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IN THIS ISSUE

Ali Spindler and Stephen G.A. Myers report on the emerging use of genetic evidence in civil litigation and provide insights on how this rapidly-advancing science can prove or disprove specific causation.

Cracking the Code: Genetic Evidence and Specific Causation

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As the concept of genetics becomes more common in everyday life, from popular DNA kits like 23andMe to treating physicians specializing in personalized medicine, genetic evidence is also becoming increasingly common in civil litigation. Moving forward, attorneys should be familiar with genetic terminology, be prepared to evaluate how genetic evidence can be utilized by both sides, and think strategically about how to use or diffuse causation arguments based on genetics.

In tort litigation, the plaintiff bears the burden of proving both general and specific causation. General causation — whether the product or substance at issue is capable of causing plaintiff's injury — is typically established though epidemiological studies that evaluate risk in large groups of people. Specific causation — whether the product or substance in fact caused plaintiff's injury — is often proven or disproven by opposing experts who apply a differential diagnosis, then offer opinions about the most likely cause of the injury. Emerging research in the fields of genomics and biotechnology have the potential to radically change the specific causation analysis. Genetic evidence can disprove the alleged cause of plaintiff's injury by uncovering other, more likely causes. In some cases, DNA evidence can prove that a plaintiff would have developed the same injury, regardless of whether she used or was exposed to a defendant's product, because of her inherited genetic makeup. In other cases, genetics can reveal that a plaintiff has no molecular "markers" of exposure to the substance at issue. All of these tools can be used to defeat a plaintiff's theory of specific causation. But genetic evidence is not without risk, because it can also be used in the opposite way, to prove plaintiff's case.

I. Introduction to Genetics and Genomics

Genetics refers to the study of particular genes, while genomics is the study of the entire human genome. The genome encompasses a person's full set of DNA, or genetic material.[1] It contains information about a person's growth and development, traits like hair and eye color, and potential to develop various diseases and medical conditions. The field of genomics has rapidly developed since the Human Genome Project was completed in 2003 and provided a molecular roadmap for the human being. By studying the genome, scientists have identified new methods for diagnosing, treating, and preventing disease.[2]

Testing for genetic variants and mutations is increasingly being performed by treating physicians. All major cancer centers in the United States now recommend genetic testing to diagnose cancer, identify its

[1] *See Genome*, NCI Dictionary of Cancer Terms, Nat'l Cancer Instit., https://www.cancer.gov/publications/dictionaries/cancer-terms/def/genome (last visited Sept. 23, 2019).
[2] *See id*.

causes, and provide targeted therapy.[3] This testing is crucial for cancer and other complex diseases, which rarely occur from one mutation; such diseases often arise as a result of several mutations in a few key genes. If genetic testing has not already been done by a plaintiff's treating physician, it can be accomplished during litigation with a routine blood sample or cheek swab.

From that sample, scientists can perform v analyses. These include whole genome sequencing, whole exome sequencing, testing for specific panels of variants in multiple genes, and testing for a single gene mutation. The first option, whole genome sequencing, identifies and analyzes the entire structure of a person's DNA, which encompasses approximately three billion nucleotides.[4] Whole exome sequencing maps only the protein-coding regions of a person's DNA, which are about one percent of the total DNA structure.[5] The exome contains approximately 85 percent of all variants known to cause rare and common diseases.[6] Both whole genome and whole exome sequencing evaluate millions of DNA fragments to identify various mutations that can contribute to a person's medical condition. By contrast, panel testing screens for mutations in particular genes that are known to increase risk of developing the disease at issue.[7] A panel test can evaluate hundreds or even thousands of relevant genes. Most conservatively, testing can be done on only one or two genes of interest. All testing methods require expensive laboratory equipment and can take weeks for completion. When selecting a laboratory for any analysis, counsel should ensure the facility is certified to perform the testing sought.

Scientists often prefer to obtain the greatest amount of data possible through whole genome or exome sequencing, because these methods can identify the greatest number of potential genetic contributors to a person's medical condition. On the other hand, such extensive testing during litigation may implicate privacy concerns, if a plaintiff argues defendants have no valid basis to crack open her entire genetic code to search for only a few relevant variants. Sequencing may also be too time-consuming or costly to complete in fast-moving cases. To that end,

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[3] *See, e.g., Familial Cancer Program*, Mayo Clinic, https://www.mayoclinic.org/departments-centers/familial-cancer-program/overview/ovc-20198527 (last visited Sept. 23, 2019); *Genetic Testing*, MD Anderson Cancer Ctr., https://www.mdanderson.org/prevention-screening/family-history/genetic-testing.html (last visited Sept. 23, 2019).

