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A New Smoking Gun in Civil Litigation

It is well established that genetic and inherited traits play a major role in the development of cancer and other diseases. Genomic science is rapidly evolving and findings its way into our legal system and providing a better understanding of causation evidence. This roundtable discussion will address typical considerations of employing genomic science in litigation including cost, requirements to perform the testing and gain Court approval, along with the admissibility of the findings. We will also discuss cases where genomic science are being used and the responses and opposition by plaintiffs' attorneys.

I. Genetics 101

Everyone has heard of genetic testing and DNA analysis being performed in criminal cases and significantly used to exonerate defendants, even those that were previously convicted and have been sitting on death row for years. The basics of DNA analysis can also apply to civil litigation and as this science continues to develop, the scope of its use and reliability as a litigation tool will further develop.

A rudimentary understanding of genomic science as applied to civil litigation is necessary to take the first step in determining whether genetic testing and DNA analysis is appropriate to assist your client in defending a particular claim.

A. Genes and DNA

1. 46 Chromosomes, 23 Pairs (half from mother and half from father)

Each of the billion+ cells in the human body contains 23 pairs of chromosomes for a total of 46 chromosomes. 23 chromosomes are maternal and 23 are paternal. Chromosomes contain your genes, which number approximately 25,000.

2. Mutations

Genetic disorders result from a gene or genes that become altered or mutated for no reason or in response to certain stimuli. A dominant genetic disorder is one that occurs when one copy of a gene pair experiences a mutation. When both copies of the gene pair have to experience mutations for a genetic disorder to occur, that is a recessive disorder.

A child conceived by a set of parents in which one has the mutated gene and the other does not, has a 50% chance of inheriting the mutated gene. That child also has the chance to develop the mutated gene on its own, which is referred to as a *de novo* mutation.

3. Germline and Somatic Mutations

Gene mutations can be a source of cancer. Mutations come in two types – Germline and Somatic. Germline mutations are present in the sperm or egg, and are heritable. Somatic mutations occur only in non-germline tissues and are non-heritable. Most cancers result from mutations in somatic cells.

Mutations can arise from environmental mutagens such as asbestos, benzene, radiation, and other naturally occurring and man-made chemicals; from normal cell metabolism; randomly from spontaneous errors in DNA replication and repair (*de novo*), or can be familial.

4. Familial Genetic Predisposition to Cancer Unrelated to Exposure

A combination of factors are indicative that a certain cancer is hereditary in nature and not due to any exposure to a mutagen. Those factors are:

- Cancer in two or more relatives on the same side of the family;
- Cancer diagnosis at an early age, generally under 50;
- Multiple primary tumor;
- Bilateral or multiple rare cancers;
- Tumors consistent with specific type of cancer such as cancers of the blood and breast and ovary;
- Evidence of autosomal dominant transmission meaning getting it from first degree relatives; and,
- Ancestry.

Benzene is a known carcinogen and Myelodysplastic syndromes (MDS) and Acute Myelogenous Leukemia (AML) associated with it. There are four familial gene variants well identified in scientific literature as RUNX1, CEBPA, GATA2 and TERT that are found in patients diagnosed with MDS and/or AML.

5. Susceptibility (genetic variation, inherited factors, metabolism, cell growth and cell repair)

There are also inherited genetic polymorphisms (genetic variant) that can increase a person's susceptibility to metabolize benzene into its toxic compounds. In other words, two people exposed to the same amount of benzene in the air may metabolize it differently depending on their genetic make-up. This assessment requires examination of genes involved in benzene metabolism (MPO, EPHX1, GSTP1), genes that protect against benzene toxicity (NQO1), genes that control hematopoietic growth and differentiation (IL1A, IL4, IL12A, VCAM1, VEGF) and genes involved in DNA damage repair of which there are approximately 12.

II. Carcinogens and Exposure

Currently, epidemiology plays a significant role in proving or disproving a plaintiff's claims in toxic tort litigation. However, that science is focused on a general population and then applying the findings relevant to a general population to the individual plaintiff. Epidemiology is also necessary to support Plaintiffs' claims of general causation and there is little dispute that such assessment of general causation is valid. The crux of a toxic tort claim however is the individual's claim of exposure and whether that exposure is sufficient to support specific causation. The emerging genomic science applicable to litigation will finally allow us to move beyond epidemiologic influence on an individual's claims and specific causation. Thus, genomic science will continue to progress in its scope relevant to litigation and evolve into a definitive "smoking gun."

