childhood immunization schedule for children 12 months and older. Id. Each of these vaccines contain residual DNA from the cell lines used for their production. Safety guidance published by the U.S. Department of Health and Human Services, the Food and Drug Administration, and Center for Biologics Evaluation and Research specified that residual DNA from "widely used human diploid cell strains, such as MRC-5 and WI-38 cells," did not present a safety concern. Pet. Ex. 90 at 42.

The graph below[52] represents a summary of Dr. Deisher's data on AD prevalence in the United States among children born between 1975 and 2002. Tr. 66. The x-axis represents birth years from 1970 to 2005; the y-axis represents the prevalence of ASD per 10,000 children. Pet. Ex. 76 at 14, fig. 1. The arrows show the change points and the vaccine(s) or vaccine event associated with each change point which Dr. Deisher opines are associated with an increase in AD prevalence.[53]

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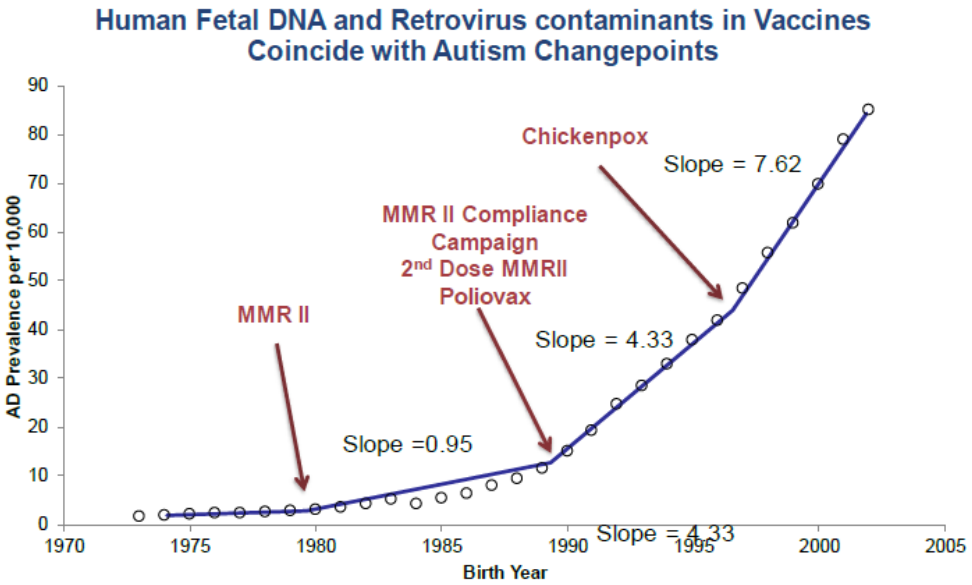
[51] The MMR vaccine was licensed for use in the United States in 1971, and MMR II vaccine was licensed for use in 1979. Dr. Halsey explained that MMR was renamed MMR II in 1979 because the rubella portion was changed from strain HPV 77, which was not manufactured using human cell lines, to RA27/3, which was manufactured using human cell lines. Resp. Ex. L at 4-5. Dr. Halsey further explained that after 1979, RA27/3 was the only strain of rubella manufactured in MMR vaccines in the United States. Id. Presumably only MMR II was available after 1981-1982. According to Dr. Deisher, however, the shelf life of the earlier HPV 77-containing MMR was two years, suggesting that uptake of the MMR II vaccine would not have been immediate. Tr. 60-61. This assertion factors into her analysis associating a 1980.9 change point to the introduction of the MMR II vaccine. The Proquad vaccine, which was first licensed for use in 2005, also contains the RA27/3 strain of the rubella vaccine. Resp. Ex L at 4; see also Food and Drug Administration, CBER Clinical Review of Studies Submitted in Support of Licensure of Proquad, available at https://www.fda.gov/downloads/BiologicsBloodVaccines/vaccines/.../ucm123800.pdf (2005) (last visited August 30, 2017).

[52] Reproduced from "Human Fetal DNA and Retrovirus Contaminants in Vaccines Coincide with Autism Change points." Pet. Ex. 76 at 14, fig. 1. These vaccines include MMR II, polio, varicella, and hepatitis A.

[53] "Chickenpox" in this graph refers to the varicella vaccine, Varivax.



The first change point is approximately 1980, which Dr. Deisher attributes to the 1979 approval of Meruvax and MMR II. See Pet. Ex. 265 at 6. The second change point occurs in "approximately 1988," which Dr. Deisher attributes to three events. First, a polio vaccination manufactured in human cell lines, Poliovax, was released in 1987. Second, the CDC and Advisory Committee on Immunization Practices ("ACIP") recommended a second dose, or "booster," of the MMR II vaccination for children. Id. at 7. The third event was an MMR II compliance campaign.[54] Pet. Ex. 265 at 7; Tr. 68, 824.

The third change point occurs in 1995, which Dr. Deisher associates with the introduction of the varicella vaccine, Varivax, which was licensed by the FDA and recommended for routine use in 1995. Pet. Ex. 265 at 7. Rather than leveling off, however, as would be expected over time, autism rates continued to increase after birth year 1998,[55] which Dr. Deisher attributes to

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[54] A measles outbreak led to an MMR II compliance campaign, which according to Dr. Deisher, "increased compliance" from ≤62.2 to 82percent between birth years 1987 and 1989. Tr. 68; Pet. Ex. 10 at 17. CDC data, however, show slightly different numbers. MMR vaccine coverage in the U.S. was 61.2percent in 1985 and increased to 82percent in 1991. Pet. Ex. 35 at 2. "No national coverage data [for the MMR vaccine] were collected from 1986 through 1990," so it is not possible to confirm Dr. Deisher's numbers. Id.

Vaccine coverage was not uniform and immunization levels of pre-school age children were often low. The "increased incidence of measles in preschoolers living in densely populated urban areas reflect[ed] low vaccination levels in these populations" (relevant to 1988 to 1989). Pet. Ex. 66 at 2. "[I]mmunization levels in some inner cities [were] as low as 49percent in children [two] years of age." Id.

[55] Dr. Deisher agrees that, from birth year 1998 forward, sociological factors could explain the continued increase in prevalence after the uptake of varicella leveled off. These sociological

the approval and introduction of the hepatitis A vaccine, Havrix. Havrix was approved in 1995, but was not included in the schedule of vaccines recommended for use until 1999 and later.[56] In 2005, it was recommended for children 12 months and older. Id.

i. Limitations and Criticism of Dr. Deisher's Change Point Analysis

There are a number of limitations to Dr. Deisher's study which call into question her conclusion that rising rates of AD are "directly related to vaccines manufactured utilizing human fetal cells." To be fair, Dr. Deisher acknowledges several shortcomings of her study. In an earlier draft of the study,[57] she acknowledges that "the main shortcoming of our analysis stems from the original autism prevalence or incidence data: the diagnosis of autism is behaviorally based and there are currently no biomarkers available to validate diagnosis." Pet. Ex. 26 at 19. She also recognizes that AD reporting systems may have contributed to "erroneous diagnoses." Pet. Ex. 265 at 12; see also Pet. Ex. 419 at 3. Respondent's experts also identified a number of weaknesses of the study, including the ecological study design, the reliance on faulty assumptions, and the study's overreaching conclusions. Resp. Ex. J at 1.

Dr. Deisher's change point study does not present reliable evidence of vaccine-caused AD. First, as best explained by Dr. Fallin, the study design, even if perfectly executed, does not allow for an inference of causation. Second, there are concerns about the accuracy of the underlying data. Third, Dr. Deisher assumes that vaccines containing residual human DNA fragments, rather than other sociologic or environmental factors, are causing an increase in AD. Fourth, the statistical software used in the study may have been a poor fit for the data analysis. These criticisms are more fully discussed below.

1. Ecological Study Design

Dr. Deisher's change point study uses an ecological study design. The goal of an ecological study[58] is to identify differences between groups that may explain the outcomes or

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factors include: (1) funding for special education approved in 1995; (2) awareness due to availability of the internet; and (3) an increase in scientific publications. Pet Ex. 61 at 12-13.

[56] Dr. Deisher states that in 1999, 17 states recommended the hepatitis A vaccine for children two years and older. In 2005, the ACIP recommended it for children 12 months and older. Compliance was not uniform, and public tracking data for the vaccine was not available until 2006. See Pet. Ex. 265 at 7.

[57] Marissa LaMadrid, et al., U.S. Autistic Disorder (1970-2002) Change Points Do Not Coincide with Change Points for Suspected Sociologic and Environmental Causes, unpublished manuscript on file with John Wiley & Sons (Mar. 16, 2011) [Pet. Ex. 26].

[58] An ecological study is a type of observational epidemiologic study which analyzes exposure and disease data at a population, rather than at an individual level. Federal Judicial Center, REF.

risk of illness or disease seen in the groups. Federal Judicial Center, REFERENCE MANUAL ON SCIENTIFIC EVIDENCE ("REF. MAN. SCI. EV.") at 561 (3d ed. 2011). That is, ecological studies examine disease trends in a population and try to infer relationships based on the co-occurrence of trends. Tr. 667. One cannot, however, assume that the relationships seen in a population group are true or accurate at the individual level. Id. at 671. What may appear to be a cause and effect relationship at the aggregate level may be misleading when examined in individuals. Id. The name for this phenomenon is "ecological fallacy." Id.

Consider Dr. Fallin's example of an ecological fallacy using the introduction of computers in the 1970s and 1980s. During this time frame, there was an increase in asthma. An ecological study could be designed to examine the frequency of computer use and the frequency of asthma. If data were gathered and plotted in a graph format, the study would likely show an association between computer use and an increase in asthma. Tr. 674. It would be erroneous, however, to assume that the use of computers caused an increase in the prevalence of asthma. This is because causation cannot by shown by an ecological study, even if the study is perfectly executed.[59] Id. at 672, 696.

Dr. Deisher's change point study used "specific discrete time points based on [ ] trends for autism," and "discrete time points based on [ ] trends in vaccine utilization," to see if the numbers, or time frames, were the same. Tr. 697. The ecological fallacy is Dr. Deisher's conclusion "that vaccines using fetal cell DNA are a cause of autism." Id. at 695. Like the example concluding that computer use causes asthma because computer use is seen in relationship to an increase in asthma, the assumption that there is a causal relationship between vaccines and autism is an ecological fallacy.

MAN. SCI. EV. at 556-57, 561 (3d ed. 2011). Ecological studies are designed to collect data from defined groups and compare it to other groups, with the objective of identifying and explaining their differences. Id. at 561. While ecologic studies are useful for identifying associations between exposure and disease, "they rarely provide definitive causal answers." Id.; see also Resp. Ex. L15.

[59] Unlike ecological studies, randomized control trial studies are considered the "experimental gold standard" for measuring causal associations. Researchers randomly assign participants to different groups in order to measure disease exposure. Tr. 666. Control groups that are not exposed to disease are compared with those who are exposed. Id. 665-66. Observational epidemiology is another study design which allows researchers to observe a cohort of individuals over a certain period of time. Id. at 666. Case control studies identify those with a particular disease and compare them to an appropriate control group. Id. Case control studies are often considered retrospective studies, because individuals are recruited and evaluated for potential risk factors and causes after they have been identified as having the disease. Id. Cross-sectional studies look at exposure to a disease and the outcome over a certain period of time, taking a "cross-section" of the information. Id. at 667.

2. Incidence and Prevalence Data

Another significant problem with Dr. Deisher's change point study derives from the inherent difficulty in accurately measuring the incidence[60] and prevalence[61] of AD data, birth data, population data, and the other data used in the study were collected from numerous sources.[62] It is "incredibly difficult" to calculate accurate and reliable data as to rates of AD for several reasons. Tr. 678. These reasons include changes in the diagnostic criteria, changes in disease reporting practices, changes in clinician and parental awareness of autism, and confounding factors[63] such as access to services and stigma, the decreasing age at diagnosis, and

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[60] Incidence is defined as the number of new cases of disease that occur during a specific period of time. Tr. 665. For example, in a total group of 100 people, 10 have disease A. Over the next year, four more develop disease A. The incidence for the year is 4 people. Id.

[61] Prevalence is defined as the total count of people with the disease in a given period. Id. In the example above, prevalence is measured by adding the 10 who already have the disease with the four who developed it, for a total of 14 out of 100 who have disease A. See Tr. 665. When measuring prevalence, it is important to know not only how many total disease cases there are (i.e. the "numerator" of a prevalence measure) but also the total number of people in the population who are eligible to get the disease (i.e. the "denominator" of a prevalence measure). Resp. Ex. J at 4.

[62] "For the U.S., autistic disorder data were obtained from the California Department of Developmental Services (DDS) (McDonald 2010; Cavagnaro 2003; Schechter and Grether (2008) and from the Individuals with Disabilities Education Act (IDEA) program website of the Department of Education (IDEA 2012). Live birth data were extracted from the CDC's 'Annual [R]eports of the Vital Statistics of the United States, (Centers of [sic] Disease Control and Prevention 2012a; Centers of [sic] Disease Control and Prevention 2012b) and birth year autistic disorder prevalence per 10,000 was then calculated. Male population data were obtained from the U.S. Census Bureau website (U.S. Census Bureau 2012a) for data prior to 2000 and the 'fact finder' website for data after 2000 (U.S. Census Bureau 2012b). Birth rates by age of father were obtained from the National Vital Statistics Reports: 'Birth Final Data' (Centers of [sic] Disease Control and Prevention 2012). Varicella and hepatitis A immunization coverage for children 19 to 35 months of age was obtained from the CDC National Immunization Survey ("NIS") (Centers of [sic] Disease Control and Prevention 2012)." Pet. Ex. 265 at 2.

[63] "Confounding occurs when another causal factor (the confounder) confuses the relationship between the agent of interest and the outcome of interest." REF. MAN. SCI. EV. at 591. For example, a study could find that individuals with gray hair have a higher rate of death than those with other hair colors. "Instead of hair color having an impact on death, the results might be explained by the confounding factor of old age …. Researchers must separate the relationship between gray hair and risk of death from that of [old] age and risk of death." Id. Thus, when a relationship is found between a disease and a potential agent, it is important to recognize and eliminate confounding factors. Id.

an increase in paternal age. All of these problems make it difficult to determine whether a true increase in AD has occurred, and if so, the amount of the increase. See id. at 679, 689. As stated by McDonald, "Distinguishing between whether the observed increases are real increases in the incidence of autism or simply an increase attributable to changes in reporting, clinical definitions, or the kinds of services offered continues to be a source of controversy. The impacts of these issues have been discussed extensively…but without definitive clarification of the overall reason for the increase." Pet. Ex. 27 at 4.

a. Changes in Diagnostic Criteria

Over time, the name or label, as well as the diagnostic criteria, for the underlying construct that we now call autism has changed. Tr. 678-79. In particular, the diagnostic criteria set forth in the DSM, which is used to diagnose autism by psychiatrists and psychologists, have changed with successive revisions. Id. at 681.

Since the original DSM was published in 1952, there have been six major revisions, the most recent in 2013. In her study, Dr. Deisher discusses five of the six revisions, including DSM-II (1968), DSM-III (1980), DSM-III-R (1987), DSM-IV (1994), and DSM-IV-TR (2000). Pet. Ex. 265 at 3, 6. Not addressed in Dr. Deisher's study, the DSM-5 (2013) made further substantive changes to the diagnostic criteria for ASDs. Charles B. Nemeroff, et al., DSM-5: A Collection of Psychiatrist Views on the Changes, Controversies, and Future Directions, 11 BMC MEDICINE 202 (2013) [Resp. Ex. J31]. Dr. Deisher's change point study encompasses the years 1975 to 2002, spanning the DSM-II to the DSM-IV-TR.

DSM-II included autistic behaviors under the diagnostic category of "schizophrenia, childhood type," which was manifested by "autistic, atypical, and withdrawn behavior; failure to develop identity separate from the mother's; and general unevenness, gross immaturity and inadequacy in development." Onset was identified as "before puberty." AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS ("DSM-II") 35 (2d ed. 1968). Significantly, in its third edition (1980), the DSM differentiated autism from schizophrenia and included a category for "infantile autism." Diagnostic criteria for infantile autism required the following: onset before 30 months of age; pervasive lack of responsiveness to other people; gross deficits in language development; peculiar speech patterns (if speech is present); "bizarre" responses to various aspects of the environment; and absence of delusions, hallucinations, loosening of associations, and incoherence as in schizophrenia. AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS ("DSM-III") 89-90 (3d ed. 1980).

Under DSM-III-R (1987), the diagnostic criteria for autism – now listed as "autistic disorder" rather than "infantile autism" – were expanded significantly. Individuals were assessed using 16 criteria divided into three lettered categories. These categories related to: (a) "qualitative impairment in reciprocal social interaction," (b) "qualitative impairment in verbal and nonverbal communication, and in imaginative activity," and (c) a "markedly restricted repertoire of activities and interests." To be considered autistic, a person would demonstrate eight of the listed criteria, with at least two impairments in reciprocal social interaction and communication and imaginative play (i.e., categories (a) and (b)) and at least one relating to a

restricted repertoire of activities and interests (category c). DSM-III-R at 38-39. Specific criteria demonstrating impairment in reciprocal social interaction included marked lack of awareness of the existence or feelings of others; no or abnormal seeking of comfort at time of distress; no or impaired imitation; no or abnormal social play; and gross impairment in the ability to make peer friendships. Specific criteria demonstrating impairment in communication and imaginative play included having no mode of communication, such as babbling, facial expression, gesture, mime, or spoken language; markedly abnormal nonverbal communication; absence of imaginative activity; marked abnormalities in the form or content of speech; and marked impairment in the ability to initiate or sustain conversation with others. Specific criteria demonstrating a restricted repertoire of activities and interests included stereotyped body movements; persistent preoccupation with part of objects; marked distress over changes in trivial aspects of the environment; unreasonable insistence on following routines in precise detail; and a markedly restricted range of interests and a preoccupation with one narrow interest. An additional diagnostic category (d) called for onset prior to 36 months. AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS ("DSM-III-R") 38-39 (3d ed. 1987).

Under DSM-IV (1994), the three categories for autistic disorder were adjusted to the following numbered categories: (1) "qualitative impairment in social interaction;" (2) "qualitative impairments in communication;" and (3) "restricted repetitive and stereotyped patterns of behavior, interests, and activities." Specific criteria demonstrating impairment in social interaction included marked impairment of the use of multiple nonverbal behaviors; failure to develop peer relationships appropriate to developmental level; a lack of spontaneous seeking to share enjoyment, interest, or achievements with others; and lack of social or emotional reciprocity. Specific criteria demonstrating impairments in communication included delay in, or total lack of, the development of spoken language; in individuals with adequate speech, marked impairment in the ability to initiate or sustain conversation with others; stereotyped and repetitive use of language or idiosyncratic language; and lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level. Specific criteria demonstrating restricted repetitive or stereotyped patterns of behavior included an encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus; apparently inflexible adherence to specific nonfunctional routines or rituals; stereotyped and repetitive motor mannerisms; and persistent preoccupation with parts of objects. To be considered autistic, an individual would demonstrate a total of six or more of these criteria, with at least two relating to impaired social interaction (category 1) and at least one each relating to impaired communication and restricted repetitive behavior (categories 2 and 3) respectively. In addition to demonstrating these traits, additional criteria required delays or abnormal functioning prior to age 3 in at least one of the following categories: social interaction, language as used in social communication; or symbolic or imaginative play. Additionally, the DSM-IV distinguished autistic disorder from Rett syndrome and Childhood Disintegrative Disorder, requiring that "the disturbance is not better accounted for" by either of those conditions. AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS ("DSM-IV") 75 (4th ed. 1994). There were no changes to the above diagnostic criteria in DSM-IV-TR. AM. PSYCHIATRIC ASS'N, DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS ("DSM-IV-TR") 70-71 (4th ed. Text Revision 1994).

In an attempt to discern whether changes in DSM diagnostic criteria accounted for the increase in incidence and prevalence of AD, Dr. Deisher studied the dissemination of DSM revisions after publication by analyzing the DSM's printing dates. See Pet. Ex. 419 at 15, tbl. 4. By looking at these dates, Dr. Deisher attempted to gauge how quickly diagnosing professionals were using the DSM changes. Tr. 49. She then used these dates to predict expected birth year change points. Pet. Ex. 419 at 13. When her calculated change points for the DSM revisions did not correspond to her autistic disorder prevalence change points, Dr. Deisher concluded that the changes in the diagnostic criteria set forth in the DSM did not account for the increase in incidence and prevalence of AD. Tr. 50; see also Pet. Ex. 419 at 12-13. However, AD is a subjective diagnosis, and Dr. Deisher assumed that the newest diagnostic criteria are uniformly used by all diagnosing clinicians. Dr. Fallin explained that it is not possible to identify discrete dates corresponding to DSM revisions, because the uptake of the new criteria for AD across DSM revisions was not instantaneous or discrete. Tr. 712. Instead, the revised criteria are implemented by healthcare providers over time. Moreover, clinicians do not unanimously or uniformly follow the most recent DSM criteria when diagnosing AD. Id.

As explained by McDonald, changes in the diagnostic criteria, and a "broadening of the definition of autism to PDD occurred during data collection relevant to the Danish and California data used for the study. Pet. Ex. 27 at 4. Even using only the diagnosis of autistic disorder, which has had fairly "consistent diagnostic criteria since about 1978" does not resolve the problem. A review of the California date from the 1990s to 2006 "suggests that changing diagnostic criteria may account for about a 2.2 fold higher cumulative incidence of autism, relative to the [seven]-fold increase observed over 11 birth cohorts." Id.

In addition to the changes and revisions to diagnostic criteria, there is the issue of how practitioners apply the criteria. Although autistic disorder has had relatively consistent criteria, "this does not necessarily mean that the diagnostic criteria have been consistently applied in practice over this time." Pet. Ex. 27 at 4. Diagnostic practices are not only based on criteria from the DSM, but also on physician training, diagnostic tests, awareness, and the relationship between certain diagnoses and available services for particular diagnostic categories. Id. In her study, Dr. Deisher acknowledges that "[the] impact of DSM revisions on the diagnosis of autism depends on the significance of changes to diagnostic criteria and on the rapidity with which the DSM revisions are disseminated and applied." Pet. Ex. 265 at 3. However, Dr. Fallin believes that Dr. Deisher did not accurately consider all of these factors and that nuances in diagnostic "classification rubrics" and training used by different professions (e.g., developmental psychologists versus pediatric neurologists) may also account for changes in diagnoses over time. Tr. 681-82.

b. Reporting Practices

Not only have diagnostic criteria changed over time, but so too have reporting practices, which affect how researchers count children who have autism. Tr. 682. Some countries, like Denmark, have a registry system which uses diagnostic reporting codes. Initially, Denmark reported and captured autism diagnoses only on inpatients. When Denmark began including

outpatient data for children diagnosed with autism, the number of reported cases significantly increased. Id. at 683-84.

Dr. Fallin cited a paper by Hansen et al.,[64] in which the authors address how changes in Denmark's reporting practices affected prevalence estimates. Resp. Ex. J12; Tr. 703. Hansen concluded that up to 42 percent of the increase in AD prevalence in Denmark in 1995 was due to the inclusion of outpatient data. Resp. Ex. J12 at 56. When including changes in diagnostic criteria and changes in reporting practices, the increase was 60 percent. Id. Hansen uses "sophisticated statistical methods to try to estimate the actual proportion of increase in autism prevalence [in Denmark] that could be attributed to this change … in reporting by including the outpatient data." Tr. 703. Dr. Fallin cited Hansen's paper as an example of why trend data like that presented in Dr. Deisher's change point study must be used with hesitation. Id. at 703-04. One must question whether the data reflects an increase in the true prevalence of autism or changes in the reporting of diagnoses. Id.

c. Access to Services and Stigma

Lack of access to health and educational services may also affect autism prevalence data. Dr. Fallin explained that younger children, not yet in preschool or any other educational system, who have little or no access to healthcare, may not be reported. Tr. 686-87. Autism prevalence data are calculated in the United States through surveillance programs tied to children's health and educational records.[65] Clinicians examine school and health records to determine whether children meet the criteria for ASD. Id. at 682. If a child with autism has not yet been diagnosed due to a lack of access to care, prevalence numbers are not accurate. Additionally, in settings or communities where there is a negative stigma attached to an autism diagnosis, families may not seek out care. Id. at 688.

Dr. Deisher disagreed that lack of access to services impacts prevalence estimates.[66] She also disagreed that there was an increase in the diagnosis of autism due to an increase in federal

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[64] Stefan Hansen et al., Explaining the Increase in the Prevalence of Autism Spectrum Disorders: The Proportion Attributable to Changes in Reporting Practices, 169 JAMA PEDIATR. 56 (2015) [Resp. Ex. J12].

