



THE LITIGATOR'S GUIDE TO USING GENOMICS IN A TOXIC TORT CASE



ToxicoGenomica

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Introduction

Genomic data reveals the genetic facts of an individual's biology. Genomics is a proven and reliable quantitative tool that has dramatically improved cancer treatment, established the practice of personalized medicine, and brought binary clarity to paternity and criminal cases. It is now transforming how civil toxic tort cases are adjudicated. We have hit a tipping point where, instead of merely relying on population-based epidemiological studies, we are augmenting with personalized information about an individual to displace qualitative theories with binary facts.

► Genomic Data Moves into Toxic Tort Cases

Deployment of cutting-edge genomic technology can be costly, and the costs go up as the testing becomes more and more robust. As with any cutting-edge technology, early genetic testing was costly. But advances in various aspects of genetic testing (chemistry, automation, computation, platforms, indexing, selective sequencing) have standardized many processes and significantly reduced overall costs. For now, genomic analysis is being applied in a rapidly growing subset of cases. Sometimes, the litigants reduce costs, but significantly increase risk, by using a rifle shot approach focused on a small set of genes. Sometimes, the litigants attempt to reduce costs at significant risk by only examining a small set of genes (out of possible thousands known to contribute to disease).

Genomic data and genomic technologies can be applied to toxic tort and personal injury cases in

ways that may assist both plaintiffs and defendants in uncovering the truth about the underlying causes of disease. Genomic information will result in more accurate and reliable decision-making. The growing number of legal cases implementing a genomics approach and sponsored research programs will continue to accelerate progress toward not only identifying liability but also understanding and ameliorating adverse conditions that lead to toxicant-induced diseases.

► What Genomics Can Do in Civil Cases

Genomics can provide information about an individual's genetic predisposition to develop inherited diseases, risks from lifestyle choices (such as sun tanning and smoking), and predisposition or susceptibility to toxicants; in some cases, it can indicate whether toxicant exposure even took place. Evidence about inherited DNA mutations has been introduced in a range of toxic tort cases, including cases involving medication(s), vaccines, benzene, asbestos, and tobacco. Over the coming years, the convergence of molecular science, genetics, and civil law will unfold across multiple issues in toxic tort cases, going beyond proof of causation, apportionment of fault and damages to issues such as life expectancy and susceptibility to multiple hazards.

Overall, the influence of genomic data in civil law will be broader and more far-reaching than its influence in criminal law. The questions answered through genetic evidence in criminal law tend toward binary outcomes (i.e., was a specific individual's DNA at a

crime scene?). In contrast, in toxic tort cases, genetic results can potentially answer questions related to causes of disease and “reasonable” life expectancies for individuals with specific inherited mutations of known biological consequence. Investigating the family’s medical history may indicate multiple cancers, and the pattern of the cancers can imply that some or all family members harbor inherited mutated genes that are part of a Hereditary Cancer Predisposition Syndrome.

The arrival of genomics in civil law leads to a range of questions. How will courts respond to discovery requests aimed at family histories? How will courts and juries assess what will or may be the impact of a genetic factor? Will plaintiff firms seek out genetic testing data for their clients before taking on a cancer case when the person falls into categories where genomic factors are more highly probable

(e.g., onset at a young age or a strong family history [pedigree] of similar diseases)? As to damages, would it be reasonable to argue that a disease condition may soon be effectively ameliorated through more intensive monitoring or preventive measures for “eggshell” individuals? Or, might it someday be reasonable to think that an inherited genetic condition could be ameliorated, or even “cured,” due to the arrival of CRISPR-Cas9 genome editing technology that is fostering rapid progress in gene therapy?

These examples only scratch the surface, demonstrating part of why the genomic revolution in civil law will be more extensive than the genomic revolution in criminal law. But let’s come down to earth and explore examples of genomic data used in toxic tort cases.

Four Legal Cases That Illustrate Genomics in Toxic Tort Litigation

Members of our team played a major role in three legal cases presented here, in which genomic data resulted in defense verdicts or favorable settlements. These cases involved alleged exposure to asbestos (Blackford-Cleeton), ionizing radiation (Guzman), and benzene (Harvey). A fourth case, in which our team did not participate, involved allegations of an eggshell plaintiff due to her genetic factors (Ortwein).

► Blackford-Cleeton

Ms. Blackford-Cleeton was diagnosed with malignant peritoneal mesothelioma at age 32. In addition, she was diagnosed with malignant melanoma eight months before. The case involved claims that indirect childhood exposure to asbestos (alleged in the legal complaint to have been carried home by her father, an oilfield worker) caused her mesothelioma.