1. Asbestos, Benzene, Radiation, and Chemicals

Asbestos is certainly the foremost toxic tort and its demise has been rumored for years. In reality that demise will eventually occur and such claims have certainly decreased. Thus, plaintiffs' attorneys continue in their efforts to diversify. Using epidemiologic principals and research, scientists have been able to identify numerous substances that known or probable carcinogens.

There are over 100 substances that are known to be carcinogenic to humans as established by the International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP). The most recent and depressing in the news is bacon. Thus it is only a matter of time until we see the case of John Q Public vs. Bacon Producer X, alleging some type of cancer diagnosis from eating a pound smoky goodness every week. All it takes for such a claim to arise is to have a plaintiff to claim they ate a lot of bacon, they were diagnosed with a cancer that has some chance (no matter how small) of being related to consumption of bacon, and a willing plaintiffs' attorney.

How many times do you think a Plaintiff's attorney was contacted by someone that had any amount of exposure to a known human carcinogen and turned that individual away because they felt the exposure was not sufficient to cause that person's cancer? Likely none.

Genomic science has clear potential to help us determine whether toxic torts claims are legitimate by putting the focus on the individual's claims of exposure and providing concrete evidence of alternative causation. Prominent toxic tort litigation is still ongoing with regard to asbestos and continues to increase for benzene, radiation, and chemical exposure. Some of the specific genes at issue in benzene litigation were noted above. A gene known as BAP1 has now been identified that can strongly predispose an individual to mesothelioma. It remains to be seen how successful alternative causation based on genetics will be in front of juries, but the groundwork is be laid.

Below are case studies for two active cases in which Mr. Hillsley and Mr. Shafer are involved alleging benzene exposure.

2. Presentation of Case Study "A" (34 year old refinery worker diagnosed with AML)

This individual is deceased after a year-long battle with AML. He has two surviving children and the Plaintiff's economic expert puts his economic loss in excess of four million dollars. He was a union employee that started working in various oil refineries around the Philadelphia area and one in Ohio. He was first a laborer and then a boilermaker. Due to the nature of union work over an 8 year period (2003-2011) in which he was working in refineries, he actually only worked in such refineries for a total time of a little over a year. Anyone familiar with refinery operations will know that these facilities are some of the most highly regulated places of employment due to a mixture of security, safety, and health concerns.

OSHA sets the standard for permissible levels of benzene exposure at 1.0 ppm per eight hour time-weighted average (TWA). This standard has been in place since 1978. Thus, is highly unlikely that exposures greater than the OSHA standard can ever occur especially in today's well regulated work environment and even less likely in highly regulated refinery work.

Through discovery in this case the defendants learned that Plaintiff's maternal grandfather was diagnosed with AML in his 30s and later died as a result. As such, the facts of the case indicate that Plaintiff's claims of developing AML from his alleged benzene exposure appear to have no basis in fact.

The defendants elected to take the necessary steps to proceed with genetic testing. Non-cancerous tissue was located. A motion for approval to conduct genetic testing was filed and argued before the Court. The Court approved the proposed plan. The non-cancerous tissue was then retrieved and provided to a pathologist to make slides that could then be used by a geneticist to perform the full scale genetic testing and DNA analysis. The results did not show a familial developed AML, but provided significant evidence that the Decedent's AML was not benzene induced, but was clearly a *de novo* AML.

Plaintiff's counsel was provided ample opportunity to be involved in the genetic testing aspect and sufficient tissue was preserved for Plaintiff's own analysis. Plaintiff's counsel elected to not pursue such analysis.

3. Presentation of Case Study "B" (24 year old in the military, development of AML)

This individual died at the age of 24 years old. Plaintiffs allege that the decedent was exposed to solvents, paints and jet fuels that caused the development of his AML. The decedent's father was diagnosed and successfully treated for Hodgkin's Lymphoma.

This individual was an air framer who worked on helicopters in the military and was assigned to the department that removed hazardous waste materials from 2004 to 2008. He

received OSHA and military training on the proper removal of hazardous materials. However, it appears the military actually removed any materials that the state of California determined to be hazardous prior to any exposure. As a result, it appears that this individual may have only had trace exposures to any hazardous materials.