[65] Dr. Fallin explained that in the United States, access to services is connected to reporting practices because most of the data about ASD is collected from children enrolled in ASD services. Tr. 686.

[66] Dr. Deisher acknowledged a study that showed an increase in autism rates correlated to the approval of special services. Pet. Ex. 419 at 2. She addressed the issue of federal funds for special education in one of her papers and identified a change point of 1998.7 for federal funding, and thus rejected this as a factor influencing the increase in autism diagnoses. Pet. Ex. 419 at 9.

funding[67] for special education, because federal funding for autistic children did not become available until 1995, and her change points precede that date. Tr. 52; Pet. Ex. 419 at 8.

However, data may be "prone to diagnostic substitution" where certain diagnoses allow a child to receive administrative services. Pet. Ex. 27 at 4. For example, in "British Columbia [and] Canada, changes in the assignment of special education codes may account for at least one-third of the increase in autism prevalence from 1996 to 2004." Id. While data from Canada were not used by Dr. Deisher, the issue remains. Diagnosis may be driven based on access to services.

d. Physician and Parental Awareness of Autism

Another factor that impacts prevalence is knowledge and awareness of autism. Tr. 684. Family advocacy efforts and social media have been instrumental in increasing parental and clinician awareness. Tr. 685. Increased parental and clinical awareness of autism impacts the number of children who are diagnosed; as awareness of the disease increases, previously undiagnosed children may now be diagnosed. See Tr. 51, 684-85.

Dr. Deisher discounts the effect of parental awareness as it relates to the prevalence of autism. To measure parental awareness, she studied Yahoo chat group messages from 1990 to 2008, totaling the number of messages sent about autism and the number of messages sent about children's health generally for each year. Tr. 51; Pet. Ex. 419 at 4. She then compared the two numbers and calculated a change point that "follows all of the U.S. autism disorder change points." Tr. 51. Dr. Deisher claimed that the autism chat group data mirrored the prevalence change points for 1980, 1988, and 1995. However, she acknowledged that Yahoo messaging was not available until 1994 and that the numbers of messages prior to 1998 were very small compared to the total. Pet. Ex. 419 at 4. Thus, her data do not account for the 1980 and 1988 change points. Because the Internet was not available in 1980, the date of her first change point, it "cannot possibly have artificially elevated autistic disorder levels" at that time. Id. Dr. Deisher discounted other avenues for physician and parental awareness when she concluded that "rising autism levels were responsible for increased parental concern about autism." Tr. 51-52.

To address the issue of professional awareness of autism as a cause of increased prevalence, Dr. Deisher reviewed trends in the number of medical professionals qualified to diagnose autism. Pet. Ex. 419 at 3. Using data published by the U.S. Census Bureau, Dr. Deisher calculated the number of psychiatrists, neurologists, pediatricians, and clinical psychologists with office practices in the United States. Id. at 4. "The annual numbers of all professionals qualified to diagnose autism were then added and normalized to the annual U.S. population." Id. (see also id. at 5, tbl. 1). Dr. Deisher reported that the number of physicians qualified to diagnose autism slightly decreased after the 1995 prevalence change point, and thus

[67] Dr. Deisher referenced the Individuals with Disabilities Education Act ("IDEA") as federal law that provides educational funding for children with autism. She stated that the Act began providing funding for autistic disorder in 1992. Pet. Ex. 419 at 8.

she concluded that an increase in physician awareness was not responsible for the increase in disease prevalence.[68] Tr. 51-52.

Dr. Fallin disagreed with Dr. Deisher's conclusions and explained that increased awareness of AD could very well have impacted prevalence numbers. Tr. 684-85. Over the last several decades, awareness of AD has spread through various mediums. Id. at 684. Increased awareness of the disease has caused stigma to decrease, and thus parents are more likely to seek a diagnosis for their child. Id. at 688. If parents know that good services are available for their autistic children, there is an incentive to go to the doctor and get their child diagnosed so that the child can receive treatment.[69] Id.

The findings in McDonald and other studies agree with Dr. Fallin that "wider awareness of autism, greater motivation of parents to seek services, and increased funding for services [] may contribute to increasing cumulative AD incidence, but these factors [can] not be documented or quantified." Pet. Ex. 27 at 4-5. With regard to data from North East London, researcher Lingam noted that the prevalence of autism increased from 1979 and then plateaued at 1992. This suggests that the earlier increase was not a true increase in prevalence but was probably due to "factors such as increased recognition, [and] a greater willingness on the part of educationalists and families to accept the diagnostic label, and better recording systems." Pet. Ex. 287 at1.

e. Paternal Age

Change or increase in the underlying risk factors for autism may also affect incidence. Evidence has established that paternal age is a risk factor for autism, and that children born to older fathers are more likely to be diagnosed with the disorder. Tr. 716-17. A Swedish study by Idring et al.[70] used registry-based information to follow children based on birth year and identify those who developed autism. Id. The results demonstrated that children born to older fathers had an increased risk of developing ASD. Resp.'s Ex. J17 at 1.

Dr. Deisher agrees that paternal age "provides an underlying risk," but she does not believe it accounts for a rise in autism prevalence. Tr. 166. Her research, based on absolute

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[68] Specifically, Dr. Deisher calculated a change point of 1997.4 for the number of autism-diagnosing professionals. Pet. Ex. 419 at 12, tbl. 2. Dr. Deisher also studied "the number of scientific publications referring to autism," and calculated a change point of 1997.5, and thus, concluded that "sociological factors such as awareness of autism disorder among parents and professionals," were not responsible for the increase in autism diagnoses. See Pet. Ex. 419 at 8.

[69] For example, the "increasing prevalence and incidence rates (in Denmark) during the 1990s may well be explained by changes in the registration procedures and more awareness of the disorders." Resp. Ex. J24 at 1339.

[70]Selma Idring et al., Parental Age and the Risk of Autism Spectrum Disorders: Findings from a Swedish Population-Based Cohort, 43 INTERNATIONAL JOURNAL OF EPIDEMIOLOGY 107 (2014) [Resp. Ex. J17].

numbers, shows that older fathers have just as many children today as they did back in 1960, when the prevalence of autism was lower. See Pet. Ex. 278 at 8, panel A. Although currently men may become fathers at a later age, statistics from the U.S. Census Bureau show that "older fathers had just as many absolute numbers of children back in the 1960s" as they do now. Tr. 166. Dr. Deisher thus reasoned that "if older age was the trigger for autistic disorder, we would have seen equivalent numbers of children with autistic disorder who were born to older fathers back in the 1960s." Id.

Dr. Fallin disputes Dr. Deisher's conclusion that paternal age has no impact on the increase in autism prevalence. Tr. 713. She further opined that whether paternal age is a contributor to the rise in autism prevalence is not a question that can be answered by the data provided in Dr. Deisher's change point study. Id. at 714. Dr. Fallin explained that Dr. Deisher's conclusions are not reliable because she relies on the absolute number of live births when she should be looking at proportions of children born to older fathers. Id. at 715. If, for example, 200 total children were born in 1960, but only 10 were born to older dads, then the proportion of children born to older fathers would be five percent. Id. In 2016, if 100 total children are born and 10 are born to older dads, then the same absolute number (10) now gives way to a different proportion (10 percent). Id. Because the absolute number of live births is different today than in 1960, Dr. Fallin opines that Dr. Deisher's analysis is misleading. Id. at 716.

f. Decreasing Age at Diagnosis

The average age at diagnosis continues to decrease with the ongoing goal of early intervention. Tr. 686. This change affects prevalence data. For example, if you have 10 autistic children, only three may be diagnosed at age three. By age seven, however, all 10 children will have the autism diagnosis. Thus, reporting at age three versus age ten results in a different prevalence measure.[71] Id.

The findings of McDonald and others agree with Dr. Fallin and have reported that "changes in diagnostic criteria and earlier age at diagnosis do contribute to some of the observed

[71] In "Sociological Environmental Causes are Insufficient to Explain Autism Change Points of Incidence," Dr. Deisher did acknowledge a study which showed that as much as 12 percent of the increase in the California autism rate could be due to an earlier age at the time of diagnosis. Pet. Ex. 419 at 2 (referencing Irva Hertz-Picciotto & Lora Delwiche, The Rise in Autism and the Role of Age at Diagnosis, 20 EPIDEMIOLOGY 84 (2009)). Ultimately, however, she disclaimed any direct assessment of this factor, stating that "[b]ecause of the known difficulties with autism ascertainment, no attempt is made in this work to quantify these sociologic factors relative to autism trends." Id. at 3. Instead, Dr. Deisher indicated that "[s]ociologic factors are represented by quantitative data such as the number of Yahoo groups discussing autism, the number of scientific publications referring to autism, and the number of professionals qualified to diagnose autism." Id.

increase in cumulative AD incidence in the California database for 1990-2006."[72] Pet. Ex. 27 at 2114.

Although research shows that more children have been diagnosed with autism in the last thirty years, all of the above factors make it difficult to determine whether there has been a true increase in prevalence, and if so, how to quantify that increase. Tr. 689. If Dr. Deisher's prevalence numbers are not accurate, then her change points are also inaccurate.

g. Vaccine Uptake and Change Points

Even assuming that her autism prevalence data are accurate, Dr. Deisher's assumptions regarding the availability and uptake of vaccines are equally problematic since vaccinations are not widely administered as soon as they become licensed by the FDA.[73] After a vaccine is approved by the FDA, the ACIP must decide whether to recommend its use. The recommendation is then reviewed by the CDC, after which the vaccine may be added to the official childhood immunization schedule.[74] This process can cause a delay in the widespread use of the vaccine.[75] For example, Dr. Deisher assumed that the 1988 change point was attributable, in part, to the CDC's recommendation that children between the ages of four and six receive a second dose of MMR. Tr. 458-59. Dr. Halsey testified that this recommendation was delayed, however, because the American Academy of Pediatrics ("AAP") disagreed with the CDC and instead recommended a second dose of MMR for adolescents between 11 and 16 years old. Id. at 459. Dr. Halsey testified that the AAP's advice was more widely followed and that the "vast majority" of children received the second dose of MMR at adolescence, years after they would have received an autism diagnosis. Id.

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[72] With regard to the California data (1990-2006), the "changing age at diagnosis," accounted for a 12 percent increase in autism incidence, while "inclusion of milder cases," accounted for a 56 percent increase." Resp. Ex. J14 at 84.

[73] For the purposes of this decision, FDA licensure and approval are synonymous terms. For further information regarding the licensing of vaccines by the FDA, see Vaccine Product Approval Process, U.S. FOOD & DRUG ADMINISTRATION, available at https://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/ucm133096.htm (last updated Aug. 24, 2015).

[74] The Journey of Your Child's Vaccine, CENTERS FOR DISEASE CONTROL AND PREVENTION, available at https://www.cdc.gov/vaccines/parents/infographics/journey-of-child-vaccine-text.html (last updated Dec. 28, 2015).

[75] Even though a vaccine is added to the immunization schedule, it may take years to achieve compliance. For 1967 and 1985, coverage for the MMR vaccine was only 60 percent and 61.2 percent respectively. Pet. Ex. 35 at 2. Children ages two to four years old are "a weak link" in vaccine coverage because of the difficulty in targeting children before they are school-age. See Pet. Ex. 26 at 6. Preschoolers living in densely populated urban areas may have low vaccination levels. Pet. Ex. 66 at 2.

As for Dr. Deisher's third autism change point in 1995, Dr. Halsey testified that it bears no relevance to the use of the hepatitis A vaccine.[76] Dr. Deisher incorrectly assumed that the hepatitis A vaccination "could have affected autistic disorder rates for children born in 1997 or later…." Pet. Ex. 265 at 7. Dr. Halsey explained that although the hepatitis A vaccine was first approved in 1996, it was not widely administered until 2006, when the CDC approved it for use at age 12 months and older. Tr. 463-64; Resp.'s Ex L at 5. Thus, Dr. Deisher's 1995 prevalence change point could not be associated with the hepatitis A vaccine because the vaccine was not widely used at that time.[77] Tr. 464.

Similarly, there was a delay in the uptake of the varicella vaccine due to different recommendations by the AAP and the ACIP at the CDC, which also makes it irrelevant to Dr. Deisher's change point study. Tr. 460. Although the AAP recommended administration of the vaccine in 1995, the ACIP did not recommend it for children until 1996, and uptake of the vaccine was slow. Id.; Resp.'s Ex L at 5 (illustrating the slow uptake of the varicella vaccine by year and showing a gradual increase).[78] Dr. Halsey testified that one "would [not] see a change point in the diagnosis of autism in the same year that [the ACIP] make[s] the recommendation …. [I]f there were to be a causative association, which there isn't, there would be a delay." Tr. 460. Because the uptake of the varicella vaccination was slow and AAP and ACIP recommendations were different, a change point associated with the varicella vaccine in 1995 is impossible. Id. at 461.

3. Use of R Software

In addition to challenging the change point study's design and the assumptions upon which it is based, respondent's experts also criticized Dr. Deisher's use of the R software to calculate

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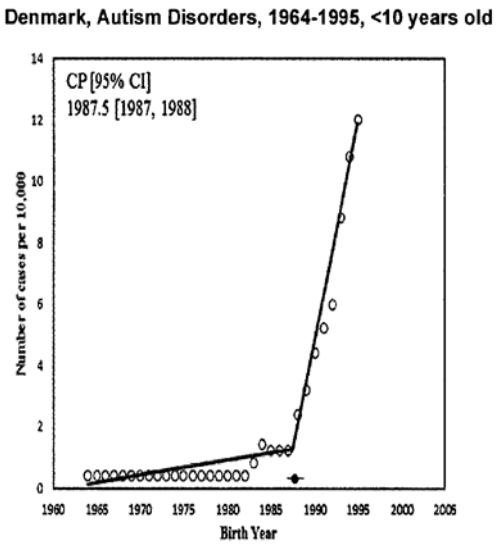
[76] Dr. Deisher responds to Dr. Halsey's criticism by stating that Dr. Halsey did not accurately read her study because her change point occurred in 1996, and not 1995. See Tr. 817. However, while describing her change point study during the hearing on March 7, 2016, Dr. Deisher testified that "the third change point is approximately 1995." Id. at 67. Even if the relevant change point is 1996, this does not matter since hepatitis A vaccine was not widely used until 2006.

[77] Significantly, although Dr. Deisher postulated that "[b]ased on approval dates and recommendation dates, hepatitis A could have affected autistic disorder rates for children born in 1997 or later," she acknowledged that "there is no[] public data tracking vaccination rates prior to 2006." Pet. Ex. 265 at 277.

[78] Dr. Halsey cited 2003, 2009, and 2015 data published by the CDC which estimated the coverage rate of the varicella vaccine. Resp. Ex. L at 5. "[I]n 1995, when the recommendation was made, there were no data on coverage, because … no children were really immunized. It took the manufacturer a while to get the vaccine out there." Tr. 461.

her change points.[79] Both Dr. Arking and Dr. Fallin opined that Dr. Deisher's graphs do not accurately portray the data, calling into question the accuracy of the change points. Moreover, Dr. Deisher's statistical analyses and graphs drawn using the R software are incorrect because the prevalence numbers upon which they are based are flawed, as described above.

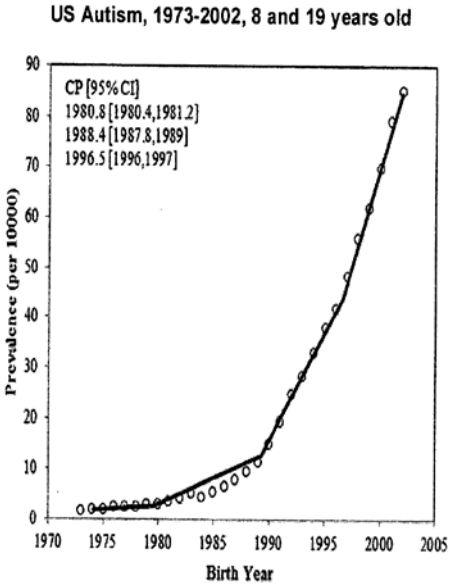
The R program used by Dr. Deisher is a statistical software package that is used to draw graphs and visualize data. If used incorrectly, it can yield incorrect results. Tr. 596, 98. Dr. Arking opined that the segmented line fitting package in the R software program used by Dr. Deisher did not yield accurate change point results because it was not appropriate for the type of data she analyzed. Tr. 598. The lines in Dr. Deisher's graphs are drawn over data points that are all zero, causing Dr. Arking to question whether the data points were correctly calculated. Tr. 596-97.[80] For example, in the figure entitled "Denmark, Autism Disorders, 1964-1995," pictured below, data points from 1965 through 1980 are all zero value. Pet. Ex. 265 at 5. Dr. Arking explained that "[t]his is not how you analyze data that has lots of zeros," and based on these concerns, Dr. Arking concluded that the graph is an incorrect application of the R program software. Tr. at 598.

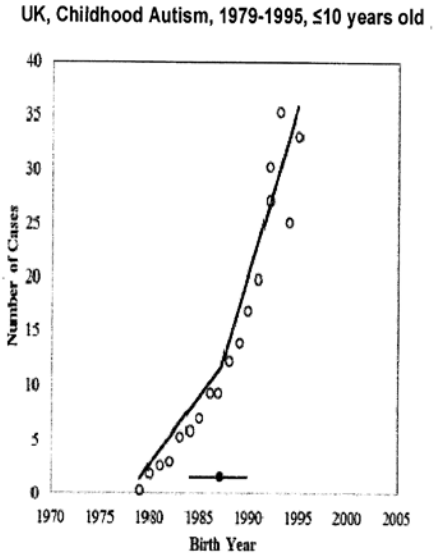


[79] During the hearing on March 8, 2016, Ms. Ngoc Doan testified about her work on the change point study. Ms. Doan is employed by Sound Choice Pharmaceutical Institute as a research associate and was involved in the data collection process for Dr. Deisher's research. Tr. 334-35. Her duties involved copying ASD prevalence data from government websites, published papers, and other publicly available sources and analyzing it with the R software. Id. at 335-36. She testified that she did not modify the data during the collection process and that Dr. Deisher validated the results in the R program. Id. at 337.

[80] Dr. Arking specifically criticized the bottom two graphs found at Pet. Ex. 265 at 4. Tr. 596.

Dr. Arking also questioned the calculated slope for the lines in many of Dr. Deisher's graphs because they contain lines that are above, rather than through, the middle of the data points. Tr. 596. For example, in the figure entitled "US Autism, 1973-2002, 8 and 19 Years Old," pictured below, almost all of the data points between 1980 and 1990 are below the line of best fit. Tr. 597; Pet. Ex. 265 at 4. Similarly, the majority of the data points in the figure entitled "UK, Childhood Autism, 1979-1995, < 10 Years Old," are also below Dr. Deisher's line of best fit. Tr. 597. Dr. Arking opined that lines like those shown below are "a very poor fit," and that the resulting change points are not reliable. Id. at 598 (referencing Pet. Ex. 265 at 5). There are better and more specific methods, including zero-inflated statistical models, which should be used to more accurately analyze this kind of data. Id.





Dr. Fallin agreed with Dr. Arking that several of Dr. Deisher's graphs did not appear to reflect a correct use of the R software program, specifically with respect to the appropriate use of a linear model. Tr. 705. For example, with regard to the figure above entitled "US Autism, 1973-2002, 8 and 19 Years Old," Dr. Fallin testified that an "exponential or curved model" would have been a better fit for the data because these data "do not overlap well with the line drawn on top of them," meaning that the change points in the graph are likely inaccurate. Id. at 707-08 (referencing Pet. Ex. 265 at 4).

ii. Other Epidemiological Studies

In contrast to Dr. Deisher's ecological study, a number of well-designed observational studies[81] have tested and rejected Dr. Deisher's hypothesis that the MMR vaccination is causally

[81] An observational study is an analytic epidemiologic study in which the investigator "observes and assesses the strength of the relationship between an exposure and disease variable. Three types of observational studies include cohort studies, case-control studies, and cross-sectional studies." Jae Song & Kevin Chung, Observational Studies: Cohort and Case Control Studies,

associated with ASD. One of these studies, Jain et al.,[82] is especially relevant to petitioners' theory, as Jain studied patients born in the United States between January 1, 2001, and December 31, 2007, and the children in the study received the MMR II vaccination at issue in this case. Resp. Ex J18 at 1534; Resp. Ex. L at 4.

Jain performed a retrospective cohort study on 95,727 children in the Optum Research Database, a database of privately insured individuals and Medicare patients across the United States. Resp. Ex. J18 at 1534. The purpose of the study was to determine whether siblings of children with ASD were at increased risk of developing autism due to the MMR vaccination. Research identified these children to be at increased risk for ASD due to the fact that they had a known sibling with ASD. Tr. 756-57. Siblings of children who have autism have a risk of one in five of developing autism, as compared with one in 68. Id. Despite being at an increased risk for autism, the authors concluded that "[r]eceipt of the MMR vaccine was not associated with the risk of ASD, regardless of whether older siblings had ASD." Id.

A large retrospective study of all children born in Denmark from 1991 through 1998 was done by Madsen, et al.[83] using Danish Registry data. In Denmark, children are assigned a civil registry number at birth, and their data are then input into the Danish Civil Registration System. Madsen obtained the children's vaccination information from the National Board of Health and collected autism diagnosis information from another central registry. Resp. Ex. J26 at 1477. A total of 537,303 children were studied. Id. Of these, 440,655 received the MMR vaccine, and the remaining 96,648 did not. Id. The risk of autism was no different between the vaccinated and unvaccinated groups. The authors found "no association between [ ] age at the time of the vaccination, the time since vaccination, or the date of vaccination and the development of autistic disorder." Id.[84]

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126 PLAST. RECONSTR. SURG. 2234 (2010).

[82] Anjali Jain et al., Autism Occurrence by MMR Vaccine Status Among U.S. Children With Older Siblings With and Without Autism, 313 JAMA 1534 (2015) [Resp. Ex. J18].

[83] Kreesten Madsen et al., A Population-Based Study of Measles, Mumps, and Rubella Vaccination and Autism, 347 N. ENG. J. MED. 1477 (2002) [Resp. Ex. J26].

[84] Dr. Deisher criticized the Madsen paper because the authors did not publish their raw data and because the immunization rate reported in the paper (82 percent) was lower than the rate which Dr. Deisher independently obtained from the Danish Board of Health's website (85.88 percent). Tr. 154-56; 220. Dr. Fallin persuasively addressed both criticisms. First, she explained that Denmark is very strict about sharing data of its private citizens contained within its registries and does not allow the data to leave its system. Id. 750-51. In order to access the data for research, one must be willing to travel to Denmark. Id. at 751. As for Dr. Deisher's criticism of the discrepancy between the percentage of children vaccinated with MMR described in the study as compared with the numbers provided on the government website, Dr. Fallin explained that the difference was likely due to inclusion and exclusion criteria used in the study. The government website numbers may be slightly higher, as it would not exclude those children

Other persuasive epidemiologic research has studied and rejected the MMR vaccine-autism causal association. In Taylor et al.,[85] researchers studied whether the incidence of autism was associated with the introduction of the MMR vaccine in the United Kingdom in 1988. Children diagnosed with autism who were born from 1979 through 1998 were identified and trends examined. Resp. Ex. J44 at 2026. As Special Master Hastings noted in Cedillo:

> The [Taylor] study took advantage of the fact that the MMR vaccine was first introduced in Britain in 1988, so that one could compare children born in earlier years who did not receive MMR vaccine with later-born children who did receive that vaccine. The study found that while there was a steady increase in autistic diagnoses throughout the study period, which was consistent with the world-wide pattern, the introduction of the MMR vaccine did not result in any significant "step-up" in that steady trend; one would have expected a clear "step-up" if the MMR vaccine were in fact contributing to autism in any significant way. 2009 WL 331968, at *85.

The study did not support a causal association between the MMR vaccine and autism. Id.

An impressive study was undertaken by The Cochrane Collaboration, a recognized world leader in performing systematic reviews of epidemiology and medical science studies, with the goal of providing a "summary conclusion" based on knowledge about MMR vaccine across different studies. Tr. 753. The authors, Demicheli et al.,[86] reviewed 139 articles related to adverse events observed following MMR vaccination and identified 31 that met their strict criteria for review. Resp. Ex. J8 at 2. Based upon a review of the 31 articles, the authors concluded that MMR vaccination[87] was not likely to be associated with autism. Id.; see also Tr. 753-55.

Specifically, Dr. Deisher opines that fetal DNA in vaccines is the environmental trigger responsible for the "regressive" form of autism. Tr. 246. "There is no standard definition of what is meant by regression. When [it] is reported, parents recall the loss of a few words or

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that would have been excluded from the study due to death, or moving out of the country. Id. at 751-52. For a more detailed explanation, see Dr. Fallin's complete discussion on this point at Tr. 751-52.