Her medical records suggested a number of alternative cause factors, including a well-characterized and clearly established germline *CDKN2A* variant; a multi-generational family pedigree (history) of related cancers; and activities associated with high incidences of cancer (tobacco smoking, indoor tanning, excess outdoor sun exposure, excessive caloric intake). In view of those factors, a systematic review of the published literature revealed that Ms. Blackford-Cleeton's *CDKN2A* variant was linked to five scientifically plausible models of how her cancers could have occurred without asbestos exposure. These alternative cause models turned out to be substantial to the defense, and the case settled favorably for the defense.

► Guzman

Ms. Guzman was diagnosed with papillary thyroid cancer under the age of 40. Her father had worked in a pipe cleaning yard for oil and gas. The lawsuit

alleged her cancer was caused by *in utero* exposure to Naturally Occurring Radioactive Material (NORM), allegedly brought home by her father from his workplace.

Members of the ToxicoGenomica team performed gene expression profiling of some of the cancer tissue because evidence in the medical literature indicated that this analysis could distinguish between thyroid cancers induced by radiation and those that were not (i.e., idiopathic thyroid cancer.) Ultimately, messenger RNA gene expression from Ms. Guzman's tissue was found in patterns ("signatures") consistent with non-radiation-induced cancers but inconsistent with cancers from irradiated populations. Additional genetic analysis indicated that Ms. Guzman tested positive for inherited mutations in eight genes associated with papillary thyroid cancers. Ms. Guzman's family history showed that her mother and aunt both had thyroid cancer. Expert testimony presented these facts and made the case that Ms. Guzman's cancer was caused by hereditary gene mutations as opposed to her exposure to NORM. The case was tried in front of a jury, which entered a not liable finding for the defendant that engaged ToxicoGenomica.

► Harvey

At age 34, Mr. Harvey was diagnosed with acute myeloid leukemia (AML). A lawsuit alleged the AML was caused by occupational benzene exposure and that he was an eggshell plaintiff with increased susceptibility.

Next-generation sequencing (NGS) conducted by members of the ToxicoGenomica team revealed a wide range of inherited mutations. Among them were 12 extremely rare, hereditary mutations in Fanconi anemia (*FANC*) genes, which guide the production of *FANC* proteins. Fanconi anemia subtype (*FANC*)

proteins function in a DNA repair pathway called “the FA pathway,” which is essential for maintaining genomic integrity. In the medical literature, those mutations have been well documented to increase the risk of developing AML by over 500%.

Genetic testing also revealed further information about genes relevant to how the molecular system metabolizes (or processes) benzene. The analysis indicated Mr. Harvey inherited a number of gene variants with some protective variants/mutations (also known as “alleles”) and did not inherit adverse mutations for processing benzene. This finding highlighted that rather than being susceptible to benzene-induced toxicity, Mr. Harvey had a genetic resistance to it. The defense used these findings to argue that his AML was caused by his genetics and that benzene exposure was not a factor in his disease. The case settled favorably for the defense.

► **Ortwein**

Ms. Ortwein was diagnosed with pleural mesothelioma while in her mid-50s. She was from a family heavily affected by mesothelioma; in fact, it had previously killed three first-generation family members. As a result, the lawsuit filed on her behalf resulted in the first mesothelioma trial emphasizing the role of a single gene in a plaintiff's effort to establish a causal link between asbestos exposure and a pleural mesothelioma. We would like to stress that using a single gene approach in a defense is very risky; we generally do not accept such projects.

The issue at trial revolved around a mutation in a single gene known as *BAP1* and its role in mesothelioma. In short, Ms. Ortwein's trial team asserted that Ms.

Ortwein was especially susceptible to asbestos fibers and that she developed mesothelioma because she inherited a mutated copy of the *BAP1* gene. Normally, all people have two working copies of this gene. The undisputed fact was that Ms. Ortwein was not “normal” because she inherited one mutated copy of the *BAP1* gene. That *BAP1* mutation prevented the production of normal amounts of the BAP1 protein that works (along with other proteins) to suppress cancers by repairing defects in cellular DNA and regulating controlled cell death (apoptosis). Moreover, genetic analysis of the tumor itself showed that Ms. Ortwein's other, normal *BAP1* allele was missing; somehow, it had been knocked out during the cancer process. Thus, the cells of Ms. Ortwein's mesothelioma contained zero normal copies of the *BAP1* gene, and therefore those cells could not manufacture BAP1 protein.