The defendants are in the early stages of obtaining pathology specimens so that genetic testing can occur.

A. What to Look for When Evaluating Cases for Genetic Testing (10 minutes)

As exhibited in Case Study "A" and "B," the facts of these cases indicate that genetic testing is worthwhile because they suggest an AML that developed from some other factor than exposure to the substances alleged by Plaintiffs. The factors to consider when assessing a plaintiff's claim that exposure to a certain substance caused their AML are below.

1. Cancer in First or Second Degree Relative to Plaintiff/Decedent

A first degree relative is either a parent, sibling or child – someone that shares approximately 50% of their genes with the Plaintiff/Decedent. A second degree relative is a blood relative which includes the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings – someone that shares approximately 25% of their genes with the Plaintiff/Decedent.

2. Early Age of Diagnosis and Earlier Diagnosis than Relative

The younger the Plaintiff is when diagnosed with AML, the more scrutiny should be applied to causation because they have not had the opportunity for the necessary exposure to substances that are known carcinogens. Also, it takes longer for cancer to develop when an individual creates their own gene mutations as opposed to when an individual is born with the particular gene mutation. When you have inherited a mutated gene, you can display symptoms caused by the mutated gene at an earlier age than the person that passed on the gene.

3. Multiple Primary Tumors, Bilateral or Multiple Rare Cancers

These three types of cancer indicate that a family cancer syndrome may be the cause of the individual's cancer due to inherited gene mutations. This phenomenon is well-supported in cancer research.

B. What is Required to Perform Genetic Testing

1. Court Approval

In order to proceed with the testing, unless the Plaintiff's attorney provides consent (even then it is likely to be difficult to obtain tissue samples from the medical facilities that possess it), you will need to obtain a Court Order approving a proposed process. The Federal Rules of Civil

Procedure provide for genetic testing of a party's DNA. Federal Rule 35(a) allows a court to order "a party whose mental or physical condition—including blood group—is in controversy to submit to a physical or mental examination by a suitably licensed or certified examiner". Most, if not all, states have rules that govern the "physical and mental examinations of persons". Since plaintiffs allege toxic exposures caused their disease, plaintiffs have placed their medical condition at issue.

In a motion for leave to conduct genetic testing, it is suggested that you include the facility you intend to obtain the tissue from and put language in the proposed Order that the facility is directed to cooperate in providing the tissue. It is also recommended that you provide basic details regarding the chain of custody and a description of how and where the testing will occur. The details help ensure you do not receive an objection from the facility maintaining the tissue and to ensure that any potential procedural roadblocks to admissibility are avoided. Most courts will consider the burden upon plaintiffs, privacy rights and inconvenience when asked to consider whether to permit genetic testing. Since the pathology materials are usually preserved during the treatment, these considerations are usually not an issue.

Typically, courts will allow plaintiffs to have any expert or representative attend any testing and pathology specimens are also maintained and made available so that plaintiffs can conduct their own testing, if they desire.

2. Availability of Non-Cancerous Tissue/Specimen

This may be the most difficult portion of conducting genetic testing. First, you need to determine facilities that possess the individual's preserved tissue, in an effort to locate non-cancerous tissue. With a thorough medical chronology related to the individual's cancer treatment and relevant prior medical history, you should be able to locate preserved tissue. The specific medical record listing the preserved tissue should elaborate whether the tissue sample was non-cancerous. It is recommended you locate as much non-cancerous tissue as possible. You should then communicate with the facility possessing that tissue about your intention to provide a Court Order to obtain the tissue and perform genetic testing. Hopefully in this step you can confirm if the facility still has the tissue and the facility's process for releasing the tissue.

Once you have your Court Order, coordinate shipment of the tissue from the facility to your retained pathologist so that the necessary segments of the tissue can be obtained and it can be confirmed that the tissue is non-cancerous. Then coordinate shipment from the pathologist to the lab where the genetic testing is to occur.

3. Pathologist, Geneticist, Toxicologist

These are the likely minimum stable of experts necessary to perform the testing and provide results/analysis that should be admissible at trial. The specific role of the pathologist is noted in the section immediately above. However, the pathologist can also provide relevant opinion on the type of cancer at issue and the results of the testing analysis.