[85] Brent Taylor et al., Autism and Measles, Mumps, and Rubella Vaccine: No Epidemiological Evidence for a Causal Association, 353 LANCET 2026 (1999) [Resp. Ex. J44].

[86] Vittorio Demicheli et al., Vaccines for Measles, Mumps and Rubella in Children, Cochrane Database of Systematic Reviews, Wiley & Sons Publishing, Ltd. (2005) [Resp. Ex. J8].

[87] The 31 studies in Demicheli's review included studies published as early as 1975 up until 2004. Presumably, because MMR II was not introduced in the United States until 1979, some of these early studies assessed by Dimicheli et al. were based on the MMR vaccine, not MMR II. See Resp. Ex. J8 at 5.

phrases acutely or over a period of time. Sometimes, the loss of language is accompanied by decreased social play or increased irritability." Resp. Ex. L6 at 4; see also Cedillo, 2009 WL 331968, at *89. "Evidence from multiple centers indicates that regression does occur in approximately one third of children with autism." Resp. Ex. L6 at 5. Although she believes her causal mechanism applies to the regressive form of autism, Dr. Deisher's change point study does not apply only to regressive autism.

Of note, in Cedillo, 2009 WL 331968, petitioners argued that epidemiologic studies were irrelevant because they did not distinguish between regressive and nonregressive autism. Id. at *89. Special Master Hastings found as follows:

> It is true that most of the epidemiologic studies discussed [in Cedillo] generally did not make any distinction between regressive and nonregressive autism. Thus, it is arguable that those epidemiologic studies, while providing very strong evidence that the MMR vaccination has not played any significant role in the overall causation of autism, do not necessarily completely rule out the possibility that the MMR vaccine might play some role in causing the subset of autism known as regressive autism.
>
> But petitioners are wrong in contending that the epidemiologic studies are completely irrelevant. First, while those studies cannot completely rule out any possibility that the MMR vaccination might play some causative role in a subset of the overall autism cases, it seems … that the failure of so many studies to find any association between MMR vaccine and autism at least casts some doubt on the proposition that the MMR vaccine ever plays a role in causing any type of autism, including regressive autism.

Id. at *89 (emphasis in original).

Moreover, several of the epidemiological studies cited in this case address the MMR vaccine and regressive and nonregressive autism. The researchers in Taylor questioned whether there was a potential causal association between MMR vaccination and age of autism onset. Resp. Ex. J44 at 2028. The study was performed on children with autism born in the United Kingdom since 1979. Id. at 2026. A total of 498 children with autism were identified, and Taylor found no evidence of association between MMR vaccination status and age of autism diagnosis. Id. at 2028. Taylor noted, "Our results do not support the hypothesis that MMR vaccination is causally related to autism, either its initiation or to the onset of regression…" Id. at 2029. And while the study did not "rule out the possibility of a rare idiosyncratic response to MMR …. [I]f such an association occurs, it is so rare that it could not be identified in this large regional sample." Id.

Fombonne also evaluated the relationship between the prevalence of PDD and MMR. Eric Fombonne et al., Pervasive Developmental Disorders in Montreal, Quebec, Canada: Prevalence and Links With Immunizations, 118 PEDIATRICS e139 (2006) [Resp. Ex. J9]. Fombonne surveyed 27,749 children born between 1987 and 1998 in Montreal, Canada and found no association between PDD and one or two doses of MMR. Id. at e139-40. Although

Fombonne's data did not distinguish regressive versus nonregressive autism, the researchers noted that "the regressive phenotype of autism has not increased over time," and stated that as a result, "our findings of a regular increase in PDD and autistic disorder prevalence while MMR vaccine uptake was decreasing during the study period are not consistent with any increase in the risk of PDD, regressive or not, that could be attributed to MMR." Id. at e148.

I thus adopt Special Master Hastings' reasoning in Cedillo, 2009 WL 331968, where he noted:

> In sum, it is true, as a statistical matter, that the epidemiologic studies detailed … above, while showing clearly that the MMR vaccination could not be causing any substantial portion of the cases of autism in general, do not completely rule out the possibility that the MMR vaccine might be associated with some small subset of autism, such as regressive autism. Nonetheless, the balance of evidence from those studies weighs against the petitioners' causation theory. First, it is indeed an exceedingly slight point in the petitioners' favor for them to claim that these many studies by different researchers in different countries have not completely ruled out the possibility of any merit to their causation claim. The larger point is that none of those many competent studies has yielded the slightest bit of evidence in the petitioners' favor – and, of course, it is the petitioners' burden to show that the MMR vaccine does likely cause autism, not the respondent's burden to show that there is absolutely no possibility of a causal link.
>
> Second, in [ ] view [of] the failure of so many studies to find any association between MMR vaccine and autism, while not completely ruling out a possible causal role with respect to a subset of autism, at least casts considerable doubt upon the proposition that the MMR vaccine ever plays a role in causing any kind of autism, including regressive autism. Id. at *89-90 (emphasis in original).

While no single study is definitive, when different scientifically reliable studies examining "the same exposure-disease relationship [ ] yield similar results," particularly when the studies are performed in "different populations by different investigators," the combined results are highly persuasive. REF. MAN. SCI. EV. at 604. The studies cited specifically looked for evidence that the MMR vaccine caused or contributed to the etiology of autism and failed to find any evidence. As persuasively explained by respondent's experts, there is an abundance of evidence showing no increased incidence of autism in children who have received vaccines as compared with controls who have not received vaccines. Tr. 432.

b. Petitioners' Theories Regarding the Mechanism of Causation

Petitioners offer two mechanisms by which vaccines containing residual DNA fragments can cause ASDs. The first is insertional mutagenesis, whereby residual DNA fragments from the vaccines integrate into and transform host cells in the brain. Tr. 82. The second is based on the theory of autoimmunity: a child develops antibodies to fetal DNA, which then causes the child's

body to attack the self.[88] Id. at 112-13. Dr. Deisher testified that it is not possible "to clinically distinguish between AD caused by DNA contamination [and] [AD] caused by something else," and that "[t]he clinical symptoms would be similar." Id. at 248.

i. Insertional Mutagenesis[89]

Insertional mutagenesis in a "mutation caused by insertion of new genetic material into a normal gene." Farlex, MEDICAL DICTIONARY FOR THE HEALTH PROFESSIONS AND NURSING (2012). The issue of insertional mutagenesis related to residual DNA in viral vaccines is not new. See generally, Pet. Ex. 350. Studies have shown, however, that integration of residual DNA is unlikely.[90] Id. at 16.

As posited by Dr. Deisher, insertional mutagenesisin the context of this case occurs when DNA is integrated into a host cell and causes a genetic mutation that is associated with an autism phenotype. Tr. 82; 100. Dr. Deisher explores four potential ways that insertional mutagenesis could occur. First, she posits that insertional mutagenesis could occur if fetal DNA fragments are integrated into hematopoietic stem cells.[91] Second, insertional mutagenesis could result from

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[88] In her initial expert report, Dr. Deisher stated that markers of oxidative stress have been found in the brains of children with ASD. See Pet. Ex. 10 at 4. Presumably, Dr. Deisher posits a causal theory related to oxidative stress. However, this theory was not further developed and so it is not entirely clear what Dr. Deisher meant by the statement. The theory of oxidative stress as it relates to autism has previously been adjudicated and rejected. See King, 2010 WL 892296, at *24. I find the reasoning of King persuasive on the theory of oxidative stress and adopt its reasoning and conclusions herein.

[89] Mutagenesis is "the induction of genetic mutation." DORLAND'S at 1213.

[90] "Ledwith and colleagues demonstrated in a rodent model that integration of a plasmid DNA vaccine occurred at a very low efficiency," confirming that DNA integration was unlikely to be a safety concern. Pet. Ex. 350 at 17 (internal citations omitted). The more germane safety concern was whether DNA integration could cause infection or "induce oncogenicity," so as to cause tumors, not autism. Additional studies were done which showed that even using a "plasmid containing a strong promoter failed to induce tumors" in mice. Id. As for MRC-5 and WI-38 cell lines, these are not tumor-derived cell lines, nor are they tumorigenic, that is, capable of forming tumors in animal studies. See Pet. Ex. 350 at 4-5, 17. The vaccines at issue here were made in "human diploid cell lines (MRC-5 and WI-38), established from cells isolated from healthy tissues." Id. at 4. Thus, the risks associated with vaccines made in tumor-derived or tumorigenic cell lines do not apply to the cell lines at issue here. As for the risk of infection, petitioners do not provide evidence that MRC-5 and WI-38 cell lines are associated with infection, or that infection caused by these cell lines is associated with autism. To the extent that the exhibits filed in this case relate to other types of cell lines or other types of vaccines, they are not relevant to petitioners' theories of causation.

[91] Hematopoietic stem cells are "blood cell progenitors that …. have the capacity for replication

particles of human endogenous retrovirus K fragments that become reactivated. Third, fetal DNA fragments could be transported to the brain by microvesicles, where insertional mutagenesis would then take place. Finally, Dr. Deisher postulates that fetal DNA fragments found in vaccines could be transported to the nervous system via retrograde transport. Dr. Deisher concedes that she does not "know the exact mechanism of action," but she opines that "all of these mechanisms are possible ..." Tr. 137. Once transported to the brain, the fetal DNA could potentially insert in "any cell within the brain … resulting in a mutation." Tr. 258.

1. Human Endogenous Retrovirus Strain K[92]

Retroviruses are a family of viruses whose genomes consist of single-stranded RNA.[93] Human endogenous retroviruses ("HERVs")[94] are "retrovirus like sequences found in the human genome, thought to constitute the remains of true retroviruses that were absorbed through evolution."[95] Retroviruses are "generally inactive," and are considered "to be innocuous." Pet.

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and differentiation and give rise to precursors of various blood cell lines…" DORLAND'S at 318.

[92] Dr. Deisher cites a number of articles about HERV-K and retroviruses, but they are not all discussed here, as they do not provide preponderant evidence to support her theory. In addition to her theory that HERV-K retrovirus fragments may play some role in the insertion of residual DNA from vaccines, Dr. Deisher seems to suggest that HERV-K fragments themselves, independent of the residual DNA central to her theory, may cause autism. This aspect of her theory is not very clear, but for purposes of this decision, I have assumed this idea to be an additional theory. For example, Dewannieux questions whether in vitro "recombinations among … HERV-K loci…can generate functional HERV-K elements," which may have the potential to produce infectious retroviruses. Marie Dewannieux, Identification of an Infectious Progenitor for the Multiple-Copy HERV-K Human Endogenous Retroelements, 16 GENOME RESEARCH 1548 (2015) [Pet. Ex. 104]. This seems unlikely because "as a general rule, these [HERV-K] elements tend to be silenced in the cells…" Id.; see also, Pet. Ex. 105. Additionally, Dewannieux questions whether "endogenous retroviruses could contaminate the vaccine virus and be injected together with the vaccine…[which] could result in [ ] infection…." Pet. Ex. 105 at 4. Assuming that this idea that HERV-K fragments may cause infection is one of the potential theories of causation posited by Dr. Deisher, I do not find this to be a viable theory, as petitioners have provided no evidence to suggest that infection caused by a HERV-K retrovirus can cause ASD.

[93] DORLAND'S at 1636.

[94] "Nearly eight percent of the human genome is composed of sequences of retroviral origin." Pet. Ex. 104 at 1548. The HERV-K family includes "endogenous retroviruses, most of which [] integrated into the genome [more than] five million years ago." Pet. Ex. 104 at 1548. These retroviruses are thought to be the "remnants of ancestral infections of primates." Id. Despite numerous studies on HERV-K viruses, researchers failed to produce a "functional provirus capable of producing infectious particles." Id.

Ex. 76 at 14. HERV strain K ("HERV-K") is a type of inactive retrovirus found in most humans. Pet. Ex. 76 at 14.

Dr. Deisher testified that fragments of HERV-K have been found in vaccines manufactured using human fetal cell lines. Tr. 271; Pet. Ex. 76 at 15 (referencing Pet. Ex. 98[96]); see also Pet. Ex. 43 at 10. She hypothesizes that these fragments may "carry" DNA from a vaccine into the host cell, triggering gene insertion or neuro-inflammation, causing ASD. Tr. 181, 271-272; Pet. Ex. 76 at 14, 15. Dr. Deisher hypothesizes that only a fragment of the retrovirus is needed to "carry" residual DNA from the vaccine into the host cell. Tr. 272. Reactivation[97] of the HERV-K retrovirus "may be relevant," but not necessary. Id.

More specifically, or perhaps in the alternative, Dr. Deisher opines that HERV-K fragments in vaccines "code[] for the integrase or the envelope protein," which "induces gene insertion or neuro-inflammation." Pet. Ex. 76 at 15 (internal citations omitted). She posits that HERV-K fragments act as an "integrase[],"[98] citing a study examining the biology of HERV-K published by Kitamura et al.[99] Pet. Ex. 76 at 15; Pet. Ex. 103 at 3302. However, the findings stated in Kitamura were quite limited. "Possibly, HERV[100] is one of the agents involved in

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[95] DORLAND'S at 1636.

[96] Joseph Victoria et al., Viral Nucleic Acids in Live-Attenuated Vaccines: Detection of Minority Variants and an Adventitious Virus, 84 J. VIROL. 6033-40 (2010) [Pet. Ex. 98]. The authors conclude that the vaccines at issue are safe and effective and raise no safety concerns associated with the finding of HERV-K in vaccines. Id. at 6039.

[97] During the latency phase of a viral life cycle, the virus does not replicate. "Reactivation is the process by which a latent virus switches to a lytic phase of replication. Reactivation may be provoked by a combination of external and/or internal cellular stimuli." C.M. Traylen et al., Virus Reactivation: A Panoramic View in Human Infections, 6 FUTURE VIROL. 451 (2011).

[98] An integrase is a retroviral enzyme that binds to the genetic material of a virus and inserts it into a host cell chromosome. Stephen Hare et al., Retroviral Intasome Assembly and Inhibition of DNA Strand Transfer, 464 NATURE 232 (2010).

[99] Yoshihoro Kitamura et al., Human Endogenous Retrovirus K10 Encodes a Functional Integrase, 70 J. VIROL. 3302 (1996) [Pet. Ex 103].

[100] In Kitamura, the authors appear to use the acronyms HERV and HERV-K interchangeably. The experiment reported in the article, however, dealt with HERVIN, a HERV-K10 integrase fusion protein. "To examine the biological activity of HERV-K, we have cloned an HERV-K10 DNA fragment encoding putative integrase and expressed it as a fusion protein in *E coli*. This report describes the expression and characterization of the HERV-K10 integrase ("HERVIN") fusion protein." Pet. Ex. 103 at 3302.

pathogenesis of seminomas[101] and immunological disorders…" Pet. Ex. 103 at 3306. The authors in Kitamura do not conclude that HERV-K fragments induce gene insertion. Instead, they state that "whether HERV can …trigger insertional mutagenesis and whether HERV can be activated to replicate in human cells remain[s] to be investigated." Id. The Kitamura study did not involve residual DNA fragments from vaccines, and the authors did not conclude that HERV-K could trigger insertional mutagenesis.

Evidence cited by Dr. Deisher in support of her theory that HERV-K fragments are involved in the etiology of autism included the report that HERV retroviruses (HERVs E, H, K, and W) have been found in the peripheral blood mononuclear leukocytes[102] of patients with autism. Pet. Ex. 76 at 15. Dr. Deisher cites an article by Balestrieri et al.[103] in support of this alleged evidence. However, this study does not support Dr. Deisher's claim. While the authors found that HERVs H and W were elevated in children with autism, HERV-K levels were approximately equal in both the group of children with ASD and the healthy control group. Pet. Ex. 110 at 1. Thus, Dr. Deisher's cite to Balestrieri is erroneous and misleading.

Respondent's expert, Dr. Halsey, provided context for the finding of HERV-K fragments in vaccines. He explained that retroviruses comprise approximately eight percent of the human genome. Tr. 481; see also Resp. Ex. L17.[104] Retroviruses have been integrated into the human genome, passed down from one generation to the next. Tr. 480. The HERV-K fragments found in the vaccines are already present in all of our genomes. Id. at 481. These fragments are not a new addition to the human genome, and therefore, their introduction into the body by a vaccine would not constitute a novel environmental factor. Dr. Halsey emphasized that Dr. Deisher provides no evidence to support her hypothesis that HERV-K plays a role in the etiology of autism, and she overstated and misinterpreted the literature. Resp. Ex. L at 3. Moreover, studies have examined the question of whether retroviruses play a role in various diseases, but to date, a causal relationship has never been established, and they may even play a beneficial role. Resp. Ex. L at 3; Resp. Ex. L17; see also Pet. Ex. 78.

Ultimately, Dr. Deisher conceded that current studies regarding HERV-K retroviruses are "observational" in nature and that the role of these retroviruses in causing disease "is not known." Tr. 182. In summary, petitioners provide no evidence to show that HERV-K

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[101] Seminomas are malignant tumors of the testes. DORLAND'S at 1690.

[102] Leukocytes are white blood cells. DORLAND'S at 1028.

[103]Emanuela Balestrieri et al., HERVs Expression in Autism Spectrum Disorders, 7 PLOS ONE 1-10 (2012) [Pet. Ex. 110].

[104] Katja Schmitt et al., HERV-K (HML-2) *rec* and *np9* Transcripts not Restricted to Disease but Present in Many Normal Human Tissues, 6 MOBILE DNA 1-13 (2015) [Resp. Ex. L17; Pet. Ex. 78].

fragments, either through insertional mutagenesis or some other process, play any role in the etiology of ASD.

2. Retrograde Transport

Another causation scenario proposed by Dr. Deisher involves retrograde transport. Dr. Deisher used an example of retrograde transport in the giant squid, where the phenomenon was first studied. Nerve terminals in the giant axon of squid[105] pick up substances that are then transported into cells in the central nervous system. Tr. 103-04. According to Dr. Deisher, nerve cells send out axons, [106] "long projections that make[] contact with … the periphery to send signals from the brain to the periphery…." Tr. 103. Those axons can also carry information back up into the brain. Id. The advantage of this mechanism, as compared to Dr. Deisher's other theories, is that DNA fragments do not have to cross the blood-brain barrier, ("BBB") [107] because retrograde transport bypasses the BBB. Id. at 248-49.

Dr. Deisher hypothesizes that "DNA fragments injected into the muscle [via vaccination] could be picked up by the terminals of axons and transported …back up to the cell body of the nerve and the central nervous system ("CNS")." Tr. 104. Once there, the DNA could insert into the genome[108] of cells in the CNS. Id. According to Dr. Deisher, insertion of the residual DNA fragments into the cell "could result in … mutations in the brain cells." Id.; see also Pet. Ex. 76 at 33-34.

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[105] A giant axon is "an axon of certain invertebrates, e.g., the squid, whose size (500 to 700 microns) has facilitated physiological studies of cell membrane excitation." DORLAND'S at 187.

[106] An axon is "the [prominence] of a neuron by which [nerve] impulses travel away from the cell body[.]" DORLAND'S at 186.

[107] The BBB is defined as "the barrier system separating the blood from the parenchyma of the [CNS]." DORLAND'S at 201. Ghadge et al. state that the blood-brain barrier is "a capillary or barrier that allows relatively little transport of blood-borne molecules." Pet. Ex. 226 at 132. Wang et al. note, "The existence of the blood-brain barrier precludes a vascular route of transgene delivery to the CNS." Pet. Ex. 217 at 658. Dr. Deisher proposes at least two other methods whereby DNA fragments could cross the BBB. First, she suggests that a pre-existing illness could "predispose a child for diminished blood brain barrier competence," allowing transport of DNA fragments into the brain. Pet. Ex. 76 at 37-37, 40. Second, Dr. Deisher stated that an immune response elicited due to vaccinations, along "with its concomitant physiological changes and cytokine expression, [is] known to increase permeability across the [BBB]." Id. at 49-40. Petitioners provide no evidence that either method could account for how residual DNA from vaccines cross the BBB to reach the brain and cause ASD.

[108] The genome is "the entirety of the genetic information encoded by the nucleotide sequence of an organism, cell, organelle, or virus …. In a human being, the genome size is approximately [three] billion base pairs of DNA and approximately 25,000 genes." DORLAND'S at 771.

Petitioners cite a number of studies for the proposition that retrograde transport could deliver DNA fragments to brain cells. Generally, the purpose of these studies is to investigate the potential for gene therapy, or delivery of genes to the CNS for treatment of disease. None of these studies address DNA fragments from vaccines or ASD. For example, Wang et al. [109] studied retrograde axon transport in rats and mice. The animals were injected with DNA and were later found to have gene expression of that DNA in their brain tissue. Pet. Ex. 76 at 39 (referencing Pet. Ex. 217 at 658). Specifically, the tongue was injected with "plasmid DNA complexed with the cationic polymer polyethylenimine ("PEI")…." Pet. Ex. 217 at 658. PEI is a non-viral vector which can be "internalized by nerve endings and retrogradely transported from the periphery into neuronal cell bodies in the CNS." Id. The purpose of the study was to determine whether an intramuscular injection of PEI could be used to "achieve gene transfer in the CNS." Id. at 659. Wang concluded that "PEI/DNA complexes can migrate by retrograde axonal transport to neuronal cell bodies after being internalized by nerve terminals in the muscle…" Id. at 663. The study "confirmed the feasibility of nonviral gene delivery to the CNS via peripheral injectional sites." Id.

Principally, the goal of the Wang study was to measure the effectiveness of PEI, a polymer known for its transfection[110] efficiency, for use in gene therapy. Pet. Ex. 217 at 659. Wang found that "[n]aked DNA, as well as PEI alone, produced no ... activity in the brain stem...." Id. at 660.

The findings in Wang do not translate to this case for several reasons. First, in the Wang experiment, DNA fragments were not used. Instead, DNA was joined with the polymer PEI to form PEI/DNA complexes to facilitate uptake. Dr. Deisher provided no evidence to suggest that the residual DNA in vaccines is like the PEI/DNA complexes. Secondly, the PEI/DNA complex was injected into tongue muscle, which is part of the rat's hypoglossal nerve system. "Motor neurons of the hypoglossal nucleus in the brain stem innervate tongue muscles." Ex. 217 at 660. Thus, there was a known nerve pathway from the brain stem via the hypoglossal nerve into the tongue. Petitioners provide no evidence of a similar nerve pathway from a child's brain to the muscle where a vaccine is administered. Third, in Wang, "naked" DNA, or DNA that was not joined with the polymer, did not produce activity in the brain. Id. This finding suggests that DNA fragments in vaccines are not capable of retrograde transport, absent their combination with a specifically designed polymer. The Wang study in no way suggests that fetal DNA fragments found in vaccines could travel to a child's CNS via retrograde transport, and the study does not contemplate this possibility.

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[109] Shu Wang et al., Transgene Expression in the Brain Stem Effected by Intramuscular Injection of Polyethylenimine/DNA Complexes, 3 MOLECULAR THERAPY 658 (2001) [Pet. Ex. 217].

[110] Transfection includes "any means of artificial introduction of foreign DNA into cultured eukaryotic (cells with a true nucleus) cells." DORLAND'S at 1952, 653.

Dr. Deisher also cited a study by Beier et al,[111] which explores the difficulty of mapping neuronal connectivity in the CNS. Scientists engineered a recombinant[112] virus, vesicular stomatitis virus ("VSV") with a rabies virus glycoprotein ("RABV-G"), and then mapped connections between neurons. Pet. Ex. 223 at 1. The recombinant virus ("rVSV-RABV-G") "spread rapidly from neuron to neuron in only a retrograde manner." Id. The study shows that recombinant viruses may be "engineered to transmit across [neuronal] synapses." Id. However, Dr. Deisher does not explain how recombinant rVSV with RABV-G, a modified virus with added glycoprotein, is in any way similar to residual DNA in vaccines.

Another study cited by petitioners was authored by Ghadge et al.[113] Pet. Ex. 76 at 39. Ghadge demonstrated "that intramuscular injection of replication-defective recombinant adenovirus[114] [manufactured with a specialized promoter and cytomegalovirus enhanced used for its vector[115] qualities] results in high-level recombinant gene expression, specifically in the CNS motor and sensory neurons that innervate the inoculated muscles." Pet. Ex. 226 at 132. More simply put, recombinant replication-defective adenoviruses were used to deliver genes into CNS neurons via retrograde axonal transport following intramuscular injection. Id.; Tr. 478-79. Ghadge explained that recombinant replication-defective adenoviruses have "a number of properties that make them attractive gene transfer vehicles." Pet. Ex. 226 at 132. Other than establishing that retrograde transport is a real phenomenon, however, petitioners do not offer any evidence that the recombinant adenoviruses used as gene transfer vehicles in Ghadge's study are

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[111] Kevin Beier et al., Vesicular Stamatitis Virus with the Rabies Virus Glycoprotein Directs Retrograde Transsynaptic Transport Among Neurons in Vivo, 7 FRONTIERS IN NEURAL CIRCUITS 1 (2013) [Pet. Ex. 223].