At trial, Ms. Ortwein's counsel presented testimony on the role of *BAP1* gene mutations in mesothelioma. The testimony supported the plaintiff's legal arguments. Ultimately, the case settled before the defense called an expert witness on the genetics issue. The Ortwein trial marked a notable first step in the use of genomics in an asbestos-mesothelioma case. However, focusing on only a single gene (*BAP1*) is a risky tactic because a more compelling case for either side may emerge depending on a particular plaintiff's combinations of inherited and/or somatic genomic alterations, social behaviors, and disease risk factors. Cancer is NOT a single gene disease; it involves the progressive loss of cellular controls which cascade down to uncontrolled cell growth. Defects in multiple genes are necessary to void redundant cellular control pathways.

Introduction to Genomics

The remainder of this white paper provides an overview of some fundamental genetic principles and examples of the use of genomic technology in toxic tort litigation.

Humans are complex biological beings made unique by the interplay between an individual's inherited genetic makeup and his or her environment (i.e., external factors such as diet, air and water quality, behaviors, exposure to chemicals). Some diseases arise purely in response to inherited genetics (e.g., autoimmune disorders). Other diseases are due to changes and mutations that occur during the lifetime, such as failure of gene repair mechanisms, which may or may not occur after the body's normal physiological balance is disrupted (e.g., by exposure to a toxicant/infectious agent). Looking across large populations, the rates of cancer and other diseases are influenced by a number of factors, including changes in human lifespan, inherited risks (genetic predisposition), lifestyle choices, and toxicant exposure.

After a disease diagnosis, some people will file lawsuits seeking damages. Historically, courts ruling on toxic tort causation issues often relied primarily on expert testimony about and inferences from population-based epidemiological studies (sometimes called "black box epidemiology"). If epidemiology experts convinced the court that there was a reliable, statistically significant increased risk of injury from the plaintiff's exposure, some courts would allow the evidence to go to a jury. These juries sometimes accepted the associations as evidence of causation and found for the plaintiffs. In other cases, defense counsel were convinced that they won because they convinced the judge or jury that the epidemiological studies were not reliable or not valid and therefore there could be no finding of a causal relationship between the exposure and the injury.

The bottom line is that these legal disputes based on black box epidemiology relied on population-based studies to make determinations about causal attribution in individuals. Genomic technologies can provide information at a much higher resolution for trial. In a growing number of cases, exposure and/or causation arguments can be refuted or verified based on an individual's objective genetic characteristics instead of inferences from population-based studies.

► What Is a Gene?

Genes are the molecular units that embody heredity. They are encoded by the chemical deoxyribonucleic acid (DNA). The building blocks of DNA are called "nucleotides." There are four possible nucleotides in DNA, which are represented by the letters A, T, C, and G. The sequence of the As, Ts, Cs, and Gs determines the genetic message. In essence, the message is the instruction manual or recipe used by a cell's protein factories (ribosomes) to manufacture proteins. In turn, these proteins perform cellular functions, such as helping to repair broken strands of DNA. However, if a gene contains mutations, then the instruction manual is not accurate and the protein may not function normally.

"Gene expression" is the process of transcribing (or "copying") the genetic information from DNA to messenger ribonucleic acid (mRNA). The transcribed mRNA is then translated by ribosomes to create proteins.

Whereas genes make up the components of DNA and RNA, the term "genome" encompasses all the genetic information (DNA and RNA) of an organism. We sometimes use the term "genomics" even more broadly to include concepts such as epigenetics and proteomics.

► Genes, Diseases, and the Environment

Like all living organisms, our state of being is determined in varying degrees by our genes and interactions with the environment. Environmental factors that affect human health include diet, lifestyle choices, and chemical exposure. Through the course of our lifetime, we are exposed to countless environmental factors with the potential to alter our DNA. For example, DNA alterations may lead to the production of aberrant proteins that cause skin cells to grow out of control, resulting in the formation of melanoma. Some people are more prone to developing skin cancer due to greater sensitivity to ultraviolet (UV) light (genetic susceptibility), while others are more prone to developing skin cancer even without excessive UV light exposure (genetic predisposition). Because every individual has a unique genetic code, population-based studies cannot fully explain or account for all the differences within, and between, specific individuals and the diseases or conditions they develop.