[4] *Whole-genome sequencing*, NCI Dictionary of Genetics Terms, Nat'l Cancer Instit., https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/whole-genome-sequencing (last visited Sept. 23, 2019).

[5] *Whole-exome sequencing*, NCI Dictionary of Genetics Terms, Nat'l Cancer Instit., https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/whole-exome-sequencing (last visited Sept. 23, 2019).

[6] Choi, et al., *Genetic diagnosis by whole exome capture and massively parallel DNA sequencing*, 106 Proc. Nat'l Acad. Sci. 19096 (2009).

[7] *Multiple-gene panel test*, NCI Dictionary of Cancer Terms, Nat'l Cancer Instit., https://www.cancer.gov/publications/dictionaries/cancer-terms/def/multiple-gene-panel-test (last visited Sept. 23, 2019).

because panel testing for a subset of mutations is a more narrowly-tailored analysis, it is arguably more likely to reveal relevant and probative information about the true cause of plaintiff's condition. Panels are currently being developed for a host of diseases, and more options are becoming available every year. However, experts typically discourage screening for a single mutation, because such limited testing will invariably leave out other relevant, and potentially more significant, information about the cause of a person's medical condition. For that reason, experts recommend at least screening for a panel of relevant mutations when possible.

II. Genetic Evidence in Civil Cases

Although genetic testing has been less commonly performed in civil litigation than in paternity or criminal cases, courts have permitted the collection of blood samples for genetic analysis in civil cases. Rule 35 of the Federal Rules of Civil Procedure – and similar rules in state courts – permits physical examination of a plaintiff whose physical health is in controversy. Such examination may include genetic testing.[8] Additionally, courts are admitting evidence of prior genetic testing performed by plaintiffs' treating physicians, and experts can rely on that information.

To date, defendants have used genetic evidence in civil litigation involving products liability, toxic torts, and medical malpractice. These cases have encompassed a wide range of substances and/or conduct at issue, including vaccines, medications, children's products, pesticides, benzene, asbestos, and talc, among others. When possible, defendants have sought to prove alternative causation through genetic evidence. In other cases, defendants have used genetic evidence to point out additional factors that likely contributed to the injury, in an effort to dispel causation or reduce damages.

For example, genetic evidence has been used to undermine plaintiff medical experts' differential diagnoses and refute their opinions on specific causation. In *Hendrix ex rel. G.P. v. Evenflo Co.*, plaintiff alleged that an infant car seat failed to protect her child during an accident.[9] As a result, she argued that the infant sustained head and spinal cord injuries that caused him to develop Autism Spectrum Disorder ("ASD") and a cyst in his spinal cord that could cause paralysis.[10] Plaintiff's medical expert opined that the child's injuries during the accident were the sole cause of his ASD, and he claimed to have eliminated other causes for it.[11] He based that on the fact that the infant had prior chromosome testing, genetic testing for Fragile X Syndrome (linked to developmental

[8] *See Burt v. Winona Health*, No. CV 16-1085, 2018 WL 3647230, at *3 (D. Minn. Aug. 1, 2018) ("Genetic testing, including [whole exome sequencing], is therefore within the array of examinations that Rule 35 envisions."); *but see Fisher ex rel. X.S.F. v. Winding Waters Clinic, PC*, No. 2:15-cv-01957-SU, 2017 WL 574383 (D. Or. Feb. 13, 2017) (denying request for sequencing).

[9] 255 F.R.D. 568, 574-75 (N.D. Fla. 2009), *aff'd by Hendrix ex rel. G.P. v. Evenflo, Co.*, 609 F.3d 1183 (11th Cir. 2010).

[10] *See id*.

[11] *Id*. at 597.

and cognitive disorders), and prenatal evaluations, all of which were normal.[12] The court found the expert's opinions unreliable, because he failed to consider numerous potential causes for the child's ASD, including at least 91 other genes linked to autism.[13] Further, the court rejected his reliance on a single test to rule out other genetic causes: "Given the plethora of genetic theories for autism, 'ruling out' Fragile X as a possible cause…far from eliminates all genetic causes of his ASD, let alone the other multitude of factors that have been linked to autism or ASD." [14] The court excluded the expert's opinions under the *Daubert* analysis.