[112] A new entity, such as a "gene, protein, cell…that results from genetic recombination." DORLAND'S at 1607.

[113] G.D. Ghadge et al., CNS Gene Delivery by Retrograde Transport of Recombinant Replication-Defective Adenoviruses, 2 GENE THERAPY 132 (1996) [Pet. Ex. 226]; see also Anne Hennig et al., Intravitreal Gene Therapy Reduces Lysosomal Storage in Specific Areas of the CNS in Mucopolysaccharidosis VII Mice, 23 J. NEUROSCIENCE 3302 (2003) [Pet. Ex. 498], discussed at Tr. 174. The findings of the study indicated that "[a]xonal transport from the retina can be used to deliver therapeutic agents into the brain," in lieu of intracranial injections. Id. at 3307.

[114] Adenoviruses belong to the family of DNA viruses with a genome consisting of a "single linear molecule of double-stranded DNA." DORLAND'S at 30. "Conditionally replicative adenoviruses," are "mutant adenoviruses that can replicate only inside certain types of tumor cells, infecting host cells with lethal abnormalities and thus being potentially useful in gene therapy for cancer." Id. In Ghadge, "replication-defective" adenoviruses were used.

[115] A vector is, generally, "a carrier." DORLAND'S at 2028. A recombinant vector carries "both the vector and foreign inert sequences." Id.

similar to residual DNA in vaccines, or that residual DNA can travel via retrograde transport so as to cause ASD.

Dr. Halsey agreed that retrograde transport is a known phenomenon and that live viruses have been shown to be transported in retrograde fashion via neurons, as was demonstrated by Ghadge. Tr. 478-79. But Dr. Halsey testified that he has never seen evidence that injection of DNA in a peripheral part of the body can lead to transport across multiple synapses in the human neural system, up to the CNS, to different areas of the brain. Id. at 503. Dr. Halsey also testified that Dr. Deisher misrepresented the findings in Ghadge and Hennig.[116] The authors did not inject DNA or DNA fragments in the mice; instead, they injected a live virus in an attempt to devise a method of gene therapy. Tr. 479-80. While viruses may be delivered by retrograde transport, the same is not true of DNA. Id. at 500.

3. Microvesicle Transport

Microvesicle transport is the third mechanism proposed by Dr. Deisher whereby DNA fragments found in vaccines could be transported in the blood circulation and taken up by a CNS cell. Tr. 106. Dr. Deisher testified as follows:

> [Another] possible way that the contaminants [residual DNA fragments] injected into a peripheral muscle, like an arm or a leg, could reach the central nervous system and potentially be taken up by a central nervous system cell and cause insertional mutagenesis is by transporting the blood in what are called microvesicles.[117] Tr. 105-06.

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[116] In Hennig, a "recombinant adeno-associated virus" was used as a vector for gene therapy via injection into the vitreous humor of the eye of mice for delivery within the CNS. Hennig et al., 23 J. NEUROSCIENCE at 3302. "The findings suggest that…trans-synaptic transfer contribute[d] to [] dissemination…within the CNS." Id. Dr. Deisher cited a number of articles about retrograde transport, but none relate to the facts and circumstances here, and none of the articles provide preponderant evidence that retrograde transport is a plausible method of delivering residual DNA fragments in vaccines to the CNS, so as to cause autism. For examples, see Ping Yang et al., Lentiviral Vector Mediates Exogenous Gene Expression in Adult Rat DRG Following Peripheral Nerve Remote Delivery, 47 J. MOL. NEUROSCI. 173 (2012) [Pet. Ex. 218] (sciatic nerve retrograde transport experiment); Zarife Sahenk et al., Gene Delivery to Spinal Motor Neurons, 606 BRAIN RESEARCH 126 (1993) [Pet. Ex. 219]; Beier et al., 7 FRONTIERS IN NEURAL CIRCUITS 1 (2013) [Pet. Ex. 223]; and Kevin Beier et al., Anterograde or Retrograde Transsynaptic Labeling of CNS Neurons with Vesicular Stomatitis Virus Vectors, 108 PNAS 15414 (2011) [Pet. Ex. 224] (VSV serve as vectors for retrograde transport). Dr. Deisher also cited studies dealing with gene therapy and retrograde transport, for example, see Devang Thakor et al., Subcutaneous Peripheral Injection of Cationized Gelatin/DNA Polyplexes As a Platform for Non-Viral Gene Transfer to Sensory Neurons, 15 MOLECULAR THERAPY 2124 (2007) [Pet. Ex. 496].

[117] Dr. Deisher defined a microvesicle as a lipid vesicle "known to carry nucleic acids." Tr. 106.

Microvesicles are a known method of transporting "nucleic acids through the circulation." Tr. 106. Dr. Deisher cites an article by Bess et al. [118] to support this theory. In Bess, the authors describe the finding of nonviral membrane protein particles, or microvesicles, in "purified preparations of immunodeficiency viruses (HIV-1)." Pet. Ex. 207 at 143. The microvesicles contained RNA and DNA. Other than showing that microvesicles contain DNA and that they are a method of transport within the circulatory system, Bess does not provide any evidence that microvesicles transport residual DNA from vaccines as suggested by Dr. Deisher.[119]

Additionally, Dr. Deisher seems to conflate or otherwise combine the theories of microvesicle transport (circulatory system) and retrograde transport (nervous system). She states that "DNA-containing microvesicles can be transported retrograde to the brain by motor nerve proteins such as kinesin[120] or its homologs, which are known to transport vesicles in axons." Pet. Ex. 76 at 37. To support this assertion, Dr. Deisher cited an article by Coy and Howard[121] related to organelle transport.[122] Id. The authors discuss the transport of materials from the nerve cell body to the axon. Pet. Ex. 208 at 662. The authors do not reference "microvesicles" or the theory posited by Dr. Deisher, but they do mention the transport of "multivesicular bodies" from synaptic terminals toward the cell bodies. Id. The article does not discuss the potential for DNA fragments to be transported to neurons by microvesicles, and Dr. Deisher does not explain how organelle transport is comparable, if at all, to the transport of fetal DNA fragments. Regardless of how this component of Dr. Deisher's theory is described, the articles[123] cited in support of it do not appear relevant to the facts presented by this case or the theories being advanced by petitioners.

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[118] Julian Bess et al., Microvesicles Are a Source of Contaminating Cellular Proteins Found in Purified HIV-1 Preparations, 230 VIROLOGY 134 (1997) [Pet. Ex. 207].

[119] Dr. Deisher also cites the Dinu paper, a discussion of the cellular function of kinesins, including the role of kinesins in "the movement of organelles and vesicles," but the article does not provide support of petitioners' microvesicle transport theory. C.Z. Dinu et al., Cellular Motors for Molecular Manufacturing, 290 ANATOMICAL RECORD 1203 (2007) [Pet. Ex. 209].

[120] Kinesin is a "family of large cytoplasmic proteins with ATPase activity that bind to vesicles and particles and transport them along microtubules, usually toward the plus end, using energy from ATP hydrolysis …. [C]ytosolic kinesins are responsible for the transport of vesicles and organelles." DORLAND'S at 987.

[121] David Coy and Jonathon Howard, Organelle Transport and Sorting in Axons, 4 CURRENT OPINION IN NEUROBIOLOGY 662 (1994) [Pet. Ex. 208].

[122] An organelle is defined as "any of the membrane-bound organized cytoplasmic structures of distinctive morphology … including such structures as the nucleus, mitochondria, [etc]." DORLAND'S at 1334.

[123] These articles include Merck, Summary For Basis of Approval: Varicella Virus Vaccine Live,

4. Hematopoietic Stem Cells

According to Dr. Deisher, the most likely mechanism for insertional mutagenesis of DNA fragments is via hematopoietic stem cells. Tr. 107. She opines that a hematopoietic stem cell in the peripheral circulation may take up a DNA fragment from a vaccine and insert it in the genome, causing a mutation in that cell. Id. Dr. Deisher testified that hematopoietic stem cells produce all blood-forming cells, including immune cells, such as lymphocytes, in the blood. She further testified that immune cells give rise to glial cells.[124] Id. Dr. Deisher stated that hematopoietic stem cells circulate in the periphery (blood vessels and lymph system) but are concentrated in the bone marrow and spleen. She also stated that hematopoietic stem cells give rise to immune modulating cells, and that the cells can replace other cells in the brain and provide new microglial cells.[125] Id. at 251. She posits that a mutated hematopoietic stem cell could lead to, or produce, a "mature glial cell, that could get into the brain." Tr. at 107. Once in the brain, Dr. Deisher believes the cells could impact "nerve signaling and nerve cell survival," which, she theorizes, may cause ASD. Id.

In support of this theory, Dr. Deisher cites a study by McNeer et al.[126] to support her opinion that DNA fragments can be inserted into the genome of hematopoietic stem cells. See Tr. 98. In McNeer, the authors developed a novel technique to modify a defective gene in mice. The goal was to devise an in vivo,[127] "site-specific gene editing" tool using hematopoietic stem

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Reference No. 90-0395 [Pet. Ex. 91]; Li Sheng et al., Oncogenicity of DNA *in vivo*: Tumor Induction with Expression Plasmids for Activated H-*ras* and *c-myc*, 36 BIOLOGICALS 184 (2008) [Pet. Ex. 86]; U.S. Dept. of Health and Human Servs., World Health Organization, Evolving Scientific and Regulatory Perspectives on Cell Substrates for Vaccine Development, Rockville, MD (Sept. 7, 1999) [Pet. Ex. 87]; World Health Organization, WHO Expert Committee on Biological Standardization, Forty Seventh Report, 878 (1998) [Pet. Ex. 88]; Coy et al., 4 CURRENT OPINION IN NEUROBIOLOGY 662 [Pet. Ex. 208]; Dinu et al., 290 ANATOMICAL RECORD 1203 [Pet. Ex. 209]; and Bess et al., 230 VIROLOGY 134 [Pet. Ex. 207].

[124] Glial cells, also referred to as "neuroglia," are "the cells of the supportive tissue of the central nervous system." There are three types of glial cells: astrocytes, oligodendrocytes, and microglia. DORLAND'S at 321.

[125] The microglia are "the small, nonneural, interstitial cells of mesodermal origin that form part of the supporting structure of the central nervous system …. They are migratory and act as phagocytes to waste products of nerve tissue." DORLAND'S at 1159.

[126] N.A. McNeer et al., Systemic Delivery of Triplex-Forming DNA and Donor DNA by Nanoparticles Mediates Site-Specific Genome Editing of Human Hematopoietic Cells *in Vivo*, 20 NATURE GENE THERAPY 658 (2013) [Pet. Ex. 184].

[127] The phrase "in vivo" describes a process, procedure, or test within an intact organism. DICTIONARY OF BIOMEDICINE, Oxford University Press (2010). In contrast, "in vitro," is an

cells for the treatment of diseases. Pet. Ex. 184 at 658. The authors note that historically, gene therapy was unsuccessful or had limited use due in part to problems with delivery, such that genes were integrated into random sites. Id. To address this problem, McNeer's group designed a tool that would be capable of specific editing of genes at their "endogenous loci."[128] Id. None of the previous techniques for "site-specific gene editing [had] been used directly to edit human genes in human cells *in vivo*." Id. The researchers combined two technologies,[129] "synthetic triplex-forming oligonucleotides and polymer nanoparticles – to modify human cells after [ ] delivery into [ ] mice." Id. at 659. Using this technology, the researchers modified the human CCR5 gene in hematolymphoid cells in the mice. Id. at 658. McNeer, however, does not support Dr. Deisher's theory as it relates to hematopoietic stem cells. Instead, McNeer establishes that the delivery and insertion of donor DNA requires "the use of molecular tools" for delivery as well as technical manipulation at every stage of the process. Id.

In addition to McNeer, Dr. Deisher cites several articles[130] about gene therapy trials in children with severe combined immunodeficiency ("SCID"), also known as "Bubble boys." Tr.

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experiment "observable in a test tube." DORLAND'S at 956.

[128] Loci is the plural form of "locus," a genetic term for "the position of a gene on a chromosome, different forms of genes (alleles) being found at the same position on homologous chromosomes." DORLAND'S at 1072.

[129] The technology used in McNeer is complex and far beyond the scope of this Decision. Specially engineered polylactic co-glycolic acid ("PLGA") nanoparticles were used to deliver peptide nucleic acids ("PNA") for the purpose of gene modification. Pet. Ex. 184 at 659.

Moreover, the McNeer researchers note that their results suggest that "PLGA nanoparticles become widely distributed throughout the mouse, where they are taken up in human cells, allowing for reliable gene modification, which was not achievable with equivalent dosages of naked oligonucleotide." Pet. Ex. 184 at 661 (emphasis added). [PLGA is "a previously engineered poly(lactic-co-glycolic acid), an FDA-approved biocompatible material, to produce nanoparticles that deliver nucleic acid cargo." Pet. Ex. 184 at 2.] In fact, there was only "low to negligible gene modification detected when naked oligonucleotides were used." Id. at 661-62 (referencing Figure 4a). Thus, McNeer shows that DNA fragments that are not specifically engineered to combine with a specialized delivery vehicle, like those in vaccines, would not be taken up by hematopoietic cells.

[130] Salima Hacein-Bey-Abina et al., A Serious Adverse Event After Successful Gene Therapy for X-Linked Severe Combined Immunodeficiency, 348 N. ENGL. J. MED. 255 (2003) [Pet. Ex. 81]; Salima Hacien-Bey-Abina et al., Insertional Oncogenesis in 4 Patients After Retrovirus-Mediated Gene Therapy of SCID-X1, 118 J. CLINICAL INVESTIGATION 3132 (2008) [Pet. Ex. 82]; Steven Howe et al., Insertional Mutagenesis Combined with Acquired Somatic Mutations Causes Leukemogenesis Following Gene Therapy of SCID-X1 Patients, 118 J. CLINICAL INVESTIGATION 3143 (2008) [Pet. Ex. 83]; David Williams and Christopher Baum, Gene Therapy: New Challenges Ahead, 302 SCIENCE 400 (2003) [Pet. Ex. 134].

206. In one of these clinical trials, 10 boys had hematopoietic stem cells extracted from their bone marrow. The researchers then combined a retroviral vector with corrected and defective gene fragments creating a transgene[131] that encoded the protein that was defective in the boys and which compromised their immune systems. Pet. Ex. 134 at 400. The treated stem cells were then transfused back into the patients. Id. Nine of the 10 boys had "clinically significant, long term improvements." Id. Subsequently, however, several of the boys developed T-cell leukemia. Further research revealed that the retroviral vector that carried the transgene inserted "near the promoter of the proto-oncogene[132] LM02."[133] Id. This unexpected downstream insertion caused leukemia.

As it relates to her theory, the SCID trials illustrate that retroviral vectors carrying a transgene can be inserted into stem cells, which may then insert into a child's genome to cause a mutation. Gene therapy, however, is not comparable to vaccination.[134] Petitioners offer no evidence to show that DNA fragments in vaccines insert into the human genome via the techniques used in gene therapy procedures. The process of removing hematopoietic stem cells and then transfusing them back into a child [135] after highly engineered gene therapy is not analogous to giving a child a vaccine.

ii. Insertion, Mutation and Proliferation

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[131] A transgene is a "segment of recombinant DNA that has been transferred from one genome to another; the term is sometimes used specifically to denote one that has been integrated into the germline of the recipient…" DORLAND'S at 1953.

[132] An oncogene is "a gene capable under certain conditions of causing the initial and continuing conversion of normal cells into cancer cells." DORLAND'S at 1321.

[133] The LMO2 gene encodes for a protein that is required for normal hematopoiesis (the formation and development of blood cells). "Aberrant expression of this [protein] has been implicated in…T cell acute lymphoblastic leukemia." Pet. Ex. 134 at 400; DORLAND'S at 833.

[134] For a complete explanation of the multi-step processes utilized in gene therapy techniques, see Pet. Exs. 81-83.

[135] Hematopoietic stem cells were harvested from the bone marrow of 10 patients with SCID. Pet. Ex. 134 at 400. There are two main components of the SCID gene therapy process: transduction and transplantation. Transduction involves introducing foreign DNA to a hematopoietic stem cell ex vivo through the use of a gamma retroviral vector carrying a transgene. Pet. Ex. 82 at 3132; Pet. Ex. 134 at 400. After the foreign DNA was introduced, the hematopoietic stem cells containing the foreign DNA were then transplanted back to the patients. Id.

Throughout her expert reports as well as during the hearing, Dr. Deisher emphasized that she did not know the exact manner in which insertional mutagenesis occurs so as to cause ASD. See Tr. 108; Pet. Ex. 76 at 31. She also testified that one or more of the mechanisms described above may combine so as to result in a mutation that causes ASD. Regardless of the exact underlying mechanism, in order to establish insertional mutagenesis as a plausible theory, petitioners must provide evidence that residual DNA from the vaccines could insert into the genome of the vaccine recipient, resulting in a mutation along with proliferation of that mutation(s), and that the mutation(s) is associated with an ASD phenotype.[136]

1. Insertion

Dr. Deisher posits that a vaccine recipient's cells take up "extracellular DNA fragments by receptor mediated endocytosis."[137] Pet. Ex. 76 at 16. Dr. Deisher stated that uptake is "most efficient at low concentrations of extracellular DNA," and peaks at two hours. Pet. Ex. 76 at 16 (citing Pet. Exs. 117[138] and 118[139]). Based on experiments cited by Dr. Deisher, fragments of nucleic acids, or DNA, "readily enter cultured cells through receptor mediated uptake[140] within [two] to [four] hours." Id. She hypothesizes that these DNA fragments then insert into a cell's genome and cause a mutation.

Dr. Deisher opines that insertion of short DNA fragments is more efficient than large DNA fragments and cites a number of studies to support this proposition. See Pet. Ex. 76 at 27-31. However, none of these studies support her novel idea that DNA fragments from vaccines are inserted into a child's genome, as opposed to being destroyed through the usual process of

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[136] Phenotype is defined as "the observable…characteristics of an individual…as determined by a combination of the genotype and the environment." DORLAND'S at 1431.

[137] Endocytosis is defined as "the uptake by a cell of material from the environment by invagination of its plasma membrane; it includes both phagocytosis and pinocytosis." DORLAND'S at 617. Phagocytosis is the uptake of cell fragments. "The material is taken into the cell in membrane-bound vesicles (phagosomes) … Phagosomes fuse with lysosomes, forming phagolysosomes in which the engulfed material is killed and digested." Id. at 1423. Pinocytosis is "the cellular uptake of extracellular fluid and its contents by enclosing them in vesicles derived from the plasma membrane." Id. at 1449.

[138] Leonid Yakubov, et al., Mechanism of Oligonucleotide Uptake by Cells: Involvement of Specific Receptors? 86 PROC. NATL. ACAD. SCI. USA 6454 (1989) [Pet. Ex. 117].

[139] Valentin Vlassov et al., Transport of Oligonucleotides Across Natural and Model Membranes, 1197 BIOCHEMICA ET BIOPHYSICA ACTA 95-108 (1994) [Pet. Ex. 118].

[140] "Receptor mediated uptake" is a synonymous term for "receptor mediated endocytosis." See infra note 137.

phagocytosis.[141] She posits that the ability of the DNA fragments to insert may turn on the size of the fragments, because insertion of short fragments is more efficient and more likely. Id. at 26. Insertion is "maximal when fragments are between 100 and 1000 base pairs[142] in length."[143] Id.

Dr. Deisher measured the size of the residual DNA fragments in the MMR, hepatitis A, and varicella vaccinations. She opines that the DNA fragments in MMR II and Varivax are shorter and thus more likely to insert, and that the fragments in HAVRIX are "relatively intact" and large, and thus, unlikely to insert. Tr. 96. Thus, she concedes that her theory of insertional mutagenesis is not a good fit for the hepatitis A vaccine.[144]

According to Dr. Deisher, the MMR vaccine contains approximately "150 nanograms [of] cell substrate [double-stranded] DNA and [single-stranded] DNA per dose, fragmented to approximately 215 base pairs in length." Pet. Ex. 76 at 12; Pet. Ex. 322 at 8; Tr. 94. Dr. Deisher performed an experiment using "Human Cot1 DNA (Invitrogen)," to measure its ability to insert. Pet. Ex. 322 at 6. She used Human Cot1 DNA because it is 315 base pairs in size, and it "has reverted epigenetically towards undifferentiated primitive fetal type cells," making it similar to the DNA fragments in MMR. Id. The results of the experiment showed "[s]pontaneous cellular and nuclear DNA uptake," within "24 to 48 hours after addition of … the Cot1 DNA to the culture media of U937 or NCCIT cells." Id. at 58. While this experiment appears to support Dr. Deisher's hypothesis of DNA fragment insertion, it did not involve the residual DNA in vaccines, and it was an in vitro experiment, where the DNA fragments were added directly to prepared cell cultures. Thus, Dr. Deisher's experiment does not simulate vaccination.

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[141] As for children who receive the vaccines at issue and who do not develop ASD, Dr. Deisher testified that DNA fragments would be engulfed and destroyed by the child's innate immune system. Tr. 324-25.

[142] Base pairs are defined as "a pair of hydrogen-bonded bases, a pyrimidine with a purine base that bind together two strands, or two parts of a strand, of nucleic acid. In DNA, the pairs are guanine-cytosine and adenine-thymine." DORLAND'S at 1363.

[143] Dr. Deisher also testified that insertion of residual DNA fragments is more likely when the vaccine contains a higher concentration of DNA fragments. See Pet. Ex. 76 at 12-13. Petitioners provide no evidence that DNA fragments insert into human cells, regardless of fragment size or concentration.

[144] Even assuming that Dr. Deisher's theory regarding insertional mutagenesis is correct, her concession that the hepatitis A vaccine is not a good fit for the insertional mutagenesis theory in turn calls into question the validity of her change point study as it relates to the hepatitis A vaccine and its association with the increasing prevalence of autism.

The paper by Petricciani and Horaud[145] further demonstrates that Dr. Deisher's hypothesis regarding insertion of residual DNA is not viable. By way of background, residual DNA is known to be circulating in our blood and is thought to be the result of the breakdown of leukocytes, bacteria, and cell necrosis. See Pet. Ex. 495 at 2-3. "Extracellular DNA is [also] present in [our] blood plasma and other interstitial fluids." Pet. Ex. 94 at 191. "Fetal DNA has [even] been detected in the blood of mothers during pregnancy." Id. DNA can also be introduced by blood transfusions of whole blood, which contain large amounts of cellular DNA. See Pet. Ex. 72 at 235. Dr. Deisher agreed that patients who receive whole blood transfusion are exposed to human DNA fragments from other persons. Tr. 269-271. However, she did not opine that insertional mutagenesis is a risk due to residual DNA from blood transfusions. Id. at 271.[146]

In Petricciani, the authors generally discuss DNA as a risk factor in a number of biological products, and they specifically address the issue of whether the high levels of DNA in blood plasma pose a risk of mutagenesis for patients receiving blood transfusions. Pet. Ex. 72 at 233. To address this question, Petricciani reviewed studies done in the 1970s in which no statistical difference was found in the incidence of leukemia in patients who received blood transfusions and those who did not. The research indicates that although foreign DNA is given to a patient receiving a blood transfusion, "substantial amounts of cellular DNA, as well as the cells themselves, do not carry a measurable risk," of insertional mutagenesis causing leukemia. Id. at 235.

Dr. Deisher cites numerous studies[147] related to uptake of oligonucleotides, presumably in support of her theory of DNA insertion. Generally, these are older reports on in vitro studies related to the delivery and uptake of nucleic acids for research and development related to gene therapy. Findings or conclusions set forth in these in vitro experiments cannot be extrapolated beyond the cell lines, culture conditions, and/or methodologies used in any particular study. As

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[145] John Petricciani & Horaud Florian, DNA, Dragons and Sanity, 23 BIOLOGICALS 233-38 (1995) [Pet. Ex. 72].

[146] Dr. Deisher testified that DNA in blood used for transfusions "is not fetal DNA," and that it does not readily insert because it is not "primitive." Tr. 271.