One goal of genetic testing is to develop strategies for early detection, diagnosis, and treatment of disease. Such testing may uncover one or more gene variants that help identify individuals at an increased risk of developing a disease. The results also may provide insights into the best possible treatments, which is the premise of modern precision medicine.

Mutations in the genome are not all the same, and rarely do single mutations operate independently. To the contrary, research has established that there are at least hundreds of different mutations within the well-known *BRCA1* and *BRCA2* genes. These variations can take the form of nucleotide changes, deletions, and insertions that alter the meaning of the genetic message. For example, a nucleotide that normally is a C may instead be a T. There may be one or more such changes. Furthermore, it is possible that one or more mutations may not have any observable impact or effect (i.e., some DNA changes are characterized as “silent” because there is no effect on an observable

trait, referred to as a “phenotype”). Conversely, other genetic differences, known as “deleterious mutations,” may influence the phenotype unfavorably (e.g., a genetic predisposition to a disease). Whether someone is genetically predisposed depends on whether that individual has inherited one or more variations in particular genes that could either increase or decrease the risk of developing an inherited disorder or disease.

► Types of Genetic Variations (mutations)

Generalizing for the purpose of this overview, variations in DNA sequence arise primarily through 1) inheritance or 2) changes during someone's lifetime. The specific variations present in an individual are often key to assessing causation. The term “variation” increasingly is used instead of “mutation,” but we use both terms interchangeably.

Broadly speaking, there are two types of genetic variations (mutations) that can be observed in an individual: germline and somatic.

Germline Mutations: When a mutation is inherited from a parent, it is often called a “hereditary” or “familial” variant. It may also be called a “germline” mutation because it was present in the “germ” cells (sperm or eggs). Families afflicted by Hereditary Cancer Predisposition Syndromes will have high incidences of related cancers in two or more generations. Breast cancer is an example of a disease where genetic testing can identify individuals carrying hereditary variants that increase their risk. Actress Angelina Jolie drew considerable attention to genetic testing when she elected to have a preventive double mastectomy in 2013. She based her decision on the presence of a specific DNA variant found in her *BRCA1* gene and her mother's death from ovarian cancer (a strongly related disease) at the age of 56.

Somatic Mutations: Mutations acquired during a person's lifetime are known as “somatic mutations.” Although the DNA replication machinery in our cells

is generally very precise, approximately once per billion nucleotides, an error is made and a mutation is created. Some of these errors occur spontaneously during cell division when a cell copies its DNA. Other somatic mutations are induced by environmental agents, such as ionizing radiation, heavy metals, gases, fibers, organic solvents, or other chemicals. Some mutations are not fixed by the DNA repair machinery, and so they survive and propagate. We refer to these as “acquired somatic mutations.” These mutations cannot be passed on to the next generation but can negatively affect the person’s health.

Genetic testing is used to identify the existence of both kinds of mutations. Some well-known types

of genetic testing include 23andMe, Ancestry, and an increasing field of diagnostic assays. However, in general, these tests provide only a partial view of important genetic characteristics. The limits arise from a range of factors, including the number of genes tested and FDA-imposed limits on the information that can be communicated as part of the results.

To establish a complete picture of the individual suitable for use in a toxic tort legal case, “whole genome” sequencing is ideal. The following section describes genetic sequencing technology generally and why whole genome sequencing is the best and most appropriate approach for toxic tort civil litigation.

Genetic Sequencing Technology

Gene sequencing typically is performed using techniques such as “Sanger sequencing” (named for the creator of the process) or NGS, although some single-strand sequencing techniques are beginning to enter the market. Each has its strengths and performance benefits. In some settings, Sanger sequencing might be viewed as the gold standard, but its use drives up time and expense when compared to NGS. Sometimes, both techniques may be used, such as relying on NGS sequencing for most genes but employing the Sanger method to further investigate the sequence data reported for a small number of genes of special interest. The equipment, processes, and data handling from sequencing are part of a well-established field of expertise that continues to increase in performance and decrease in cost year after year.

To sequence DNA, there must be a sample of the DNA. It is almost always optimal to use DNA extracted from properly preserved fresh blood or fresh tissue. In the absence of fresh blood, DNA from tissue preserved in paraffin blocks or slides is also acceptable. DNA can also be extracted from saliva, inner cheek cells (known as “buccal” swabs), or even hair. DNA can be (and has been) extracted from ancient mummies or “animals prepared by taxidermy”- a process some refer to as “museumomics.” In sum, fresh blood or tissue is generally best, but there are other possibilities depending on the amount of time and money available.