The geneticist will help in the evaluation/investigation phase and also design the proposed testing, conduct the testing and provide the analysis of the testing data. Each segment of the work of the geneticist expert will likely involve extensive scientific literature review.

The toxicologist can provide a medical opinion on the impact of the claimed mutagen based on the genetics of the individual, considering the individual's metabolism of the claimed mutagen, genes related to same, as well as susceptibility and predisposition to the claimed cancer. This expert can also analyze the genetic testing data/report to determine what medical conclusions, if any, can be drawn from the genetic markers contained in the preserved, inanimate tissue.

3. Cost and Time

In general, genetic testing can take several months and can be costly. It is critical to determine all potentially available pathology specimens. In the event that the specimen(s) is determined to be cancerous or contains insufficient genetic material, other sources will have to be identified, if testing is to proceed.

The costs have been substantially reduced over the past couple of years as technology advances. Presently, the cost of genetic testing ranges from $200,000 to $250,000, which does not include the fees of the pathologist (for preparing the specimens) and toxicologist (for reviewing and offering a medical conclusion based upon the data).

III. Admissibility

A. Frye/Daubert

In order for evidence to be admissible, it must be relevant. Here, genetic testing in exposure cases can determine whether or not plaintiffs were exposed to a toxin and whether or not they had an increased susceptibility or genetic predisposition for the specific type of disease alleged to have resulted from exposure. As discussed above, much information can be obtained from the genetic testing. Currently, expert witnesses typically rely on inexact methods to evaluate causation, such as "differential diagnosis" and statistical inferences. Because genetic evidence in an exposure case could prove or disprove essential elements of a plaintiff's claim, it is certainly relevant.

In federal courts, as in many states employing a Daubert-type analysis, the Daubert analysis is flexible, and it is not necessary for evidence to satisfy each factor to be admissible. It is necessary pursuant to Rule 702, that scientific opinions offered by experts sound in terms of the scientific method and valid procedures.

Since Daubert was decided, federal courts have considered additional factors including whether the witness had adequately accounted for alternative explanations for the effect whose cause is at issue; whether the witness proposed will testify based on matters arising from research they have conducted independently or solely for the purpose of testifying; whether the offered field of expertise is capable of reliably reaching results of the type proposed by the

witness; whether any hypotheses relied on in formulation of the expert opinion have been tested; and whether the methodology is subjective.

In Frye jurisdictions, scientific evidence is admissible if the methodology that underlies the evidence has general acceptance in the relevant scientific community. As an example of a Frye jurisdiction, Pennsylvania law provides for the admission of expert testimony under Pennsylvania Rule of Evidence 702, which provides:

A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:

(a) the expert's scientific, technical, or other specialized knowledge is beyond that possessed by the average layperson;

(b) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue; and

(c) the expert's methodology is generally accepted in the relevant field.

Parties may challenge expert testimony under the Frye standard, however, if the scientific evidence is novel.

The Frye test, adopted in Pennsylvania in Commonwealth v. Topa, 471 Pa. 223, 369 A.2d 1277 (Pa. 1977), states that novel scientific evidence is admissible if the methodology that underlies the evidence has general acceptance in the relevant scientific community.

In order to be admissible under the Frye standard, Pennsylvania courts require the proponent of the evidence to prove "that the methodology an expert used is generally accepted by scientists in the relevant field as a method for arriving at the conclusion the expert will testify to at trial." The Frye test has two steps. A party opposing the evidence first must show that the scientific evidence is 'novel' by demonstrating that there is a legitimate dispute regarding the reliability of the expert's conclusions. Second, if the moving party has identified novel scientific evidence, then the proponent of the evidence must show that the expert's methodology has general acceptance in the relevant scientific community despite the legitimate dispute. The proponent does not have to prove, however, that the scientific community has also generally accepted the expert's conclusion.

Currently, genetic testing is being performed at all of top cancer hospital in the country. In most cases, the procedure used to obtain genetic information by Next Generation Sequencing (NGS) will not be challenged. The courts and plaintiffs have and likely will question or challenge the application of the genetic findings to current medical literature that associates genetic mutations to the development of certain cancers.