[147] See Vlassov et al., 1197 BIOCHIMICA ET BIOPHYSICA ACTA 95 [Pet. Ex. 118]; Frank Orson et al., Oligonucleotide Inhibition of IL2Rα mRNA Transcription by Promoter Region Collinear Triplex Formation in Lymphocytes, 19 NUCLEIC ACIDS RESEARCH 3435 (1991) [Pet. Ex. 119]; Paul Zamecnik et al., Inhibition of Replication and Expression of Human T-cell Lymphotropic Virus Type III in Cultured Cells by Exogenous Synthetic Oligonucleotides Complementary to Viral RNA, 83 PROC. NATL. ACAD. SCI. USA 4143 (1986) [Pet. Ex. 120]; S.L. Loke et al., Characterization of Oligonucleotide Transport into Living Cells, 86 PROC. NATL. ACAD. SCI. USA 3474 (1989) [Pet. Ex. 121]; and E.H. Postel et al., Evidence that a Triplex-Forming Oligodeoxyribonucleotide Binds to the *c-myc* Promoter in HeLa Cells, Thereby reducing *c-myc* mRNA Levels, 88 PROC. NATL. ACAD. SCI. USA 8227 (1991) [Pet. Ex.123].

the researchers in Loke concluded, "whether there is a physiological role for oligo transport is unknown. We may, nevertheless, utilize our understanding of the properties of the uptake process to design oligos that are transported more efficiently and are more resistant to degradation." Pet. Ex. 121 at 3478. This sentiment is echoed by Vlassov, as follows: "Although the existing methods of delivery of nucleic acids into cells allow easy transfection of any kind of cells in vitro, the in vivo incorporation of oligo and polynucleotides in heterogeneous populations of different cells in organism[s] remains a problem." Pet. Ex. 118 at 95-96.

Another idea advanced by Dr. Deisher is that DNA, once inserted into a host cell, may contribute to chromosomal "breaks or rearrangements." Pet. Ex. 76 at 7. In variations on this theme, she also posits that DNA fragments could more easily insert during ongoing cellular processes "such as DNA repair, recombination, and replication." Id. at 22. Cells can "repair by homologous recombination[148] and by illegitimate recombination of DNA fragments." Id. She suggests that this cellular repair process "provides the opportunity for insertion of DNA fragments." Id. Petitioners, however, provide no evidence that DNA fragments from vaccines are involved in chromosomal breaks or rearrangements, or that they insert in the cell's genome during the cellular repair process described here.[149]

Dr. Deisher opines that DNA "integration is opportunistic and most likely occurs during gene repair which is maximized during periods of disruption, such as…when a child's neurons are being pruned, i.e. from [one] to [three] years of age." Pet. Ex. 76 at 5. However, petitioners provided no evidence that residual DNA fragments from vaccines integrate into the genome during "pruning." Further, Dr. Deisher proposes that "[m]eiotic recombination involves highly regulated pathways of double strand break formation and repair. [It] occurs at clustered sites within the human genome, termed recombination hotspots….Sites of [meiotic recombination] have been demonstrated to be [] susceptible to double strand breaks and mutations." Pet. Ex. 76 at 24. Dr. Deisher suggests that hotspots are areas where DNA fragments from vaccines could insert into the genome and cause a mutation. Id. at 23-26; 34-35. Petitioners offered no evidence to show that DNA fragments from vaccines could insert in this manner.

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[148] Recombination is "the process that creates new combinations of genes by shuffling the linear order of the DNA, such as occurs naturally by crossing over of homologous chromosomes during meiosis or of homologous DNA sequences in somatic cells during mitosis, or occurs in vitro when DNA or RNA is manipulated for genetic engineering." DORLAND'S at 1607. Homologous recombination "comprises a series of interrelated pathways that function in the repair of DNA double-stranded breaks…. [it] plays a prominent role in faithfully duplicating the genome by providing critical support for DNA replication…" Xuan Li & Wolf-Dietrich Heyer, Homologous Recombination in DNA Repair and DNA Damage Tolerance, 18 CELL RES. 99 (2008).

[149] Dr. Deisher also opines that "[a]ltered double strand break formation and repair pathways may be a commonality among the extremely diverse genetic mutations observed in ASD." Pet. Ex. 76 at 26. She suggests that residual DNA from vaccines may insert during the repair process, and that this would account for the many diverse genetic mutations reported in ASD, but petitioners offer no evidence to support this idea.

One of the reasons that Dr. Deisher favors hematopoietic stem cells as the most likely mechanism is due to their use in gene therapy studies.[150] In these experiments, researchers use specifically designed DNA fragments as "agents for gene replacement therapy." Pet. Ex. 127 at 2293. "Gene targeting modifies a gene in its chromosomal location, preserving existing mechanisms to regulate its function in cells, and thereby holds great promise as a medical treatment strategy." Id. These experiments may result in uptake or insertion of small fragments of DNA but with specifically produced "DNA constructs." Id. Yakubov provides a brief summary of the different types of DNA constructs used in those experiments. See also Pet. Exs. 131, 132. Dr. Deisher does not provide evidence that these experiments simulate the conditions of vaccination.

Another variation on the theme of insertion relates to insertions and deletions. Dr. Deisher states that "[w]hole exome sequencing of DNA [] from the peripheral blood of 20 children with [ASD] has identified non-inherited insertions and deletions….Insertions/deletions are known to cause subsequent additional mutations and therefore, this observation requires further studies to determine the DNA source for the[se] de novo insertions." Pet. Ex. 76 at 42. This idea adds an additional step to the process. Dr. Deisher suggests that DNA fragments from vaccines cause insertions/deletions, and that these insertions/deletions cause additional mutations which cause ASD.

Ultimately, however, Dr. Deisher concedes that even if insertion could be proven, the question then becomes how "such an insertion would impact neural development or would occur within a cell in the [CNS], [given that] autism spectrum is a neurodevelopmental disorder." Pet. Ex. 76 at 31.

2. Mutation

Assuming that DNA fragments from vaccines could insert into a host genome, the next question is whether there is evidence that insertion could cause a mutation.[151] Fundamental to Dr. Deisher's theory is that "small DNA fragments efficiently insert into the recipients' genome … [and are] involved in de novo mutations."[152] Pet. Ex. 76 at 41. She states that approximately nine to 10 percent of children with ASD have de novo mutations. Pet. Ex. 76 at 42 (referencing

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[150] Dr. Deisher states that the Chin and Liu studies both demonstrate "the efficiency of DNA integration into stem cells." Pet. Ex. 76 at 30 (referencing Pet. Exs. 184 and 185).

[151] Dr. Deisher also stated that, "DNA can insert into a genome, cause mutations upstream or downstream of that insertion and then be excised from the genome, a phenomenon termed [h]it-and-run." Pet. Ex. 76 at 41. She suggests that this idea may make it difficult to measure genomic insertions, presumably caused by vaccines. Id. at 42. Petitioners offer no evidence to show how this idea is relevant to their theories.

[152] Dr. Deisher also posits that "DNA fragments could cause "de novo mosaic mutations among nerve cells." Pet. Ex. 76 at 34. Petitioners offered no evidence to support this idea as it relates to her theory here.

Pet. Ex. 238[153]). She believes these de novo mutations are caused by vaccines (postnatally). Tr. 132, 185. Additionally, Dr. Deisher posits that the genes associated with ASD "have a more concentrated susceptibility for insults to genomic stability" as compared to other genes, and that "regions of the genome where meiotic recombination[154] occurs," (i.e. hotspots) may be "highly predisposed … to disease causing mutations." Pet. Ex. 322 at 4.

Dr. Deisher readily conceded that there is a problem of evidence. She stated, "this observation [of de novo mutations] requires further studies to determine the DNA source for the de novo insertions and whether the DNA fragments contained in childhood vaccines may provide the DNA documented in de novo insertions." Pet. Ex. 76 at 42. Thus, by her own admission, current studies do not provide evidence that DNA fragments in vaccines cause the mutations at the heart of her theory.

While Dr. Deisher did not provide an evidence-based explanation as to how these de novo mutations occur, she testified that many studies demonstrate that children with ASD have diverse mutations in lymphoblastoid cell lines.[155] Tr. 125-26; see also Pet. Ex. 283. The

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[153] Brian O'Roak et al., Sporadic Autism Exomes Reveal a Highly Interconnected Protein Network of De Novo Mutations, 485 NATURE 246 (2012) [Pet. Ex. 238].

[154] Meiotic recombination ("MR") is defined by Dr. Deisher as the process during meiosis in which "genomic material is exchanged between the maternal and paternal chromosomes." Pet. Ex. 322 at 50. "Hotspots are sites in the genome … where MR occurs most frequently." Id. "[R]egions of the genome where [MR] has occurred (hotspots) have been shown to be highly predisposed to … disease causing mutations." Id. She further hypothesizes that autism associated genes ("AAGs") have a "concentrated susceptibility for insults to genomic stability…" Id. at 48. Specifically, she suggests that X-chromosome genes may be susceptible to DNA fragment insertion, which could "lead to de novo mutations." Id. at 55-59. Dr. Deisher urges "additional study and investigation of this potential relationship." Id. at 59.

[155] Dr. Deisher opined that de novo mutations account for approximately 10 percent of ASD cases. Pet. Ex. 10 at 6. She proposes that residual DNA fragments from vaccines could insert into lymphocytes, which are derived from hematopoietic stem cells. Tr. 130. A lymphocyte is "any of the mononuclear, nonphagocytic leukocytes, found in the blood, lymph, and lymphoid tissues, that are the body's immunologically competent cells and their precursors." DORLAND'S at 1084. A lymphoblast is "an activated lymphocyte that has that has been transformed in response to antigenic stimulation." Id. After a lymphoblast is activated, it divides and makes clones of the original cell, and the copies of the original all carry the same mutation. In this way, lymphoblastoid cell lines are useful tools for researching genetic diseases.
When a lymphocyte becomes activated by an antigen, it creates a lymphoblast, which then divides and creates more lymphocytes. This process creates lymphoblastoid cell lines, and all of the cells in the lineage are identical. Dr. Deisher points to several genetic studies which have found that "rare diverse mutations" are present in the lymphoblastoid cell lines of children with ASD. Tr. 125. She cites to the 2012 O'Roak paper to support her theory that de novo mutations

mutations cause "deletions in exomes"[156] that result in the lack of a protein, or a "truncated protein that may not work." Tr. 127-28.

Dr. Arking strongly disagreed with Dr. Deisher's theory of insertional mutagenesis. A de novo mutation is a mutation seen in the child that is not found in the parent. Tr. 572-73. When a de novo mutation occurs postnatally,[157] it will only be observed in the cell that mutates and the cells that divide from that mutated cell. It will not be observed in other sets of cells in the body. Id. at 574. Thus, a single mutated cell, even one that divides exponentially, may lead to a disease, such as a localized tumor, but would not cause a diffuse brain disease like ASD.

Further, there is a question about how a mutation in a single cell could cause ASD. An individual neuron with a mutation does not cause disease. Tr. 575.[158] For neurons to cause disease, Dr. Arking testified that the mutation must occur in a significant percentage of cells.[159]

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found in lymphoblastoid cell lines could cause ASD. Tr. 130 (referencing Pet. Ex. 238; Resp. Ex. H7).

O'Roak compared the lymphoblastoid cell lines of children with autism with their non-autistic siblings and found that both affected and unaffected children had de novo mutations that their parents did not have. Pet. Ex. 238 at 585. The results also showed that affected children had insertions and deletions ("indels") that their unaffected siblings did not have. Id. at 586. Dr. Deisher testified that because the de novo mutations were found in lymphoblastoid cell lines, the O'Roak results demonstrate that ASD can be caused by de novo mutations. Tr. 126. She further postulates that the de novo insertion mutations are caused by residual DNA fragments found in vaccines. Id. at 130, 132. However, the O'Roak paper does not contemplate the mechanism for the creation of indels, nor do the authors hypothesize that residual DNA fragments from vaccines could cause insertion mutations.

[156] An exome is part of the genome formed by exons, or "coding sequences in a gene." DORLAND'S at 660.

[157] Postnatal mutations occur after the child's birth (as the result of vaccinations, as posited by Dr. Deisher).

[158] The brain is tolerant to mutations in individual neurons; people with normal development may have abnormal neurons. To affect function, one must have the "same mutation in lots of neurons." See Resp. Ex. H10; Tr. 589. Even assuming that DNA from a vaccine can get into the brain and cause a mutation, "the brain is robust to those mutations." Id. at 589-90.

[159] Under Dr. Deisher's theory of insertional mutagenesis, once DNA reaches the brain, it then must integrate into the genome of neurons. Tr. 255. Dr. Deisher testified that the quantity of DNA that reaches the brain is irrelevant. Even "a very small percent[age]" may be sufficient. Id. Using her method of hematopoietic stem cells as a vehicle for DNA insertion as an example, Dr. Deisher testified that six percent of hematopoietic stem cells with the mutation would be sufficient to cause disease. Id. at 257. "[T]heoretically, uptake from a very small percent[age] of

The only way that a mutation can be found in a substantial number of neurons is for it to occur early in the prenatal period, not postnatally, when children receive vaccines. See id. at 575. Respondent filed six articles to support his position that genetic mutations which cause ASD most likely occur prenatally.[160]

One paper cited by respondent, O'Roak, suggests that the majority of mutations found in ASD occur pre-conception, in the sperm of the father. Tr. 585, 574; see also Resp. Ex. H7 (Pet. Ex. 238). A mutation in the sperm cell of the father could be in all of the cells of the child. Tr. 574. The earlier a mutation occurs post-conception, but before birth, the more cells will be affected. Id. If, for example, the mutation occurs when the embryo is 64 cells, then the vast majority of the cells will have the mutation. If the mutation occurs later, it may be tissue specific, depending on what stage the mutation occurs during development. Id. at 574.

Dr. Arking also cites the Iossifov et al.[161] paper to support his opinion that de novo mutations associated with ASD occur prenatally. Tr. 599; Resp. Ex. H4; Pet. Ex. 641. Iossifov

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the hematopoietic stem cells could lead to a mutated cell that takes over and outgrows the other cells." Id. at 258. However, Dr. Deisher concedes that the mutation of one neuron does not trigger autism. Id. at 261. And she does not know the percentage of mutated cells that would be required to cause autism. Id. at 259-60.

In addition to the issue of what percentage of mutated cells are required to cause disease, there is also the issue of whether insertional mutagenesis would give rise to one type of mutation, or many mutations. Dr. Deisher gave contradictory answers when asked whether neurons would have to share the same mutation as a result of insertional mutagenesis to result in ASD. Initially, she testified that "I would not necessarily expect [] other neurons to share the same mutation." Tr. 262. Later, she testified that if the mutated cell gives rise to a monoclonal cell line, then all of the cells would carry the same mutation. Id. at 265. However, she then testified that based on published studies, children with ASD "all have different mutations …. [and] each child has a different mutation." Id. at 266. She posits that her theory of insertional mutagenesis contemplates that "insertion is a random event," leading to "diverse mutations." Id.

[160] O'Roak et al., 485 NATURE 246 [Resp. Ex. H7; Pet. Ex. 238]; Annapurna Poduri et al., Somatic Mutation, Genomic Variation, and Neurological Disease, 341 SCIENCE 43 (2013) [Resp. Ex. H9]; Xuyu Cai et al., Single-Cell, Genome-Wide Sequencing Identifies Clonal Somatic Copy-Number Variation in the Human Brain, 8 CELL REP. 1280 (2014) [Resp. Ex. H10]; Michael McConnell et al., Mosaic Copy Number Variation in Human Neurons, 342 SCIENCE 632-37 (2013) [Resp. Ex. H11]; Frederico Azevedo et al., Equal Numbers of Neuronal and Nonneuronal Cells Make the Human Brain an Isometrically Scaled-Up Primate Brain, 513 J. COMP. NEUROL. 532-41 (2009) [Resp. Ex. H12]; Rich Stoner et al., Patches of Disorganization in the Neocortex of Children with Autism, 370 N. ENG. J. MED. 1209 (2014) [Resp. Ex. H24].

[161] Ivan Iossifov et al., The Contribution of *De Novo* Coding Mutations in Autism Spectrum Disorder, 515 NATURE 216 (2014) [Resp. Ex. H4].

focused on ultra-rare mutations passed from parent to child, as well as genes expressed in the embryonic brain, and concluded that evidence suggests that de novo mutations causing ASD occur prenatally. Tr. 599-601.

Dr. Arking also cited a paper by Poduri et al.,[162] regarding de novo mutations that arise in the germline cells,[163] as well as "after fertilization during embryonic development", which cause somatic mutations associated with neurodevelopmental disease. Resp. Ex. H9 at 43. While Poduri suggests that somatic mutations can cause disease, these mutations are thought to "occur during [ ] cell divisions that generate the embryo after fertilization and zygote formation." Id. at 44. That is, these mutations "occur early enough in development to be present in many tissues." Id. at 46. Moreover, "patients can show dysfunction … when only [eight] to 35 percent of the brain cells carry the mutation." Id. at 43. Dr. Arking testified that the eight percent of neurons referenced in Poduri would be impossible to achieve with Dr. Deisher's insertional mutagenesis hypothesis. Tr. 588. Even if one accepts Dr. Deisher's idea that DNA can get into the brain and cause a mutation, it would not affect a sufficient number of neurons to cause autism. Id. at 590. And a mutation of one neuron would not lead to an observable phenotype such as ASD. Id. at 592.

3. Proliferation

A fundamental problem with Dr. Deisher's theory, as explained by Dr. Arking, is that she posits that autism is caused by a postnatal mutation, which by its very nature would only affect a small number of cells, as opposed to a mutation found throughout all the cells of the brain. Tr. 643. Autism is a diffuse syndrome of the brain, and thus it is not conceivable that a single cell mutation occurring postnatally could affect a sufficient number of cells so as to cause such a diffuse process. Tr. 639-40. This is why cell proliferation, the idea that the mutated cells multiply so as to cause ASD, is a basic tenet of Dr. Deisher's theory.

One of the reasons Dr. Deisher favors hematopoietic stem cells as a mechanism is that they have a "survival advantage," and proliferate much more than other cells.[164] Tr. at 260. Presumably, if a stem cell has a mutation, it would multiply and take over so as to outgrow other cells. To illustrate her hypothesis that hematopoietic stem cells proliferate and can lead to the

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[162] Poduri et al., 341 Science 43 [Resp. Ex. H9].

[163] A mutation in the sperm or egg is called a germline mutation. "Mutations in germline cells are transmitted to progeny; those in somatic cells (all other body cells) are not." DORLAND'S at 773.

[164] Dr. Deisher testified that she could not comment on what quantity of fetal DNA in the brain required to cause autism, because "experiments have not been done to determine that." Tr. 254. Although she testified that "one mutated nerve cell," could cause "significant disease," she does not believe that the mutation of a single neuron is a trigger for autism, and that is not one of her theories. Id. at 259, 261.

development of autism, Dr. Deisher cited articles by Lu et al.,[165] Naik et al.,[166] Cheung et al.,[167] Busque et al.,[168] Smith et al.,[169] Garrits et al.,[170] and Verovskaya et al.[171] Generally, these articles discuss experiments in mice using cellular barcoding analysis of hematopoietic stem cells. Barcoding allows tracking of individual stem cells with the goal of better understanding clonal[172] dynamics and characteristics, including size, age, lineage, and proliferation tendencies. After reviewing the articles, the most that can be said is that "the number of hematopoietic stem cells that contribute[] to blood formation and the dynamics of their clonal contribution is a matter of ongoing [research and] discussion." Pet. Ex. 691 at 523.

For example, in the Lu article, individual hematopoietic stem cells were tracked using "barcodes" that allowed the researchers to follow and measure the proliferation of an individual cell. Pet. Ex. 685 at 928. The researchers then transplanted 9,000 stem cells into irradiated mice. Id. at 932. Twenty-two weeks after transplantation, the mice were sacrificed and

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[165] Rong Lu et al., Tracking Single Hematopoietic Stem Cells *In Vivo* Using High-Throughput Sequencing in Conjunction with Viral Genetic Barcoding, 29 NAT. BIOTECHNOL. 928 (2002) [Pet. Ex. 685]. According to Dr. Deisher, the researchers in this study used a process known as bar coding in order to track blood cell cloning. Tr. 858.

[166] Shalin Naik et al., Diverse and Heritable Lineage Imprinting of Early Hematopoietic Progenitors, 496 NATURE 229 (2013) [Pet. Ex. 686] (discussing the clonality of the blood system); see Tr. 680.

[167] Alice Cheung et al., Analysis of the Clonal Growth and Differentiation Dynamics of Primitive Barcoded Human Cord Blood Cells in NSG Mice, The American Society of Hematology, (2013) [Pet. Ex. 687] (cited by Dr. Deisher to show the clonality of the blood system); see Tr. 861.

[168] Lambert Busque et al., Recurrent Somatic *TET2* Mutations in Normal Elderly Individuals with Clonal Hematopoiesis, 44 NAT. GENET. 1179 (2012) [Pet. Ex. 688] (cited by Dr. Deisher to show the clonality of the blood system); see Tr. 680.

[169] Laurie Smith, Clonal Analysis of Hematopoietic Stem-Cell Differentiation *In Vivo*, 88 PROC. NATL. ACAD. SCI., USA 2788 (1991) [Pet. Ex. 689] (cited by Dr. Deisher to show the clonality of the blood system); see Tr. 860.

[170] Alice Gerrits et al., Cellular Barcoding Tool for Clonal Analysis in the Hematopoietic System, 115 BLOOD 2610 (2010) [Pet. Ex. 690].

[171] Evgenia Verovskaya et al., Heterogeneity of Young and Aged Murine Hematopoietic Stem Cells Revealed by Quantitative Clonal Analysis Using Cellular Barcoding, 122 BLOOD 523 (2013) [Pet. Ex. 691].

[172] Clonal is defined as "one of a group of genetically identical cells or organisms derived … from a single common ancestor." DORLAND'S at 373.

analyzed, and approximately 50 to 80 of the 9,000 originally transplanted cells had begun to proliferate in the mice. Id. This finding "suggests that [hematopoietic stem cells] do not equally contribute to blood cells after irradiation-mediated transplantation." Id. at 928. Dr. Deisher used the Lu experiment to opine that only "seven or eight hematopoietic stem cells at any one time are making all the cells in the body, and one or two of them are actually making the most of the cells …." Tr. 858. Thus, Dr. Deisher infers that a mutation in a single stem cell could proliferate sufficiently to cause ASD.[173] Id.

Dr. Arking explained why these barcoding studies do not support Dr. Deisher's hypothesis. Resp. Ex. P at 2. All of the studies were performed in mice, whose native hematopoietic stem cells had been lethally irradiated, which is very different from the normal human blood cell production process. Id. The researchers "recovered barcodes after the infected [hematopoietic stem cells] had undergone proliferation and differentiation *in vivo*." Pet. Ex. 685 at 935. This means that "50 [to] 100 cells … originally engrafted … expanded to replace the radiation destroyed native [stem cells], over time expanding out to the [approximately] 15,000 [stem cells] that a typical mouse requires to maintain its blood cells." Resp. Ex. P at 2. It does not mean that under normal circumstances, the body only uses 50 to 100 hematopoietic stem cells to make all of the blood in the body. The most one can say based on the Lu experiment is that hematopoietic stem cells may not equally contribute to the formation of blood cells in mice

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[173] Dr. Deisher also cited the SCID gene therapy trials to support her idea that "a mutation in [a] single cell could … contribute significantly to a disease other than cancer." Tr. 856. She also cited to a paper by Josef Prchal et al. for the proposition that "just a handful of stem cells contribute to all of the blood cells of our body, and that [their] contribution is stable over time." Id. at 857 (referencing Pet. Ex. 864). She further testified that Prchal's research shows that the majority of blood cells come from a single clone.[173] Id. (referencing Pet. Ex. 864, Table 1, at 563).

Dr. Arking disagreed that the SCID trials support Dr. Deisher's notion of cell proliferation. He explained that in the SCID trials, 20 million cells per kilogram of body weight were removed from each child. After gene therapy procedures were performed, the cells were infused back into the children. Tr. 594. Thirty-five percent of the cells given back to the children had the abnormal gene, which propagated in the child's bone marrow, ultimately causing leukemia.