Once DNA has been extracted, quality tested, preserved, and “amplified,” the next step is to sequence it. Sequencing is performed through sophisticated machines that most often use processes involving combinations of reagents (chemicals), hardware, and software to read the precise order of the 3.2 billion nucleotides (A, C, G, or T) that make up a human genome. In the most common system, a DNA

read is generated by observing physical characteristics of the nucleotides as they pass by the reader. The readings are recorded in software. The reading process is repeated many times (often hundreds) to verify the accuracy of the results.

For more specifics and some graphics, *Nature* magazine provides a readable, open access paper that describes the fundamentals of sequencing technology:

<https://www.nature.com/scitable/topicpage/dna-sequencing-technologies-690#>

► **Comparing Genes: From One to Thousands to Whole Genome Analysis**

Based on costs, time available, and needs, it is possible to examine only a few genes or many. For example, it might make sense to focus on as little as one or two genes (e.g. *BRCA1*, *BRCA2*, *TP53*, *BAP1*) if there is a specific medical need (e.g., suspicion of a predisposition toward breast cancer). That kind of limited testing is often performed using an assay that captures the person's DNA for only one or a few genes of interest. However, much broader assays are often used that involve hundreds or even thousands of genes related to a specific type of disease. For example, an assay might include a few hundred genes thought to be associated with a specific disease or condition or a group of more than three thousand genes that are commonly involved in cancer. Assays can also test for other genomic characteristics, such as chromosomal breaks or gene fusions.

Instead of sequencing only a specific set of genes, an alternative process is “whole genome sequencing” (WGS), wherein the entire set of known genes is sequenced. “Whole exome sequencing” (WES) is a slightly less expensive but less encompassing

approach in which sequencing is limited to the portions of genes (the exomes) that are directly involved in providing the instruction manual for the production of proteins.

In general, we discourage single gene testing in favor of broader types of genetic testing in a toxic tort case. This broader approach allows experts to more fully understand the molecular factors at work in a particular person. *In general, cancer seldom occurs from a single mutation in a single gene. Instead, it usually involves multiple mutations within several key genes, including proto-oncogenes, tumor suppressor genes, and DNA repair genes.* However, we acknowledge that situations vary, and as of today, there is no single sequencing strategy is equally applicable to all legal cases.

► Evolution in Sequencing Technology

Gene sequencing is far faster, affordable and reproducible/reliable than it was in the past thanks to a wide range of technological advancements in sequencing technology (e.g., better readers, better software, faster computers). The resulting improvements have led to a rapidly increasing list of major scientific and medical breakthroughs related to more effective and higher quality sequencing. These improvements in technology are often referred to as NGS. Overall, NGS is a powerful, cost-effective technology designed to study a person's genes (DNA) and gene expression (RNA). NGS is characterized as a "high throughput" approach because it allows fast and reliable sequencing of the entire genome of a person, an animal, or a plant.

The evolution of sequencing is remarkable. The Human Genome Project (HGP) was the first time an entire human genome was sequenced. When the HGP was completed in 2003, the cost was estimated in the range of \$2–3 billion. Thanks to new science and massive computing power, costs today for WGS are exponentially lower. Depending on the accounting

(e.g., including only direct costs or adding indirect costs as well), the cost could range from \$1,000 to \$50,000 (or more). The challenge, however, is that each new generation of sequencers produces more and more data, so there is a continuing rise in the computing requirements for the associated bioinformatics analysis of the data. This has slowed the rate at which costs for sequencing are declining. The next major decrease in price will require a new generation of technology.

► Bioinformatics—Deriving Gene Mutations from Sequencing Data

Ultimately, for one gene or many, the output from sequencing includes a string of nucleotides that are A, C, G, or T. The bottom line is that they are obtained through a repeatable and reliable process. An analysis is conducted using computational program specifically designed for genomics, referred to as "bioinformatics software tools." In the bioinformatics process, the sequences of letters for the individual's genome is compared to a reference genome. From that comparison, using peer-reviewed databases, specific genes and variations within those genes are identified. While at the end of the HGP, there were only a few reference genomes with which to make comparisons, today there are hundreds of thousands of published genomes available through public and/or private databases.

With massive computing power to compare whole genome DNA sequence information, researchers can look for DNA sequence variations among and within populations. This allows a litigator to interrogate a plaintiff's DNA and determine whether his or her sequence has mutations relevant to the pertinent injury.