Defendants have also used genetic evidence to argue that, more likely than not, plaintiffs' injuries were caused by inherited genetic factors, rather than the substance or conduct at issue. Courts have repeatedly accepted genetic testing results in cases brought under the National Vaccine Injury Compensation Fund, in which plaintiffs alleged their children's medical conditions were caused by vaccines. In *Snyder v. Sec'y Health & Human Servs.*, for example, parents claimed their children developed seizures from the diphtheria-tetanus-pertussis vaccine.[15] Defendants introduced genetic test results that had been performed by one child's treating physician, which revealed that she carried genetic mutations associated with seizure disorders.[16] In light of that evidence, the court held the child's parents were unable to establish that but-for the vaccine, she would not otherwise have suffered seizures.[17]

Additionally, in *Bowen v. E.I. De Pont De Nemours and Co.*, plaintiffs claimed that children developed birth defects as a result of their mothers' exposure to agricultural products during pregnancy.[18] The lower court ordered one child to undergo genetic testing for mutations associated with medical conditions similar to the mother's.[19] That testing revealed that the child had an inherited mutation known to cause CHARGE syndrome, a disorder associated with developmental abnormalities during infancy or early childhood. Plaintiff's medical expert opined that the child's genetic variant interacted with defendants' product to cause her injury.[20] After finding that the expert was unqualified to testify about genetics and that his opinions were not based on reliable science, the court found "no evidence of any cause other than [plaintiff's genetic] mutation" and upheld summary judgment in favor of defendants.[21]

[12] *Id.*
[13] *Id*. at 598.
[14] *Id*.
[15] 553 F. App'x 994 (Fed. Cir. 2014).
[16] *Id*. at 996-97.
[17] *Id*. at 1003.
[18] No. Civ. A. 97C-06-194 CH, 2005 WL 1952859 at *5 (Del. Super. Ct. June 23, 2005).
[19] *Id*. at *5.
[20] *Id*. at *6.
[21] *Id*. at *11.

III. Alternative or Exacerbating Causes: Genetic Predisposition and Susceptibility

The prior examples highlight the role of potential genetic "predisposition" in causing a specific injury. Predisposition is the likelihood that a person will develop a medical condition solely due to inherited genetic variants. That predisposition occurs regardless of external factors or exposures to particular substances. For example, approximately 44 percent of women who inherit a BRCA1 mutation, and 17 percent of women with an inherited BRCA2 mutation, will develop ovarian cancer, independent of exposure to alleged carcinogens such as talc.[22] Researchers have uncovered inherited mutations that predispose individuals to certain diseases normally associated with exposure to toxins, such as benzene, radiation, tobacco, and asbestos.

Predisposition may implicate the related concept of genetic "susceptibility." Susceptibility is the increased likelihood that an external factor, such as exposure to a substance, will cause injury in a person due to his or her specific genetic makeup. This can present another version of the "eggshell plaintiff" theory. Not all genetic mutations are associated with increased susceptibility to disease or injury, but courts, attorneys, and even experts sometimes refer to predisposition and susceptibility interchangeably. This confusion can undermine defense arguments that a plaintiff was predisposed to the same injury, regardless of external factors. Thus, it is critical for counsel to understand the difference between predisposition and susceptibility and to be aware of the potential for susceptibility arguments before raising genetic defenses in any case.

One example of the tension between genetic predisposition and susceptibility is BRCA-associated protein 1 ("BAP1") and its role in talc and asbestos litigation. Inherited BAP1 mutations are associated with development of mesothelioma. Currently, scientists are divided as to whether BAP1 mutations cause predisposition to developing mesothelioma, independent of asbestos exposure, or increase susceptibility to developing mesothelioma after exposure. Thus, both sides can make countervailing arguments about the significance of the BAP1 mutation. It should be noted, however, that numerous genetic variants are linked to mesothelioma and may not carry the same concerns as BAP1 on predisposition and susceptibility. Evidence of such inherited mutations, even if coupled with a BAP1 mutation, may support more viable alternative causation arguments for defendants.

Despite the controversy over BAP1, courts have permitted testing for inherited BAP1 mutations. In *Thrash v. Boeing Co.*, in which plaintiff alleged he developed peritoneal mesothelioma from asbestos exposure, the court granted defendants' motion to compel

[22] *BRCA Mutations: Cancer Risk and Genetic Testing*, Nat'l Cancer Instit., https://www.cancer.gov/about-cancer/causes-prevention/genetics/brca-fact-sheet (last visited Sept. 25, 2019).

a blood sample to screen for the BAP1 mutation.[23] Defendants argued that an inherited BAP1 mutation would "make it a certainty or near certainty" that plaintiff would have gotten that cancer, regardless of asbestos exposure.[24] Plaintiff objected for privacy concerns and relevancy, arguing that the mutation would only make him more susceptible to getting cancer from asbestos.[25] Both sides submitted affidavits from medical experts with differing opinions on the significance of the inherited BAP1 mutation.[26] With respect to plaintiff's privacy, the court reasoned that defendants' compelling interest in discovering a mutation that could disprove causation outweighed plaintiff's privacy interest in his genetic information.[27] Further, the court refused to limit discovery based on competing expert opinions about the BAP1 mutation causing predisposition or susceptibility to mesothelioma.[28] The court found defendants had shown good cause and a compelling need to perform genetic testing. Notably, the court only permitted (and defendants only sought) testing for the limited purpose of identifying a hereditary BAP1 mutation; the court did not permit testing for other, potentially relevant mutations.[29] Similarly, other courts have permitted genetic testing for inherited mutations in mesothelioma cases.[30] At least two courts have admitted evidence of plaintiffs' inherited BAP1 mutations at trial, although the juries did not reach the issue of alternative causation in either case.[31]