Dr. Arking further testified that Dr. Deisher incorrectly cited the Prchal study, stating that the paper does not address "the number of active [hematopoietic stem cells] for normal blood production." Resp. Ex. P at 2 (referencing Pet. Ex. 684).

after "irradiation-mediated transplantation." Pet. Ex. 685 at 928; see also Resp. Exs. P1[174] and P2.[175]

In summary, Dr. Arking explained that a mutation arising from a vaccination, occurring after birth, cannot result in autism for several reasons. First, the timing is wrong. The current state of scientific knowledge suggests that autism is a neurodevelopmental disorder that occurs prenatally during brain development. Tr. 575. Second, effects on individual neurons, through the process of insertional mutagenesis as contemplated by Dr. Deisher, will not have an effect on the number of cells that would be necessary to cause disease. Id. For the effect to be observed, the mutation would need to be present in a substantial portion of cells. And for that to occur the mutation would need to occur prenatally, during the first or second trimester. Id. If the mutation occurs postnatally, as suggested by Dr. Deisher, it will be found in far fewer cells. If the mutation occurs in a single cell, as contemplated by Dr. Deisher, then mutations would only be observed in that cell and immediately around that cell as it divides. Id. at 574. Third, the brain is robust to postnatal somatic mutations. Tr. 201 (citing Resp. Ex. H10; Resp. Ex. H11).

iii. Autoimmunity

Dr. Deisher's second proposed mechanism is that human DNA fragments in vaccines cause an autoimmune reaction that causes ASD. Tr. 82; Pet. Ex. 10 at 3. She opined that "autoimmunity is demonstrated to be a likely mechanism by publications that have come out since 2012, in approximately 40 percent of children with autistic disorder." [176] Tr. at 256. Dr. Deisher testified that an autoimmune response can occur due to homology between the DNA fragments in the vaccine and the DNA of the vaccine recipient. Id. at 116. Although she opined that autoimmunity may be a "possible mechanism," she did not focus on it in her written papers, in part because, in its Summary Basis of Approval for the varicella vaccine, Merck reported that "they had not seen any potential antibody responses that could trigger an autoimmune response." Tr. 97-98 (citing Pet. Ex. 28 at 3).

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[174] Katrin Busch et al., Fundamental Properties of Unperturbed Haematopoiesis [sic] From Stem Cells in Vivo, 518 NATURE 542 (2015) [Resp. Ex. P1] ("[B]arcoding of transplanted [hematopoietic stem cells] suggest that very low numbers of [hematopoietic stem cells] perpetuate a continuous stream of differentiating cells. However, the numbers of productive [hematopoietic stem cells] during normal hematopoiesis, and the flux of differentiating progeny remain unknown.")

[175] Katrin Busch and Hans-Reimer Rodewald, Unperturbed vs. Post-Transplantation Hematopoiesis: Both in Vivo but Different, 23 CURRENT OPINION HEMATOLOGY 295 (2016) [Resp. Ex. P2] ("Noninvasive genetic experiments in mice have identified a major role of stem and progenitor cells downstream from [hematopoietic stem cells] as drivers of adult hematopoiesis, and revealed that post-transplantation differs quantitatively from normal steady-state hematopoiesis.").

[176] It is not clear which studies Dr. Deisher is referencing.

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Dr. Deisher testified that "autism is probably a multi-hit disease, similar to [] other autoimmune diseases, where [] children may have underlying genetic susceptibility, exposure to something that[] … trigger[s] antibodies against their own DNA, and then perhaps a viral insult … [or] infection breaks down the blood-brain barrier," with the result being that "circulating antibodies are … present to the brain." Tr. 123. She referred to this as "exposure and opportunity." Id. at 124. She posits that an "autoimmune attack" could cause permanent damage to the child's brain. Id.

Dr. Deisher stated that HERV-K fragments may also cause an autoimmune response and have been "associated with several autoimmune diseases." Pet. Ex. 76 at 15. She cites articles by Tai, Freimanis, and Dickerson[177] in support of these assertions but does not further explain how they apply to her theory. Id. (referencing Pet. Ex. 111-113). The article by Tai et al. discussed the expression of a HERV-K envelope protein and its potential role in the development of multiple sclerosis. Pet. Ex. 111 at 1176. Freimanis et al. studied the potential role of HERV-K in causing rheumatoid arthritis, noting that a significant percentage of patients with rheumatoid arthritis showed serological increases of HERV-K. Pet. Ex. 112 at 340. Dickerson et al. studied HERV-K in the context of individuals with schizophrenia who are also at risk of developing type 2 diabetes. Pet. Ex. 113 at 121. However, none of these articles discuss HERV-K in the context of ASD, nor are they based on residual HERV-K fragments found in vaccines. The authors of these studies do not contemplate that HERV-K fragments in any way create an autoimmune reaction that leads to the development of ASD.

Dr. Deisher also posits that from birth to approximately three years of age, "nerve cell death occur[s] on a massive scale. During periods of intense brain cell death such as this, DNA not otherwise found extracellularly would be present and serve as the target for autoimmune attacks, originally triggered by exposure of a young child to the fetal DNA fragments found in vaccines." Pet. Ex. 76 at 21-22. This idea appears to add another step in the theoretical process. Dr. Deisher seems to suggest that once residual DNA from vaccines triggers an autoimmune process, the extracellular DNA from the breakdown of the child's own neurons during a period of intense cell death causes ASD. Petitioners provided no evidence to support this idea.

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[177] A.K. Tai et al., Human Endogenous Retrovirus-K18 Env as a Risk Factor in Multiple Sclerosis, 14 MULTIPLE SCLEROSIS 1175 (2008) [Pet. Ex. 111]; G. Freimanis et al., A Role for Human Endogenous Retrovirus-K (HML-2) in Rheumatoid Arthritis: Investigating Mechanisms of Pathogenesis, 160 Clinical and Experimental Immunology 340 (2010) [Pet. Ex. 112]; Faith Dickerson et al., Polymorphisms in Human Endogenous Retrovirus K-18 and Risk of Type 2 Diabetes in Individuals with Schizophrenia, 104 SCHIZOPHRENIA RESEARCH 121 (2008) [Pet. Ex. 113].

1. Auto-Antibodies and Autoimmunity[178]

Petitioners cite several papers published by Mostafa and his colleagues that report an increase in autoantibodies, antibodies directed against the self, in children with autism as compared to controls.[179] For example, in a study published in 2014,[180] Mostafa demonstrated the presence of anti-double-stranded-DNA antibodies[181] and anti-nuclear antibodies ("ANA")[182] in a group of autistic children. Pet. Ex. 551 at 94. These antibodies were assessed in 80 children with autism and 80 controls. Significantly higher levels of the antibodies were found in children with autism as compared to the control group.[183] Id. at 97. In a 2010 study by Mostafa[184] analyzing a subgroup of children with severe autism, the finding was more pronounced. Pet. Ex. 620 at 464. The authors postulate that these antibodies may cause diffuse brain abnormalities, however, "it is far from clear whether autoimmunity to neuronal antigens is a consequence of the

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[178] I also note prior cases in which the theory of autoimmunity as a mechanism for ASD has been rejected. See R.K., 2015 WL 10911950; Cunningham v. Sec'y of Health & Human Servs., 2016 WL 4529530 (Fed. Cl. Spec. Mstr. Aug. 1, 2016); mot. for rev. denied 2017 WL 1174448 (Fed. Cl. 2017); R.V., 2016 WL 3882519.

[179] See Gehan Mostafa et al., Systemic Auto-Antibodies in Children with Autism, 272 J. IMMUN. 94 (2014) [Pet. Exs. 481, 551]; Gehan Mostafa et al., The Relationship Between the Increased Frequency of Serum Antineuronal Antibodies and the Severity of Autism in Children, 16 EUROPEAN J. PAEDIATRIC NEUROL. 464 (2012) [Pet. Exs. 489, 620].

[180] Mostafa et al., 272 J. IMMUN. 94 [Pet. Ex. 551].

[181] Anti-DNA antibodies are a subtype of anti-nuclear antibodies. "The anti-DNA antibody test is useful for the diagnosis and follow-up of systemic lupus erythematosus." MOSBY'S MANUAL OF DIAGNOSTIC AND LABORATORY TESTS, ("MOSBY'S") (5th ed.) at 78. (2014). There are two types. "The first and most commonly found is the antibody against double-stranded DNA ("anti-ds-DNA"). The second type is the antibody against single-stranded DNA ("anti-ss-DNA")." Id.

[182] ANAs are "autoantibodies to intracellular antigens." Pet. Ex. 481 at 94. They are "used to diagnose systemic lupus erythematosus ("SLE") and other autoimmune diseases." MOSBY'S at 88.

[183] The words "anti-human anti-double stranded DNA antibodies," "antineuronal antibodies," and "anti-double stranded DNA antibodies" are generally synonymous for purposes of this decision. See Tr. 119; see also Tr. 469.

[184] Mostafa et al., 16 EUROPEAN J. PAEDIATRIC NEUROL. 464 [Pet. Ex. 620]; see also, Pet. Ex. 481 at 97 ("[I]ncreased frequency of autoimmune disease among families of patients with autism may … point to [ ] auto-immune background."). However, replication studies of larger samples are warranted to validate whether autoantibodies are "a mere association or have some pathogenic role."); Pet. Ex. 489 at 466 ("However, it is far from clear whether autoimmunity to neuronal antigens is a consequence of the autoimmune diseases or actually initiates the process.").

autoimmune diseases or actually initiates the process." Id. at 466.[185] Dr. Deisher concedes that while anti-DNA antibodies have been found in autistic patients, it is not known whether they represent a pathological finding or a compensatory response. Tr. 278.

Dr. Halsey testified that while the Mostafa studies provide an interesting observation, they do not provide evidence of causality. Tr. 469. Dr. Halsey provides context for understanding the findings reported in the Mostafa studies. He cites to a paper by Aggarwal,[186] which explains that autoantibodies are found in the general population as well as in those with autoimmune disorders. Tr. 470-71. Thus, "the presence of autoantibod[ies] alone do[] not make a diagnosis." Resp. Ex. L24 at 907. "The pathological significance of autoantibodies in the causation of disease is limited." Id. at 909. For many autoimmune disorders, the presence of antibodies is believed to be a secondary effect, caused by the breakdown of human cells. Tr. 543. DNA left from the destruction of cells may trigger the formation of antibodies. Id. Thus, the presence of antibodies is not evidence that the antibody caused the illness. Id.

Dr. Deisher testified that with regard to children who receive a vaccine with DNA fragments who do not develop any adverse autoimmune reaction, the body's innate immune system would recognize the DNA as foreign, and it would engulf and destroy the residual DNA fragments through the process of phagocytosis. Tr. 324-25.

A varicella vaccine safety study[187] was performed by the manufacturer to assess whether residual DNA in the vaccine could induce a harmful anti-DNA response. The study was performed on 293 people who received the vaccine. Pet. Ex. 28 at 14. Anti-DNA titers were tested before vaccination, at six weeks, and one year after vaccination. There was no significant change in titers before or after the vaccination.[188] Id. Dr. Halsey testified that the study showing "no increase in autoantibod[ies] after two doses of [the] vaccine … is evidence against the hypothesis that the residual DNA might induce an immune response to the DNA." Tr. 475.

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[185] In Mostafa, the authors speculate that an autoimmune reaction to neurons might be triggered by infectious agents (chronic bacterial infections), food allergies, heavy metals, and latex. Further studies are recommended. Pet. Ex. 620 at 467.

[186] Amita Aggarwal et al., Role of Autoantibody Testing, 28 BEST PRACT. & RESEARCH CLIN. RHEUMATOLOGY 907 (2014) [Resp. Ex. L24].

[187] Merck and Company, Summary For Basis of Approval: Varicella Virus Vaccine Live, Reference No. 93-0395 [Pet. Ex. 28].

[188] Dr. Deisher was critical of the study's use of the phrase "mammalian DNA." "They do not specify what species of DNA (human vs. another mammal) they are using to look for antibody responses in the children. That's very odd." Tr. 86.

Ultimately, Dr. Deisher agrees with Dr. Halsey that "autoimmunity can [at] times, be a reaction and not a cause." Tr. 828. With regard to whether DNA from the vaccines may cause an autoimmune response, Dr. Deisher concedes that "causality has not been examined." Tr. 828.

2. Analogy to PANDAS

Petitioners' expert, Dr. Burkhard,[189] hypothesized that the varicella vaccine causes an autoimmune response that attacks a child's brain, interfering with development and causing autism. Tr. 369-70. Her hypothesis is derived from pediatric autoimmune neuropsychiatric disorders after strep infection ("PANDAS"). She explained that PANDAS is associated with certain neuropsychiatric disorders, including obsessive compulsive disorders, Tourette's syndrome,[190] and abnormal movement disorders. Id. at 369. She posits that if strep infection can cause neuropsychiatric disorders, then the varicella vaccine could cause autism. Id. at 369-70.

In 2015, Dr. Burkhard reviewed data[191] related to the incidence of autism and noted an "abrupt increase in the rate of autism," within a year in countries that mandated that children receive the varicella vaccine. Tr. 371. She cited the Walker[192] article to support her hypothesis that vaccine-related autism is an autoimmune illness like PANDAS. Tr. 378. Walker provides a summary of studies that used diffusion tensor imaging[193] ("DTI") to study the brains of children

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[189] Dr. Burkhard has no training in the field of immunology or infectious disease. Tr. 407. She did not review the expert reports of Dr. Halsey, Dr. Fallin, or Dr. Arking. Id. Her understanding of genetics appeared to be limited, and with regard to questions in medical articles by Iossifov (Pet. Ex. 641), she deferred to a scientist with knowledge in the field. Tr. 409-10.

[190] Tourette's syndrome is "a syndrome comprising both multiple motor and one or more vocal tics, occurring over a period of at least one year, at least intermittently but sometimes as frequently as many times daily. Obsessions, compulsions, hyperactivity, distractibility, and impulsivity are often associated. Onset is in childhood and tics often lessen in severity and frequency and may even remit during adolescence and adulthood." DORLAND'S at 1831.

[191] Dr. Burkhard testified that an intern completed this research. She did not produce the data or research referenced. Tr. 371.

[192] Lindsay Walker et al., Diffusion Tensor Imaging in Young Children with Autism: Biological Effects and Potential Confounds, 72 BIOL. PSYCHIATRY 1043 (2012) [Pet. Ex. 644].

[193] DTI is defined as "a magnetic resonance imaging ("MRI") technique that allows in vivo investigation of compositional, microstructural, and architectural characteristics of tissues … and is currently the most common method for examining the architecture of white matter in the human brain." Pet. Ex. 644 at 1043. Fractional anisotropy and mean diffusivity are calculations used in the evaluation of DTIs. Fractional anisotropy is "a measure indicating the overall directionality of water diffusion that is greater in organized white matter tracts and lower in [cerebrospinal fluid] disorganized fibers." Kristi Clark et al., Mean Diffusivity and Fractional Anisotropy as Indicators of Disease and Genetic Liability to Schizophrenia, 45 J. PSYCHIATR. RES. 980 (2011). Mean diffusivity "describes the rotationally invariant magnitude of water

with autism. Pet. Ex. 644 at 1043; Tr. 378. Dr. Burkhard testified that 80 to 90 percent of the studies showed dysfunctional myelitis in the brain, including areas of the brain responsible for executive functions.[194] Tr. 379. Dr. Burkhard suggested that the studies show "widespread and diffuse dysfunction of myelin [or white matter] in brains of … children with autism." Id. Dr. Burkhard testified that the abnormal areas seen on the imaging correspond to the functional abnormality in the brains of autistic children. Id. at 388-90. She further testified that certain childhood diseases thought to be autoimmune in nature are thought to be caused by an attack on the myelin by autoantibodies. Tr. 379.

In Walker, DTI was used to make images of the brains of 39 children with autism and 39 controls. The authors found "reduced fractional anisotropy ("FA") and increased mean diffusivity ("MD") in [the] children with autism." Pet. Ex. 644 at 1043. The authors also reviewed similar studies done by other researchers summarizing the brain regions of statistically significant differences. Id. at 1044. The goal of the study was to "characterize the regional distribution of differences in the brains of children with autism," as compared to children with "typical development." Id. at 1045. The DTI images of autistic children "revealed widespread differences of FA and MD in brain parenchyma," as compared to the control group, with a "predominant pattern of reduced FA and increased MD." Id. at 1047-488.[195] While most of the studies showed the same changes of reduced FA and increased MD, the regions of the brain affected were inconsistent. Pet. Ex. 644 at 1048.

Walker strongly cautioned against drawing false conclusions from the data and using the study to suggest that reduced FA is a measure of "white matter integrity" or evidence of demyelination. Pet. Ex. 644 at 1049.[196] In spite of the caveat issued by Walker, Dr. Burkhard

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diffusion within brain tissue." Id.

[194] "Executive function refers to a domain of cognitive abilities (e.g., self-regulation, set maintenance, cognitive flexibility, planning, prioritizing, organizing time and space) that provides support for organization, anticipation, inhibition, working memory, and control and autoregulation of behavior." Kenneth F. Swaiman, Pediatric Neurology: Principles & Practice 892 (4th ed. 2006).

[195] I note the caveat that some of the studies looked at the entire brain, while other only imaged certain regions. See Pet. Ex. 644 at 1044.

[196] The authors go on to state, "For example, in healthy white matter the underlying organization of fibers heavily influences the value of anisotropy (i.e., the more coherent the fiber organization, the higher the measured value of FA. In regions with complex white matter architecture, FA might even paradoxically increase after white matter degeneration. More recently, it was shown that FA values increased in perilesioned cortex after traumatic brain injury in a rat model, because of organized gliosis, not axonal regeneration. In healthy white matter, diffusion anisotropy is known to increase during postnatal maturation, although the relative importance of each specific maturational process (i.e. change in the size of the extracellular space, composition of the extracellular matrix, and degree of myelination) in driving the FA increase is not clear."

testified that Walker shows "widespread and diffuse dysfunction of myelin in the brains of [ ] children with autism." Tr. 379. Walker also cautioned that "DTI studies of autism should be interpreted with caution, because their small magnitude[197] make these measurements particularly vulnerable to the effects of artifacts and confounds, which might lead to false positive and/or false negative biological inferences." Pet. Ex. 644 at 1043. Moreover, Walker did not discuss any of the theories proposed by petitioners as to the cause of autism, especially Dr. Burkhard's theory of autoimmunity.

Moreover, postmortem studies cited by respondent do not support Dr. Burkhard's testimony that autistic brains show "widespread and diffuse dysfunction of myelin." Resp. Ex. J3 at 183. Bauman and Kemper[198] have extensively studied the autistic brain, and they report few gross abnormalities. Id. at 184. Specifically, they state that "patterns of myelination have appeared to be comparable to that of controls…." Id. Bauman and Kemper have found abnormalities in the cerebellum, brainstem, and cerebral cortical area, suggesting a prenatal origin, and a "pattern consistent with developmental curtailment." Id. "Available data provides evidence for a prenatal onset of at least some of the neuroanatomic abnormalities reported in the autistic brain." Id. at 184.

In a more recent article, Stoner et al.[199] described abnormal "prefrontal and temporal cortical tissue," which suggests a problem with "neuronal differentiation at prenatal development stages." Resp. Ex. H24 at 1209. Further, while a number of neurobiological mechanisms have been proposed, "there is no firm pathological evidence to support any of these suggested hypotheses." Resp. Ex. J3 at 186. Suggested mechanisms identified by Bauman and Kemper include "brain over growth," and neurogenesis, "decreased neuronal cell death, increased production of non-neuronal brain tissues (i.e. glial cells), decreased synaptic pruning and abnormalities of myelin." Id.

IX. Petitioners have failed the Althen Test For Determining Causation-In-Fact

In Althen, the United States Court of Appeals for the Federal Circuit discussed the issue of "causation-in-fact" in Vaccine Act cases. The court stated:

> [Petitioner's] burden is to show by preponderant evidence that the vaccination brought about [the child's] injury by providing: (1) a medical theory causally

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Pet. Ex. 644 at 1049.

[197] In fact, Walker states, "[E]quating FA to a specific measure of integrity of white matter is misleading." Pet. Ex. 644 at 1049. The finding of reduced "FA in widespread regions," and MD "only in posterior regions" of the brain is indicative of a pattern that "could be consistent with global differences in the level of tissue maturity between groups, abnormal maturation, or degenerative processes." Id.

[198] Bauman & Kemper, 23 INT. J. DEVL. NEUROSCIENCE 183 [Resp. Ex. J3].

[199] Stoner et al., 370 N. ENG. J. MED. 1209 [Resp. Ex. H24].

> 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 the vaccination and injury. If [petitioner] satisfies this burden, she is entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine.

Althen, 418 F.3d at 1278 (internal citations and quotations omitted). In the pages above, I have provided a detailed explanation of how petitioners have failed to demonstrate preponderant evidence of "causation-in-fact." The next section shows how that analysis fits within the Althen test. For the reasons set forth below, I find that petitioners have failed to satisfy the Althen test and are therefore not entitled to compensation.

a. Althen Prong One: Lack of a Reliable Medical Theory

As noted at the outset, the sole issue to be decided is whether Dr. Deisher's theory of vaccine-caused autism meets petitioners' burden in this case under Althen Prong One. Petitioners must set forth a medical theory explaining how the vaccines could have caused V.J.M.'s autism. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009); Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355-56 (Fed Cir. 2006).

Although petitioners need not identify the exact mechanism involved, their theory of causation must be informed by a "sound and reliable medical or scientific explanation." Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994); see also Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 300aa- 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioners rely upon medical opinions to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d at 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it.") (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980)). However, petitioners are not required to file medical literature proving their theory. As the Federal Circuit noted in Althen, "the purpose of the Vaccine Act's preponderance standard is to allow the finding of causation in a field bereft of complete and direct proof of how vaccines affect the human body." Althen, 418 F.3d at 1280.

Petitioners argue that the evidence they have presented "satisfies the criteria for establishing a plausible theory of causation, as that criteria is recognized by the scientific community." Pet. Prehrg Br. dated January 15, 2016 (ECF No. 202) at 6. They concede that "the precise way the DNA fragments from the human cell lines cause the injury in issue is subject to debate." Id. They state that "where expert opinions extrapolate from existing data, the weight to be given to an expert's opinion is based, in part, on the size of the gap between the science and the opinion proffered." Id. at 7 (citing Cedillo v. Sec'y of Health & Human Servs.,

617 F.3d 1328 at 1339 (Fed. Cir. 2010) (quoting Gen. Elec. Co., 522 U.S. 136, 146 (1997))). They also agree that evidence of causation must be "more than a mere scintilla," and that to establish relevant and reliable evidence there much be "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." Id. at 7. (citing Huvis Corp v. United States, 570 F.3d 1347, 1351 (Fed. Cir. 2009) (quoting Consol. Edison Co. v. NLRB, 305 U.S. 197, 229 (1938))). Cases in which there are close calls "must be resolved in favor of the petitioner." Id. Evidence "should be viewed under the preponderance standard, as it is understood in civil courts, and 'not through the lens of the laboratorian.'" Id. at 9 (citing Andreu, 569 F.3d at 1380.

Respondent disagrees that petitioners have established Prong One. Respondent argues that Dr. Deisher "has not set forth a cogent theory of vaccine causation that makes sense to unbiased, knowledgeable scientists." Resp. Prehrg Br. dated February 8, 2016 (ECF No. 222) at 2. Respondent further argues that Dr. Deisher's "methodology is unscientific," and that her expert reports contain "scientifically inaccurate or dubious propositions." Id. at 3.

i. Hill Criteria[200]

Both parties cited the Hill criteria, developed by Arthur Bradford Hill in 1965, as a method to evaluate Dr. Deisher's theories of causation in this case. See Pet. Prehrg Br. at 5; Resp. Ex. J at 3. The criteria are:

> (1) strength of association (e.g. correlation coefficient); (2) consistency across data sets and populations; (3) specificity of finding to a particular cause and particular outcome; (4) evidence that the causal factor occurred prior to disease onset; (5) evidence for dose-response; (6) biological plausibility; (7) coherence with other types of evidence (e.g., animal models); (8) experimental evidence that removing the causal factor prevents the outcome; and (9) analogy to other known causes of the outcome.

Resp. Ex. J at 3.