Expert Testimony

Expert witness are needed to perform genetic, genomic and epigenetic (DNA/RNA/miRNA/methylation based) testing to provide scientific data for interpretation by a qualified medical doctor. That qualified medical doctor will then draw inferences as to whether a plaintiff has specific genetic mutations in a series of genes, known to be associated with the onset of (A) familial myeloid malignancies (in particular, AML), as well as, germline mutations in genes associated with known (B) hereditary cancer syndromes that affect children, adolescents, and young adults.

In benzene exposure cases, the experts use a combination of both NGS and quantitative sequencing approaches to screen for all the known germline (and/or somatic) mutations associated with familial myelodysplastic syndromes, as well as hereditary cancer syndromes. As published and peer reviewed scientific literature progresses and become more available, the genetic findings can be used to offer opinions as to whether a particular cancer is associated with familial genetic mutations, environmental exposures or is *de novo*. In fact, all current national genome sequencing projects at The Cancer Genome Atlas Research Network (http://cancergenome.nih.gov/) from the National Institutes of Health (NIH) now evaluate/require sequencing of genetic material (DNA, RNA, miRNA) from both the primary tumor, as well as matched normal skin/buccal samples from each patient, to assist with the final diagnoses. A recently published study about the genomic and epigenomic landscapes of adult *de novo* AML was published, and comparative analyses would be able to demonstrate if the genomic architecture of a plaintiff/decedent's specific AML resembles that of the 200 sequenced, known *de novo* AML cases (The Cancer Genome Atlas Research Network, 2013).

2. Courts Decisions

Guzman v. Exxon Mobil Corporation in Jefferson Parish, Louisiana (Radiation)

Easter v. Aventis Pasteur, Inc. 358F. Supp. 2d 574 (E.D Tex 2005) (Vaccine)

Bowen v. E.I. Du Pont de NeMours & Co., No. 97C-06-194 CH, 2005 WL 1952859 (Del. Super. Ct. Aug 5, 2005)
(Pharmaceutical)

Cassidy v. SmithKline Beecham Corp., No. 99-10423, WL 33645128 (Pa. Ct. Com.Pl. Dec 1999)
(Vaccine)

B. Response by Plaintiffs' Attorneys

In benzene litigation, plaintiffs' attorneys have not chosen to conduct their own genetic testing or even send an expert or representative to oversee the defense testing. Most defense experts will videotape all of the testing in the event that that there is a challenge to the methodology.

You should, however, anticipate objection to any effort to conduct genetic testing and any evidence you intend to present at trial based on same. One of the main reasons is that the testing results are indisputable. For example, the p53 gene is so far the most prominent gene associated with the development of cancer. Greater than 50% of all cancers occur when this gene is either not present, or has changed. Specific cancers and the genes associated with them are continually being studied. If the genetic testing performed on a patient reveals a missing or changed p53 gene, they fit into that statistic. The only way to prevent identification of suspect genes from being communicated to a jury is to prevent the genetic testing or by having the results excluded.

Every one of the top 100 cancer hospitals in the United States employs genetic testing to classify cancers and select the most effective treatment. This is a powerful statistic that should weigh in favor of permitting genetic testing.

As noted above, counsel should be prepared to educate the court on the methodology and science that underlies the evidence. The experts will need to demonstrate that evidence has been generally accepted in the relevant scientific community and whether data relied upon as been peer reviewed and published. Plaintiffs' attorneys may argue that the relevant data relied upon is different or irrelevant to the issue that is being litigated. As a result, the literature and studies relied upon should be narrowly tailored and based upon the particular disease at issue.

In some cases, plaintiffs' attorneys have argued that genetic testing shows familial genetic mutations cause plaintiffs to be at an increased risk for disease (i.e., asbestos exposure and cigarette smoking). However, the most experts well versed in the literature can quickly refute these allegations.

In Case Study "A," in response to the Defendants' Motion to Compel Genetic Testing, Plaintiff presented only oral argument in seeking a Motion for a Protective Order. The basis of Plaintiff's objection to genetic testing was that the testing would be destructive and the results would be unreliable. Sufficient tissue was preserved for Plaintiff and his other argument was not proper under the discovery standard. The Court denied Plaintiff's motion and permitted the genetic testing. We fully expect that Plaintiff will raise admissibility arguments in pre-trial motions at the appropriate time.