IV. Signatures for Causation: Genetic Biomarkers

Additionally, as genetic research progresses, scientists are identifying biological markers to confirm whether a person was exposed to a particular substance or not. These "biomarkers" are biologic and molecular signatures of exposure to different substances. Genetic biomarkers, which show whether a person's DNA reflects changes consistent with exposure, have already been identified for certain chemicals and medications. Research is underway to identify DNA markers for other substances. As new biomarkers are detected, they have the potential to disprove the alleged cause of a plaintiff's injury (*i.e.*, exposure to a substance or product) and prove its true cause.

[23] No. 17-cv-01501-JST, 2018 WL 2573097 (N.D. Cal. Mar. 2, 2018).
[24] *Id*. at *1.
[25] *Id*. at *2.
[26] *Id*. at *1, 3.
[27] *Id*. at *3.
[28] *Id.*
[29] *Id*. at *4.
[30] *See, e.g.*, *Bergstrom v. 84 Lumber KCG, Inc.*, No. 1322-CC09325 (Circuit Court for City of St. Louis, State of Missouri); *Lamb v. CertainTeed Corp.*, No. C15 00057 (Contra Costa Superior Court, State of California); *Lanzo v. Cyprus Amax Minerals Co.*, No. L-7385-16 (Middlesex County Superior Court, State of New Jersey) (allowing testing in a talc-asbestos case); *Ortwein v. CertainTeed Corp.*, No. RG13701633 (Alameda County Superior Court, State of California).
[31] *Lamb v. CertainTeed Corp.*, No. C15 00057 (Contra Costa Superior Court, State of California); *Ortwein v. CertainTeed Corp.*, No. RG13701633 (Alameda County Superior Court, State of California).

For substances with identified molecular biomarkers, courts have accepted genetic evidence as probative of specific causation. In *Henricksen v. ConocoPhillips Co.*, plaintiff claimed to have developed Acute Myelogenous Lymphoma ("AML") from exposure to benzene.[32] AML can be classified as primary, meaning that it is "idiopathic" or unrelated to external factors, or secondary, meaning that it is caused by external factors like chemical exposures. Researchers have identified specific chromosomal changes (biomarkers) that indicate whether a person is likely to have primary or secondary AML.[33] In *Henricksen*, plaintiff showed no signs of any chromosomal abnormality, which strongly suggested that his AML was primary, not caused by benzene exposure.[34] Additionally, plaintiff's cancer was a genetic subtype not associated with chemical exposures.[35] The court held plaintiff's medical expert unreasonably failed to consider genetic evidence, as well as other causes of plaintiff's AML, and excluded him under *Daubert*.[36]

Just as biomarkers can be used to refute alleged causation, however, the reverse can also be true. In *Walsh v. BASF Corp.*, plaintiff alleged that he developed AML from exposure to chemicals in pesticides.[37] In support of his specific causation opinion, plaintiff's medical expert pointed to test results showing that plaintiff had two chromosomal abnormalities consistent with secondary AML.[38] Stated differently, he relied on evidence of genetic biomarkers for chemical exposure. The court found that the expert's reliance on those chromosomal changes, coupled with use of a differential diagnosis to rule out other causes of plaintiff's AML, was admissible under the *Frye* analysis.[39] In such an instance, defense counsel could offer countervailing expert testimony about the biomarkers' significance or attempt to resolve the case.

V. Conclusion

New developments are rapidly being made in the field of genomics, and courts are increasingly accepting genetic evidence in civil litigation. In the right cases, genetic evidence can be a powerful tool to dispel specific causation. By understanding the basics of genetic predisposition, susceptibility, and biomarkers, as well the practicalities of genetic testing, attorneys can strategically incorporate this science into their practices.

[32] 605 F. Supp. 2d 1142 (E.D. Wash. 2009).
[33] *Id*. at 1149-50.
[34] *Id*. at 1150.
[35] *Id*.
[36] *Id*. at 1162-63.
[37] 191 A.3d 838 (Pa. Super. 2018).
[38] *Id*. at 841.
[39] *Id*. at 848.

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