It is important to note that these criteria or guidelines are generally considered "only after a study finds an association to determine whether that association reflects a true causal relationship." REF. MAN. SCI. EV. at 598-599. Dr. Deisher's change point study, however, uses

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[200] I include Bradford Hill criteria in my analysis, because petitioners urge that Dr. Deisher's study and opinion should be found persuasive when viewed in the context of the Hill criteria. Pet. Prehrg Memo at 5. Several courts have cited the Hill criteria as a helpful tool for determining whether an epidemiological study establishes causation. See, e.g. Amorgianos v. Nat. R.R. Passenger Corp., 137 F. Supp. 2d 147, 168 (E.D. N.Y. 2001) (stating that "epidemiologists generally look to several additional criteria to determine whether a statistical association is indeed causal."); In re Breast Implant Litig., 11 F. Supp. 2d 1217, 1243 (D. Co. 1998) ("Plaintiffs have not demonstrated that Dr. Blais' methodology or opinions are generally accepted in the scientific community. To the contrary, the accepted method for determining the cause of disease is epidemiology and, if necessary, the Bradford Hill criteria."). Other courts, however, have held that the Hill criteria are not "necessary or helpful" when considering reliability under Daubert. In re Phenylpropanolamine Prod. Liab. Litig., 289 F. Supp. 2d 1230 (W.D. Wa. 2003). In any event, the Hill criteria are not necessarily dispositive even when viewed as helpful. In re Viagra Prod. Liabl. Litig., 572 F. Supp. 2d. 1071, 1081 (D. Mn. 2008) ("The court agrees that the Bradford Hill criteria are helpful for determining reliability, but rejects Pfizer's suggestion that any failure to satisfy those criteria provides independent grounds for granting its Daubert motion."). In that regard, prior vaccine cases have included consideration of the Hill criteria in conjunction with other factors in deciding whether petitioners have provided preponderant evidence of a theory of causation. See Koehn v. Sec'y of Health & Human Servs., 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), mot. for rev. denied 113 Fed. Cl. 757 (2013), aff'd 773 F.3d 1239 (Fed. Cir. 2014); Baker v. Sec'y of Health & Human Servs., 99-653-V, 2003 WL 22416622 (Sept. 26, 2003). In this case, I need not reach the question of how much weight to place on the Hill criteria, because I have found, for the reasons detailed below, that Dr. Deisher's opinion in this case is not in accord with the Hill criteria. Further, my decision in this case does not turn on my analysis of the Hill criteria, and even without it, I find petitioners have not proven Althen Prong One by preponderant evidence.

an ecological design, which, as discussed above, is not well suited to establishing causation. See REF. MAN. SCI. EV. at 561. As such, Dr. Deisher's study cannot answer the question of whether an association exists between exposure to vaccines which contain residual DNA fragments and autism. Moreover, Dr. Deisher's change point study, and her causal conclusions, are "built on [an] unproven link." See Pet. Ex. 62 at 7. Nevertheless, the Hill criteria provide a framework to analyze the evidence. The criteria are useful to evaluate the question of whether there is a "true cause-effect relationship." REF. MAN. SCI. EV. at 597.

1. Strength of Association

The first Hill criterion assesses the strength of the association between the exposure (vaccines) and the disease (autism). See REF. MAN. SCI. EV. at 602. Strength of association is often measured by relative risk, the "ratio of the incidence rate … of disease in exposed individuals to the incidence rate in unexposed individuals." REF. MAN. SCI. EV. at 566. "The higher the relative risk, the greater the likelihood that the relationship is causal." Id. at 602. For example, for cigarette smoking, the "estimated relative risk for lung cancer is very high, about 10. That is, the risk of lung cancer in smokers is approximately 10 times the risk in nonsmokers." Id.

Petitioners argue that this criterion has been met because the change point study showed an increase in autism following the introduction of or increased doses of the vaccines at issue in the geographical areas studied. Pet. Prehrg Memo at 5. Respondent disagrees, and counters that the study only shows a correlation between the change points and the dates of vaccine licensure, "although this is at the ecological level and based on unverified assumptions." Resp. Ex. J at 5.

Dr. Fallin explained that in ecological studies, the strength of association is often measured by a correlation coefficient, which is a measurement of the strength of the correlation of the amount of exposure at the group or aggregated level, and the amount of outcome at the group or aggregated level. Tr. 719. Dr. Deisher's change point study does not contain any such "numeric metric" by which to measure the correlation. Id. at 720. Because her study does not contain measurable correlation parameters, Dr. Deisher's claim that the association between fetal manufactured vaccines and AD prevalence change points are consistent across each different geographic location cannot be verified. Id. at 721. The only way to compare prevalence data sets from Denmark and prevalence data sets from California is by looking at the year in which the prevalence was measured and comparing it with the year that fetal manufactured vaccines were licensed. This comparison, however, does not meet the first Hill criterion for measuring the strength of association, using relative risk, correlation coefficient, or other verifiable parameters.

2. Consistency[201]

The second Hill criterion, the consistency factor, assesses whether "the findings are consistent with other relevant knowledge." REF. MAN. SCI. EV. at 606. Relevant to this criterion is whether other epidemiological studies have shown an association between vaccines and autism. Tr. 721; Resp. Ex J at 5. Petitioners argue this criterion was satisfied because there was "an increase in autism follow[ing] every introduction or increased dose of [the] vaccines in every jurisdiction studied." Pet. Prehrg Br. at 5. Respondent disagreed, noting that no other studies verified Dr. Deisher's results, and numerous studies have shown that there is no association between vaccines and autism. Resp. Ex. J at 5.

Dr. Fallin cited a number of epidemiological studies, all of which found no association between vaccines and autism.[202] Moreover, there are no studies or literature, other than Dr. Deisher's study, which show any association between fetal manufactured vaccines and autism. See Tr. 219.

Dr. Deisher's 1988 change point was reported by McDonald. In effect, Dr. Deisher verified McDonald's 1988-1989 change point. However, McDonald cited the numerous studies on the MMR vaccine and the 2004 IOM report and rejected a causal relationship between the MMR vaccine and autism. Pet. Ex. 27 at 2. McDonald did not identify the other two change points reported by Dr. Deisher, and Dr. Deisher conceded that no one else has confirmed her change points in published literature.[203] Tr. 236-237.

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[201] Petitioners refer to this criterion as "the consistency of the association in varied circumstances." Pet. Prehrg Br. at 5. However, the REF. MAN. SCI. EV, quoted by petitioners, uses the phrase, "consistency with other knowledge." REF. MAN. SCI. EV. at 600, 606. Dr. Fallin's explanation of this criterion appears more accurate than petitioners'.

[202] These studies include Jain et al., 313 JAMA 1534 [Resp. Ex. J18]; Madsen et al. 347 N. ENG. J. MED. 1477 [Resp. Ex. J26]; Taylor et al., 333 Lancet 2026 [Resp. Ex. J44]; Demicheli et al., Cochrane Database of Systematic Reviews [Resp. Ex. J8]; Fombonne et al., 118 PEDIATRICS e139 [Resp. Ex. J9]. These articles are discussed earlier in the epidemiology section. See also Robert Schechter and Judith Grether, Continuing Increases in Autism Reported to California's Developmental Services System, 65 ARCH. GEN. PSYCHIATRY 19 (2008) [Resp. Ex. J41]; Anne Hurley et al., Thimerosal-Containing Vaccines and Autism: A Review of Recent Epidemiologic Studies, 15 J. PEDIATR. PHARMACOL. THER. 173 (2010) [Resp. Ex. J16]; and Yota Uno et al., Early Exposure to the Combined Measles-Mumps-Rubella Vaccine and Thimerosol-Containing Vaccines and Risk of Autism Spectrum Disorder, 33 VACCINE 2511 (2015) [Resp. Ex. J45].

[203] Dr. Deisher testified that "several independent scientists have corroborated" her change points, but this information is not published. Tr. 294.

Dr. Deisher's study and her theories of causation are not consistent with other relevant and reliable knowledge, and her findings have not been reported by others or verified by epidemiological studies.[204]

3. Specificity

The third Hill criterion, specificity of the association, requires a showing that the effect of exposure on a particular outcome is specific to that outcome. Tr. 722. "An association exhibits specificity if the exposure is associated only with a single disease or type of disease." REF. MAN. SCI. EV. at 605. The rationale behind this criterion is that the "vast majority of agents do not cause a wide variety of effects." Id. at 605-6.

When asked whether this criterion had been met, Dr. Deisher testified that she is not claiming vaccines are "responsible for all childhood diseases." Tr. 220. Instead, she is studying the "relationship and the biology that would tell us how [children with autism] could be harmed by the vaccine." Tr. 220. Petitioners' theory is only designed to explain the cause of autism, not other diseases.

Dr. Fallin explained that specificity could not be assessed by Dr. Deisher's change point research. Resp. Ex. J at 5. In order to meet this criterion, Dr. Deisher would need to compare children with autism to children with other developmental disabilities and demonstrate "evidence of specificity to autism specifically as opposed to other kinds of disorders." Tr. 722. Thus, Dr. Deisher's study does not address specificity.

4. Temporal Relationship[205]

"A temporal, or chronological, relationship must exist for causation to exist. If exposure causes disease, the exposure must occur before the disease develops." REF. MAN. SCI. EV. at 601. Dr. Fallin testified that this factor is met when exposure to the cause of the disease predates the actual disease. Tr. 722-23.

Dr. Deisher testified that she did not address this criteria in her study. Tr. 220. In order to fully investigate whether vaccine exposure occurred prior to disease onset, Dr. Deisher

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[204] I stress that I am not requiring petitioners to provide epidemiological evidence of their mechanisms of causation. However, petitioners cited epidemiological evidence, so I may evaluate it. See W.C. v. Sec'y of Health & Human Servs., 704 F.3d 1352 (Fed. Cir. 2013); Grant v. Sec'y of Health & Human Servs., 956 F.2d 1144 (Fed. Cir. 1992).

[205] For purposes of this decision, I am applying the temporal relationship factor as part of my analysis of Althen Prong One, as it is a factor in the Hill criteria. This section is not meant to constitute a discussion of Prong Three of Althen, which measures the temporal relationship between the receipt of a vaccination and the onset of the injury.

testified that she would need access to the VSD[206] so that she could study children on an individual basis. Tr. 221. Dr. Fallin agreed that this criterion was not satisfied. The change point research contains imprecise dates and ecological data. Resp. Ex. J at 5.

Moreover, Dr. Fallin testified that "the field [of epidemiology] overwhelmingly now believes that the … most likely environmental susceptibility window [for ASD] is in utero," which is prior to the time that children receive vaccinations. Tr. 723. Dr. Deisher's change point study and theories of causation contemplate exposure after birth, during vaccine administration. Thus, the theory is inconsistent with current scientific knowledge with regard to exposure.

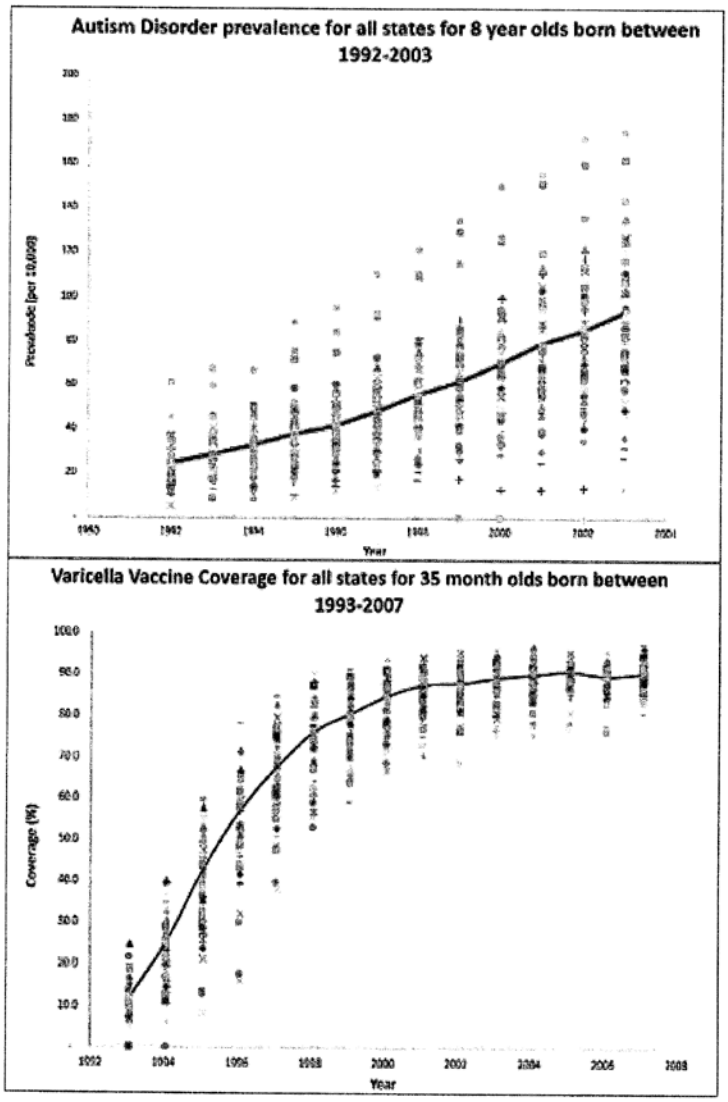
There is also an issue with regard to disease onset relevant to the criterion of temporal association. Dr. Deisher opined that autism disease onset due to her theory "could be as short as a few days … up to a few years from a first exposure." Pet. Ex. 10 at 23. "If the phenomenon is genomic insertion into a stem cell, onset … could be … even years." Id. It is not clear whether Dr. Deisher's change point study takes into account this wide range of exposure to disease onset from a few days to years.

5. Dose-Response

A "dose-response relationship means that the greater the exposure, the greater risk of disease. Generally, higher exposures should increase the incidence (or severity) of disease." REF. MAN. SCI. EV. at 603. In this case, the greater the coverage of a vaccine, the higher the prevalence of the disorder should be, if there is evidence of dose-response. Tr. 725. Dose-response is often confirmed by correlation, and the higher the correlation, the greater the evidence of dose response. Id. at 724.

Dr. Deisher testified that petitioners "clearly demonstrated evidence for a dose-response," by evaluating "autistic disorder prevalence compared to uptake" with the varicella and hepatitis vaccines. She attempts to demonstrate dose-response by displaying the graphs below, which depict autism prevalence and varicella vaccine coverage over time, respectively. Pet. Ex. 265 at 10. Recall that Dr. Deisher attributes the third change point in approximately 1995, in part, to the varicella vaccine.

[206] Dr. Deisher explains in her affidavit that "[t]he [VSD] contains data regarding immunizations and autism disorder for hundreds of thousands of children." Pet. Ex. 10 at 25. She testified that she was denied access to the VSD partly due to lack of funding. Tr. 327.



The graphs show the increase in autism prevalence over time, and the coverage and uptake of the varicella vaccine over time. Pet. Ex. 265 at 10; Tr. 725. Dr. Deisher opines that increased coverage of the varicella vaccine results in higher prevalence of autism. Id. However, the graphs raise a significant question. In the bottom graph, varicella coverage plateaus at approximately 2002, but the top graph shows that the prevalence of autism continues to increase. If the two were causally associated, one would expect that autism prevalence would level off as varicella coverage plateaus. The charts do not explain why autism continues to increase when the coverage of the varicella vaccine coverage levels out. Tr. 725. Moreover, Dr. Deisher concedes that her study "does not rule out the possibility of sociologic effects artificially elevating AD prevalence after 1996." Pet. Ex. 419 at 19. As such, I find there is insufficient evidence of a dose-response relationship.

6. Coherence

The sixth Hill criterion measures coherence with other types of evidence, including animal models. Tr. 222; Resp. Ex J at 6; Tr. 726. Dr. Deisher testified that anti-double-strand-DNA antibodies and published evidence of mutations in lymphoblastoid cell lines are evidence of "actual clinical observation in autistic children." Tr. 222. There is, however, no evidence which establishes that anti-double-strand-DNA antibodies found in autistic children are caused by vaccines. Likewise, there is no evidence that mutations in lymphoblastoid cell lines are associated with vaccines. Therefore, Dr. Deisher's testimony on this point is erroneous.

Dr. Fallin opines that coherence with other types of evidence such as animal models has not been shown. Dr. Deisher's hypothesis is not consistent with current autism research,

especially with regard to the time of exposure (prenatal vs. after birth). Resp. Ex. J at 6. I agree with Dr. Fallin that Dr. Deisher's research and theories do not meet this criterion.

7. Effect of Ceasing Exposure

The seventh Hill criterion explores whether the outcome (autism) could be prevented by removing the causal factor (vaccines). Tr. 727. "If an agent is a cause of disease, then one would expect that cessation of exposure to that agent ordinarily would reduce the risk of the disease." REF. MAN. SCI. EV. at 605.

Dr. Fallin testified that ecological studies can never meet this criterion. Tr. 727. This criterion requires an experimental study design with randomized control trials to assess exposure and outcome. Tr. 727. Even at an individual level, experimental evidence can be difficult to demonstrate, because the exposure of interest has to occur in subjects that are reasonably alike. Dr. Deisher's research reaches conclusions at an aggregate level and thus cannot meet this criteria. Id.

Dr. Deisher testified that this criterion was satisfied by her paper published in 2015, an ecological study about autism incidence following the "Wakefield scare."[207] Tr. 223. For this study, Dr. Deisher obtained autism prevalence data from five sources: two from Norway, two from the UK, and one from Sweden. She reported that the "average MMR coverage" for Norway, Sweden, and the UK fell below 90percent after Dr. Wakefield's 1998 paper. Pet. Ex. 675 at 2. During the same time frame, she reported that the prevalence of average ASDs in these same three countries decreased "substantially after birth year 1998 and gradually increased again after birth year 2000." Id. She concluded that the "Wakefield scare" resulted in decreased vaccine coverage, which "created a natural experiment that may demonstrate a causal relationship between fetal cell-line manufactured vaccines and ASD prevalence." Id. Dr. Deisher testified that when the vaccines were removed, autism decreased, and when the vaccines were reintroduced, autism increased. Tr. 218.

Dr. Arking testified that Dr. Deisher's presentation of the data could be misleading because it came from "multiple sources within a country and multiple sources across countries." Tr. 735-38. Using the same data used by Dr. Deisher, Dr. Arking hand-plotted it separately for each country, yielding different results. There was a decrease in autism for the UK, but for Norway, there was an increase, and for Sweden, there was no change and then an increase. Id. at 738. Dr. Arking then plotted data from just one of the UK studies (Wales), and that data was

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[207] In 1998, Dr. Andrew Wakefield published a paper in The Lancet, "suggesting a link between MMR and autism." Tr. 217. Dr. Deisher testified that there was widespread coverage by the media in the three countries referenced above, and "compliance with the MMR…decline[d] abruptly." Id. Subsequently, Wakefield was discredited by Kaye's paper published in the British Medical Journal, and others. James A. Kaye et al., Mumps, measles, and rubella vaccine and the incidence of autism recorded by general practitioners: a time trend analysis, BRIT. MED. J. 322 (2001). Dr. Deisher testified that once Wakefield was discredited, "compliance rose again in those countries." Tr. 217. For a full discussion of the Wakefield paper and the subsequent course of events, see Cedillo, 2009 WL 331968.

"almost flat." Tr. 739. While Dr. Arking emphasized that his illustrations and examples were cursory, they served to illustrate that using data at an aggregate level can be misleading. Id. at 740. "Every time you aggregate, you lose something." Id. Dr. Arking concluded that Dr. Deisher's paper regarding the "Wakefield scare" did not provide evidence of a decrease in vaccine coverage associated with decreased autism prevalence. Id. He also made another important point: rigorous epidemiological studies using individual level data have shown no association between vaccines and autism. If Dr. Deisher's theories were correct, studies about the MMR vaccine would have shown an association. See id. at 741-42. On these points, Dr. Arking was more persuasive.

8. Analogy to Other Known Causes

The eighth Hill criterion measures whether the hypothesized cause of the outcome is analogous to any other known causes of the outcome. Resp. Ex. J at 6; Tr. 728. According to Dr. Deisher, petitioners have presented:

> [A] large body of scientific evidence in multiple disciplines … immunology, virology, gene therapy, genetic engineering, manufacturing, process development, clinical interventions in autoimmune diseases, and actual empirical evidence from the SCID gene therapy trials, that the potential damages of the contaminants found in the vaccines are real and present; that the mechanisms of action are not only plausible, but possible.

Tr. 223. Respondent disagrees. Dr. Fallin explained that Dr. Deisher's research does not meet this criterion because "other known causes [of autism] are rare genetic anomalies that occur at the time of conception, or very close [there]after." Tr. 728. Recent research overwhelmingly shows that the greatest potential for autism risk factors points to the prenatal period. Id.

An example of an autistic disorder known to be caused by a "germline mutation," is Rett syndrome. Tr. 133, 185, 246. Dr. Deisher agrees that Rett syndrome is caused by a de novo germ cell mutation that leads to autism. Id. at 133, 185. A germline mutation is a mutation occurring in the parent's egg or sperm cells. Therefore, it is an example of a mutation occurring in the prenatal period that is known to cause autism.

I find respondent's position more persuasive. Dr. Deisher's research and theories suggesting that fetal manufactured vaccines are a cause of autism is not analogous to the current understanding of the timing or mechanisms of the potential causes of autism, or to the example of Rett syndrome and thus do not show evidence of any other analogous causes.

9. Biological Plausibility

"Biological plausibility is not an easy criterion to use and depends upon existing knowledge about the mechanisms by which the disease develops." REF. MAN. SCI. EV. at 604. "The saliency of this factor varies depending on the extent of scientific knowledge about the cellular and subcellular mechanisms through which the disease process works." Id. at 605.

With regard to environmental causes of autism, "[t]he majority of autism research to date implicates the gestational period as the window of risk."[208] Resp. Ex. J at 5. Based on existing knowledge about the mechanisms by which autism develops, respondent's experts unanimously agree that "the idea that there can be an adequate amount of human DNA transferred to the children and that then within each child enough of that can insert itself into the genome of cells in ways that would manifest disease [postnatally] is unlikely." Tr. 726.

10. Replication of the Findings

Another Hill criterion not specifically enumerated by petitioners, but generally recognized as a Hill criterion, as well as important factor to "assess whether a causal inference is appropriate," is whether the results of a study have been replicated. REF. MAN. SCI. EV. at 600. "Rarely, if ever, does a single study persuasively demonstrate a cause-effect relationship. It is important that a study be replicated in different populations and by different investigators before a causal relationship is accepted by epidemiologists and other scientists." Id. at 604.

Dr. Deisher concedes that her theories, as well as her change point study findings, have not been published by anyone else. "The need to replicate research findings permeates most fields of science." REF. MAN. SCI. EV. at 604. Without replication, it is very difficult to draw any reasonable inferences from Dr. Deisher's study or her theories.

In summary, Dr. Deisher's change point study does not offer persuasive evidence of causation based on the Hill criteria. The study does not contain any parameters by which to measure the strength of association between the vaccines at issue and the prevalence of autism. Dr. Deisher's epidemiological study has not been verified and her findings have not been

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[208] In support of this assertion, Dr. Fallin referenced studies by Patricia Rodier et al., Embryological Origin for Autism: Developmental Anomalies of the Cranial Nerve Motor Nuclei 370 J. COMP. NEUROLOGY 247 (1996) [Resp. Ex. J38]; A. Bailey et al., A Clinicopathological Study of Autism 121 Brain 889 (1998) [Resp. Ex. J2]; Bauman and Kemper, 23 INT. J. DEVL. NEUROSCIENCE 183 [Resp. Ex. J3]; Joachim Hallmayer et al., Genetic Heritability and Shared Enviornmental Factors Among Twin Pairs with Autism, 68 ARCH. GEN. PSYCHIATRY 1095 (2011) [Resp. Ex. J11]; Sally Ozonoff et al., Recurrence Risk for Autism Spectrum Disorders: A Baby Siblings Research Consortium Study, 128 PEDIATRICS e488 (2011) [Resp. Ex. J34]; Matthew Johnson et al., Functional and Evolutionary Insights Into Human Brain Development Through Global Transcriptome Analysis, 62 NEURON 494 (2009) [Resp. Ex. J19]; Irina Voineagu et al., Transcriptomic Analysis of Autistic Brain Reveals Convergent Molecular Pathology, 474 NATURE 380 (2013) [Resp. Ex. J46]; Willsey et al., 155 CELL 997 [Resp. Ex. J47]; Marilyn T. Miller, Thalidomide Embryopathy: A Model for the Study of Congenital Incomitant Horizontal Strabismus, LXXXIX TR. AM. OPTH. SOC. 623 (1991) [Resp. Ex. J29]; K. Stromland et al., Autism in Thalidomide Embryopathy: A Population Study, 36 DEVL. MED. AND CHILD NEUROL. 351 (1994) [Resp. Ex J43]; Lonnie Zwaigenbaum et al., Behavioral Manifestations of Autism in the First Year of Life, 23 INT. J. DEVL. NEUROSCIENCE 143 (2005) [Resp. Ex. J48]; and A.N. Bhat et al., Relationship Between Early Motor Delay and Later Communication Delay in Infants At Risk for Autism, 35 INFANT BEHAV. DEVL. 838 (2012) [Resp. Ex. J4].

replicated by others. Moreover, her results are directly contrary to many other epidemiological studies which do not demonstrate a correlation between vaccines and autism. The change point study does not demonstrate that exposure to vaccines containing human DNA fragments is specific to the outcome of autism. Due to the ecological design of the study, it cannot provide evidence that the vaccines were given prior to the onset of autism. Dr. Deisher's study does not show evidence of dose-response, and her hypothesis is not consistent with current autism research. She has not demonstrated that autism could be prevented by discontinuing the use of vaccines manufactured with residual DNA fragments, and her causal theories are not analogous with existing and current knowledge and understanding that the timing of the cause of autism is likely during prenatal development. To the extent that there may be environmental triggers involved in the etiology of autism, these are thought to occur during the prenatal period. Dr. Deisher has not offered a biologically-plausible mechanism by which vaccines containing residual DNA could cause autism.

ii. Epidemiological Evidence

In addition to arguing that they have satisfied the Hill criteria, petitioners assert that Dr. Deisher's change point study satisfies the following three questions, set forth in the REF. MAN. SCI. EV.:

1) Do the results of an epidemiology study reveal an association between an agent and disease?
2) Could this association have resulted from limitations of the study (bias, confounding or sampling error), and, if so, from which?
3) Based on the above analysis, and on other evidence, how plausible is a causal interpretation of the association?

Pet. Prehrg Br. at 10.

These three issues arise when an epidemiology study is used in a legal dispute. To assess "the methodological soundness of a study and its implications for resolution of the question of causation," these three questions must be addressed. REF. MAN. SCI. EV. at 554.

Respondent's counsel generally argues that Dr. Deisher's change point study is flawed, and that "no reliable scientific conclusions" can be drawn from it due to its "substandard methodology." Resp. Prehrg Br. at 7.

1. The results of Dr. Deisher's Study Do Not Reveal an Association Between Vaccines and Autism

Dr. Deisher employed an ecological study design which, by definition, is one in which data is collected about a group or groups. Generally, the goal of ecological studies is to identify a difference between different groups, so as to study disease trends in a population. While ecological studies are useful for identifying associations, "they rarely provide definitive causal answers." REF. MAN. SCI. EV. at 561. Ecological studies provide "nearly no evidence on causality." Tr. 451. That is because what appears to be a cause-and-effect relationship at the

group level may not be true at the individual level. This can lead to an ecological fallacy, such as the example given by Dr. Fallin with computer use and asthma. Therefore, Dr. Deisher's change point study, even if perfectly executed, cannot reveal an association between residual DNA in vaccines and autism.

2. Dr. Deisher's Study Has Numerous Limitations Which Render Its Conclusions Invalid

There are a number of limitations to Dr. Deisher's change point study which call into question her conclusions. There are many sources of potential error in the data used to calculate incidence and prevalence data which may have produced erroneous results. As carefully and thoughtfully explained by Dr. Fallin, the changes in diagnostic criteria changed over the time frame relevant to the study. Four different DSM editions and revisions were published, with changes to the number of symptoms needed to establish a diagnosis of autism. For example, from 1968 to 1980, symptoms that described what is now called autism were described under the diagnostic rubric for schizophrenia, childhood type. In 1980, the diagnosis "infantile autism" was published in the DSM-III. McDonald and others have suggested that the changes in diagnostic criteria accounted for a 2.2-fold higher incidence of the autism diagnosis in the California data used.

How physicians and other health care providers apply the criteria presents another issue. Because autism is a clinical diagnosis, the criteria for diagnosis are subject to the interpretation of the person applying them. There is no easy way to quantify how this problem affects prevalence data.

Once autism is diagnosed, it must be reported to be counted in incidence and prevalence data. Reporting practices changed over the time frame relevant to Dr. Deisher's study. For example, in Denmark, the prevalence of autism increased, perhaps as much as 60 percent once outpatient data and changes in diagnostic criteria were accounted for. Similarly, access to services presents an issue, which may account for why children who have not started school may be underreported. Funding for programs to treat children with autism may affect whether children are diagnosed or reported. Data may change due to "diagnostic substitution," where a certain diagnosis is required in order for a child to receive services. Physician and parental awareness, stigma, geographical location – all may affect whether accurate data is reported. The average age at the time of diagnosis continues to decrease, which has been noted by McDonald and others as a cause of the increase in autism incidence in the California data. For all of these reasons, the prevalence data in Dr. Deisher's study may not be accurate.

Another source of error which may have contributed to a false result in Dr. Deisher's change point study is the inappropriate use of R software. If an exponential or curved model had been used, as suggested by Dr. Fallin, the study may have shown different change points, or no discrete change points at all. And Dr. Deisher's analysis of the vaccine uptake data and her use of vaccine licensure dates are also problematic.

The change point study may also lack reliability due to Dr. Deisher's failure to adequately account for confounding factors. Confounding factors create interference so

as to "distort the association being studied between two variables." DORLAND'S at 403. Confounding can occur "when a confounder is both a risk factor for the disease and a factor associated with the exposure of interest." REF. MAN. SCI. EV. at 591. An example of a potential confounding factor here is paternal age. As shown by Dr. Fallin, Dr. Deisher's analysis as to the effect of paternal age on her study was inadequate.

The most glaring source of error in Dr. Deisher's study is her underlying presumption that residual DNA in vaccines cause autism. This may be viewed as "information bias" as "a result of inaccurate information about either the disease or the exposure status of the study participants or a result of confounding." REF. MAN. SCI. EV. at 585. This may also be viewed as a conceptual problem with the study. See REF. MAN. SCI. EV. at 590. This bias by Dr. Deisher to attribute the disease of autism to a vaccine-related cause affects the overall reliability and validity of the study.

Dr. Deisher's conceptual bias against the use of human fetal cells for vaccines has been identified before in other contexts.[209] In 2011, Dr. Deisher, as principal investigator for Sound Choice, applied to the NIH for funding for a study entitled, "Safety Study of Human Fetal DNA and HERVK Contaminants in Childhood Vaccines."[210] See Pet. Ex. 62. Members of the Scientific Review Group ("SRG"), noted professors from prestigious universities and medical schools, were asked to review and comment on the application. Id. at 1. Dr. Deisher proposed three studies:

> 1) A trend analysis of Varicella vaccination and autism using the Vaccine Data Safety Link database, 2) an ecological analysis of the association between MMR vaccine and autism using data collected through web searches and contact with Southeast Asian and African health officials, and 3) a lab based study to measure DNA incorporation into human cell lines.

Pet. Ex. 62 at 2.

The application was reviewed and three written critiques were issued by the SRG. The first reviewer acknowledged the importance of ongoing safety evaluations for vaccines, but expressed concern that Dr. Deisher's approach was "heavily biased, including an assessment of the current literature that fails to adequately consider the recent data that has rebuked the association between vaccination and autism." Pet. Ex. 62 at 2. The reviewer also noted additional weaknesses, including that "the concept of birth year change points is a weak approach to defining causal links between vaccine exposure and adverse outcomes." Id. The reviewer criticized the study design, stating that, "the ecological analysis proposed…is unlikely to generate significant, valid results given multiple threats to internal validity." Id.

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[209] Dr. Deisher's company, Sound Choice, is "opposed to the use of exploitation of [human embryos] for biomedical research." Tr. 239. Further, Dr. Deisher was a plaintiff in a lawsuit filed to halt federal funding for embryo-destroying stem cell research. Tr. 244. Sherley v. Sebelius, 644 F.3d 388 (D.C. Cir. 2011).

[210] The application discussed was filed as Pet. Ex. 62.

The second reviewer agreed that the ecological study design was problematic. Dr. Deisher's proposed research "relies heavily on ecological associations that would not advance this line of research." Pet. Ex. 62 at 4. The third reviewer stated that "all the epidemiological and scientific evidence suggest that there is no link between autism and vaccines. Yet, the entire application is built on this unproven link." Id. at 7.

Dr. Deisher formed Sound Choice for the purpose of informing the public about human exploitation in biomedical research and to conduct research into the link between human fetal manufactured vaccines and autism. Tr. 45. She spent 18 months working with Japanese manufacturers to develop animal cell lines and to work on licensing these vaccines in the U.S. Tr. 163-164. She also had discussions with a Japanese vaccine manufacturer, Takeda, about bringing back their animal-based MMR vaccine. Tr. 164. She had similar discussions with Merck and the Kitasato Institute. Tr. 229. Ultimately, these discussions were not successful, and Dr. Deisher did not pursue developing, or aiding in the development of vaccines to replace the current MMR vaccine used in the U.S.[211] However, her moral opposition to the use of human cell lines and her business plan to develop alternative animal manufactured vaccines are issues that raise grave concerns about her ability to present objective data and conclusions, especially when she ignores the weight of the evidence presented by countless epidemiology studies which have been performed using much more rigorous methodology.

3. Dr. Deisher's Causal Interpretation Is Not Plausible

Possible theories or mechanisms are insufficient to establish causation by a preponderance of evidence. "Expert medical testimony which merely expresses the possibility – not the probability – of the occurrence of a compensable injury is insufficient, by itself, to substantiate the claim that such an injury occurred." LaCour v. Sec'y of Health & Human Servs., 90-316V, 1991 WL 66579, at *5 (Fed. Cl. Spec. Mstr. April 15, 1991); accord Burns v. Sec'y of Health & Human Servs., No 90-953V, 1992 WL 365410 (Fed Cl. Spec. Mstr. Nov. 6, 1992), aff'd 3 F.3d 415 (Fed. Cir. 1993).

The Federal Circuit has made clear that the mere possibility of a link between a vaccination and a petitioner's injury is not sufficient to satisfy the preponderance standard. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 (Fed. Cir. 2010) ("proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence.); Waterman v. Sec'y of Health & Human Servs., 123 Fed. Cl. 564 (2015) (denying petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard). While certainty is by no means required, a plausible or possible mechanism does not rise to the level of preponderance. Id.; see also de Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1351 (Fed Cir. 2008); Capizzano, 440 F.3d at 1323.

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[211] In 2011, Dr. Deisher ceased her efforts to develop a vaccine that did not use fetal cell lines. Tr. 312.

In her expert reports and during the hearing, Dr. Deisher candidly and not infrequently acknowledged the speculative nature of her theories by using the words "possible," "possibly," and "possibility." For example, in her initial report, Dr. Deisher stated that "[w]hile not yet proven medically," in reference to her assertion that the "manufacturing process is the cause of the increase in autism." Pet. Ex. 10, ¶ 21, at 18. Throughout her reports, Dr. Deisher stated, "[w]e don't, at this point, know what the mechanism is." Id., ¶ 27, at 23. She goes on to state that, "[w]e do not yet know how the debris from the manufacturing process is causing [autism]." Id.[212]

In her second expert report, Dr. Deisher stated that "we cannot show exactly what effect these insertions are having by experimentation." Pet. Ex. 76 at 2. Again, referencing her theory of insertional mutagenesis, she says, "We do not know the exact mechanism for how DNA insertion reaches the brain to elicit autism." Id. at 31-3. Repeatedly, Dr. Deisher testified that she does not know how DNA reaches the CNS. She testified that her different theories were "possibilities" of how DNA might get into the CNS. Tr. 249. She also testified about the "possibilities" of her mechanisms. Tr. 829.

Referencing her proposed mechanism using hematopoietic stem cells and the survival advantage of certain cells, she stated "that advantage could increase the possibility." Tr. 847. As for the proposed theory related to microvesicle transport, Dr. Deisher testified that it was "a second possible way that contaminants injected into a peripheral muscle … could reach the CNS." Tr. 105-06.

Dr. Deisher's use of words suggesting her theories are speculative constitute expert scientific testimony which "merely expresses the possibility – not the probability" of her proposed theories, and thus, her opinions are insufficient to substantiate petitioners claim. LaCour, 1991 WL 66579, at *5

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[212] Although petitioners are not required to provide a specific biological mechanism, the theory they propose must be plausible. Knudsen, 35 F.3d at 548-49 ("The determination of causation in fact under the Vaccine Act involves ascertaining whether a sequence of cause and effect is 'logical' and legally probable, not medically or scientifically certain."); see also Colon v. Sec'y of Health & Human Servs., No. 04-44V, 2007 WL 268781, at *19 (Fed. Cl. Spec. Mstr. Jan. 10, 2007) ("While the [p]etitioner is not required to propose or prove that a specific biological mechanism can and did cause [the child's] death, she must still proffer a plausible medical theory that causally connects the vaccine with the injury."); Betancourt v. Sec'y of Health & Human Servs., No. 04-458V, 2007 WL 4820969, at *22 (Fed. Cl. Spec. Mstr. Dec. 10, 2007) ("[p]etitioner is not required to propose or prove definitively that a specific biological mechanism can and did cause the injury leading to his condition, he must still proffer a plausible medical theory that causally connects the vaccine with the injury alleged.").

iii. Adverse Inference Rule

In their prehearing memorandum, petitioners' counsel argue that respondent's failure to provide Dr. Deisher with access to the VSD[213] warrants application of the adverse inference rule, giving rise to "an inference that the evidence is unfavorable" to respondent. Pet. Prehrg Br. at 13-15. Petitioners' counsel further argue that Dr. Deisher's change point study should therefore be "deemed conclusive." Id. at 16.

In support of this argument, petitioners cite Federal Rule of Evidence 301[214] and Langford v. Norris, 614 F.3d 445, 462 (8th Cir. 2010). In Langford, however, the court of Appeals did not apply the adverse inference rule because there was no evidence to show that the documents at issue "were destroyed or misplaced." Further, the court stated that where a party fails to produce evidence in their control, the adverse inference "is open always to explanation by circumstances which make some other hypothesis a more natural one than the party's fear of exposure." Id. at note 8 (internal citations omitted).

Similarly, there is no evidence in this case that the VSD has been destroyed or misplaced. A formal application process is in place for researchers to access VSD data. See Resp. Ex. C at 35-37. In fact, Dr. Deisher sought access to the VSD and was denied such access prior to her involvement as an expert in this case. As previously discussed, in 2011, she applied for an NIH grant for a study that would provide access to the VSD. Tr. 245. In her application, Dr. Deisher proposed a "trend analysis of varicella vaccination and autism using the [VSD] database." See Pet. Ex. 62. The application was

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[213] Petitioners filed several motions requesting that the Court give them access to the VSD. The first motion for access to the VSD was filed on February 3, 2012, while former Chief Special Master Patricia Campbell-Smith was assigned to the case. Chief Special Master Campbell-Smith denied petitioners' motion in a detailed order filed on June 12, 2013. [redacted], 2013 WL 3368236. Shortly after the order was issued, the case was transferred to Special Master George Hastings. On July 12, 2013, petitioners filed a motion for reconsideration of Chief Special Master Campbell-Smith's Order. Respondent requested additional time to respond to the motion, which was granted, and several managed care organizations whose data are held in the VSD also filed responses. On October 24, 2013, Special Master Hastings denied petitioners' motion for reconsideration. [redacted], 2013 WL 6038670.

After I was assigned to the case, petitioners made a third attempt to gain access to the VSD on October 1, 2015. (ECF No. 164). On August 30, 2016, I denied petitioners' motion. [redacted], 2016 WL 5362878. On May 11, 2017, petitioners made a fourth attempt to renew their motion for access to the VSD during the rebuttal testimony of Dr. Deisher, which I denied from the bench. Dr. Deisher's requests for access to data from Norway and the United Kingdom were also denied. Tr. 318-19.

[214] Petitioners incorrectly cite FRE 301, which states, "In a civil case, unless a federal statute or these rules provide otherwise, the party against whom a presumption is directed has the burden of producing evidence to rebut the presumption. But this rule does not shift the burden of persuasion, which remains on the party who had it originally."

reviewed by prestigious scientists and physicians from preeminent medical schools and universities across the country. Three reviewers read and critiqued Dr. Deisher's application, providing specific reasons for denying it. See Id. One reviewer concluded that the "proposed methods are weak" and that there were "major methodological concerns throughout." Id. at 2. Another said there was inadequate "evidence of prior experience working with [the VSD] or similar large scale epidemiological databases." Id. at 3. Another reviewer stated "[t]he investigator is not trained as a statistician or epidemiologist and does not acknowledge the assumptions and complexities of interpreting data analyzed in the way it is proposed." Id. at 5. With regard to Dr. Deisher's 2011 application for use of VSD data, the reviewers gave reasonable explanations as to why Dr. Deisher was not granted access to VSD data.

Once Dr. Deisher became an expert in this case, petitioners filed several motions seeking access to the VSD. Each time, there was a detailed and reasoned order issued explaining the basis for denial of the motion. There is no evidence of bad faith or negligence by respondent. As such, the adverse inference rule is not applicable. Likewise, there is no support for petitioners' assertion that Dr. Deisher's study "should be deemed conclusive." Pet. Prehrg Br. at 16.

Previously, I stated:

> [A] party seeking an adverse instruction on the basis that evidence was not produced in time for trial must show: (1) that the party having control over the evidence had an obligation to timely produce it; (2) that the party that failed to timely produce the evidence had a "culpable state of mind"; and (3) that the missing evidence is "relevant" to the party's claim or defense such that a reasonable trier of fact could find that it would support that claim or defense.

[redacted], 2016 WL 5362878, at *8 (citing Residential Funding Corp. v. DeGeorge Financial Corp., 306 F.3d 99, 107 (2d Cir. 2002)). Now, as then, it is reasonable to conclude that the adverse inference rule is not appropriate in this situation.

iv. Summary of Analysis of Petitioners' Theories of Causation

At the outset of the hearing, petitioners identified their focus – to show that DNA fragments in vaccines "can cause damage to brain cells by disrupting their function, manifesting clinically as symptoms, now diagnosed as autism."[215] Pet. Prehrg Br. at 3. Respondent countered by identifying "a fatal shortcoming" – the failure to present a "plausible scientific

[215] Petitioners also state in their prehearing memo that DNA fragments in vaccines "can cause an encephalopathy manifesting clinically as autism." There is no evidence in this case that V.J.M. had encephalopathy. To the extent that they argue that DNA fragments or HERV-K fragments cause encephalopathy, that argument is also rejected, for all the reasons cited herein.

explanation" as to how DNA fragments or HERV-K fragments in the vaccines "reach the brain." Resp. Prehrg Br. at 9. I agree with respondent that petitioners have failed by preponderant evidence to provide a plausible scientific explanation as to how fragments of DNA or HERV-K reach the brain of a child so as to cause ASD. There are, however, many other problems with petitioners' theories that are just as fatal to their claim as the problems with petitioners' epidemiologic evidence discussed above. As for HERV-K retroviruses, Dr. Deisher concedes that current studies as to these retroviruses are "observational" and that their role in causing disease is not known. As for DNA fragments, Dr. Deisher did not proffer preponderant evidence showing that retrograde transport was a viable hypothesis. While viruses have been shown to travel from neuron to neuron in a retrograde manner, the petitioners provided no study or experiment to show that peripheral intermuscular injection of DNA fragments from vaccines travel in the same way, neuron to neuron, in a retrograde fashion.

Dr. Deisher's hypothesis about microvesicle transport is similarly undeveloped. Assuming that microvesicles are transported in the circulatory system, Dr. Deisher did not provide a plausible hypothesis as to how they could cross the BBB. As for Dr. Deisher's most likely hypothesis, that DNA fragments are taken up by hematopoietic stem cells, she failed to adequately explain and provide evidence of how stem cells cross the blood brain barrier, reach the brain and cause disease. While she suggested that vaccination might set up an immune response, or an ill child might have an infection at the time of vaccination, either of which might allow a breakdown of the BBB so that DNA fragments could reach the brain, the evidence was woefully lacking.

Another fundamental flaw is that there is no evidence that residual DNA in vaccines cause genetic mutations. Petitioners provided preponderant evidence that ASD is associated with many different mutations, including de novo mutations. But there was no evidence presented that any mutation associated with any disease, let alone ASD, is caused or could be associated with residual DNA in the vaccines at issue. Dr. Deisher readily conceded that there is a problem of evidence. She advocates for more studies to determine whether residual DNA in vaccines presents a safety issue. But a lack of evidence is not evidence.

In contrast, Dr. Arking carefully and persuasively testified about the current state of knowledge regarding genetics. Dr. Arking's report, testimony, and medical literature provide a more credible and plausible explanation as to how mutations, particularly de novo mutations, play a causal role in the development of autism.

Similarly, petitioners failed to provide preponderant evidence that residual DNA or HERV-K retrovirus fragments in vaccines trigger an autoimmune process that causes ASD. The studies cited by petitioners about auto-antibodies did not support their hypothesis. All that can be said is that auto-antibodies have been found in autistic individuals. What this means is simply not yet known.

The testimony by Dr. Burkhard drawing an analogy to PANDAS was not persuasive. Neither was her testimony as to the findings on DTI studies and how they support petitioners' theories. She provided no evidence to tie together the findings on the imaging studies with an autoimmune response secondary to residual DNA or HERV-K fragments from vaccines. Her

testimony on this point also ignored the caveat issued by the author of the study cited, that DTI studies of autism should be interpreted with caution.

Dr. Deisher specifically opines that her causal theories apply to autism caused by de novo mutations, which account for approximately 10 percent of ASD cases, and/or autoimmunity, which accounts for 40 percent of ASD cases. See Pet. Ex. 10 at 6; Pet. Ex. 76 at 25. However, her change point study appears to address all cases of autism, regardless of etiology. Additionally, Dr. Deisher opined that her causal mechanisms applied to "regressive" autism. Again, her change point study does not appear to address only the regressive form of autism, which accounts for approximately one-third of all autism cases. Thus, there appear to be disconnects between her change point study and her causal mechanisms, which also call into question their validity.

My decision in this case does not turn solely on the deficiencies in Dr. Deisher's change point study. Even if the study provided credible and reliable evidence of the three change points presented, petitioners failed to provide preponderant evidence of causation because their proposed theories lack an evidentiary foundation. Many of Dr. Deisher's hypotheses are pulled from medical articles and are taken out of context. Petitioners' counsel argues that it is acceptable for experts to "extrapolate from existing data," and that the "weight to be given to an expert's opinion is based, in part, on the size of the gap between the science and the opinion offered." Pet. Prehrg Br. at 7 (citing Cedillo, 2009 WL 331968). However, the gaps between the science and the opinion offered in this case are too large and too many.

Moreover, petitioners often make conclusory statements not supported by the evidence. For example, petitioners state that DNA fragments can "enter the brain via any gap in the [BBB]," but this was not shown by preponderant evidence. See Pet. Prehrg Br. at 1-2. They state that DNA fragments "disrupt[] cell function," but offer no evidence that this could occur. See id. They state that the DNA fragments from the vaccines at issue are "homologous with the protein in the tissues of the vaccine recipient." Id. But this was not shown. They also state that "the injury (from residual DNA from vaccines) can be detected in relevant areas of the brain." Id. Again, this was not shown. Ultimately, petitioners concede that, "as is the case with many human diseases, we know what happens but we do not know how it happens." Id. But here, they have provided no evidence of "what happens" or "how it happens."

Petitioners ask me to consider the following concept of biological plausibility: "The concept of biological plausibility…asks whether the hypothesized causal link is credible in light of what is known from science and medicine about the human body and the potential offending agent." Pet. Prehrg Br. at 3 (citation omitted). I agree with petitioners that "substantial evidence means 'more than a mere scintilla' and 'such relevant evidence as a reasonable mind might accept as adequate to support a conclusion.'" Pet. Prehrg Br. at 7. I find, however, that petitioners have failed to show by preponderant evidence that residual DNA fragments and/or HERV-K fragments from the vaccines at issue in this case cause autism. Petitioners have failed to prove by preponderant evidence Dr. Deisher's theory of vaccine-caused autism, and therefore have failed to meet their burden under Prong One of Althen.

X. Conclusion

I extend my deepest sympathy to the petitioners and V.J.M. for the difficulties and challenges they have faced. However, I cannot decide this case based upon my sympathy for the family but by my analysis of the evidence.

For the reasons discussed above, I find that petitioners have not established entitlement to compensation and thus that their petition must be dismissed. **Therefore, this case is dismissed for insufficient proof.**[216] **The Clerk of Court SHALL ENTER JUDGMENT in accordance herewith.**

IT IS SO ORDERED.

s/ Nora Beth Dorsey
Nora Beth Dorsey
Chief Special Master

[216] The 23 cases in the mini-omnibus include: J.M. et al. (02-010V), J.K.R. et al. (09-143V), Fuesel (02-095V), E.H. et al. (09-206V), Arranga (02-1616V), B.W. (14-375V), J.H.R. et al. (03-1156V), M.P. et al. (07-750V), Coiro-Lorusso (04-258V), S.O. et al. (08-125V), Young (05-207V), Graddy (08-416V), C.B. et al. (05-1168V), Eworonsky (04-992V), C.B. et al. (08-131V), King (05-717V), F.J.D. et al. (08-254V), P.R. et al. (10-096V), F.J.D. et al. (08-253V), Torres (15-561V), N.P. et al. (08-388V), M.J. et al. (16-434V), and A.E.R. (17-470V). This Decision applies to all of these cases.