► Variant Identification

When mutations are identified, they are compared against the rapidly increasing body of knowledge

contained in public/clinical databases and built upon peer-reviewed research publications. These databases help determine whether a variant produces a significant biological outcome (phenotype), and if so, what are the known functional connections of that mutation to the onset or initiation of disease. Ultimately, NGS enables a whole genome approach to identifying gene variants that might cause a disease. Sanger sequencing sometimes will be used to further confirm the specifics of a variant.

As shown above, the plaintiff brought forward the evidence of an inherited mutation in the Ortwein case to argue increased susceptibility. However, in other toxic tort cases, defendants have looked for and presented familial (inherited) variants to argue that the sole cause of disease lies in the variants in a particular individual, thus invalidating claims of a toxicant-induced causation. NGS also may be used to generate evidence to assess whether the observed injury can be attributed to spontaneous somatic mutation(s) instead of an inherited familial variant(s), or a combination of both.

► **Development of Genetic Signatures and Uses in Toxic Tort Litigation**

NGS has also revolutionized RNA research. As a reminder, RNA is a key to translating the instructions within DNA into the actual production of proteins, which is commonly referred to as “expression” of the instructions within the DNA. Gene expression profiling (or mRNA expression) is now performed at the whole transcriptome level using RNA (simultaneously measuring the expression of all known genes). Researchers can characterize all the genes expressed in a certain tissue and under specific conditions. With mRNA expression information generated from NGS, it frequently is possible to precisely characterize an individual's response to specific environmental exposures. For example, exposure to many substances (medications, ionizing radiation, benzene, heavy metals, etc.) leaves behind a measurable gene

expression signature.

Over the past decade, many research groups have worked on developing and validating gene expression signatures that indicate such exposures. Using these published and validated gene signatures, we often can differentiate exposed from non-exposed individuals.

As genetic techniques become more accessible to litigants, there are increasing opportunities to search for and utilize gene mutations and genomic signatures in toxic tort litigation. The careful and transparent development of objective, genomic data for diseases and conditions will reduce the need for courts and jurors to rely solely on inferences obtained from classic black box epidemiological studies built upon broad associations within general populations. Genetic techniques enable us to investigate and discover well-characterized associations that can provide answers for specific individuals instead of broad populations.

► **The Pace of Growth of Genomic Information**

The number of papers published on genetic variations and the genomics of diseases is growing exponentially. Every month, new knowledge is added to the wealth of existing material. For both signatures of exposure and gene variants for predisposition, there may already exist genetic signatures and robust genetic assays relevant to a legal case. In other situations, newly published scientific literature contains groundbreaking or additional information that may be valuable to understanding the relationship between a genomic marker and a specific cancer or other disease.

In general, this new information needs to be mined and critically evaluated to form working hypotheses and datasets suitable to the claims in a legal case. Working with a court or counsel, Toxicogenomica can help evaluate whether an appropriate study can be designed to inform questions about the specific

mode of action (MOA) and disease states involved in a particular legal claim. ToxicoGenomica uncovers facts and knowledge via a suite of genomics tools and specialized software and can analyze the relevant tissue samples and generate appropriate datasets for the courtroom (DNA sequence, mRNA expression, epigenetic gene expression [i.e., miRNA expression], and spontaneous somatic, and/or inherited gene variations).

► **Legal Admissibility and Discovery of Genetic Information**

Our experience is that judges around the country are generally open to receiving genomic information. Nevertheless, we understand that the use of DNA in civil litigation is new to many civil judges and lawyers, as it was for those involved in criminal law cases. Accordingly, we are not surprised when questions or concerns are raised about discovery or whether genomic data will be admitted as part of expert testimony when evaluated under standard(s) for scientific evidence, such as the *Frye* and *Daubert* standards. While this has become a diminishing issue for ToxicoGenomica, we hope that courts and lawyers will come to more fully appreciate that genetics and genomic testing are not new science.

When considering the power and reliability of genomic information for understanding cancer, one overall indicator is the broad use of genomics in the clinical and research applications related to cancer in major medical centers and research labs. In our surveys of the literature, we see that 100% of advanced cancer treatment hospitals utilize some degree of genetic or

genomic testing to classify the source of tumors and determine an appropriate treatment protocol based on a specific tumor's mutational footprint. Therefore, in our view, it is logical that genetic testing data and techniques satisfy admissibility criteria, at least when properly utilized by people with appropriate knowledge and experience. ToxicoGenomica has provided genomic analyses and scientific support in nearly two dozen legal cases where genetic evidence was investigated and developed, with some cases going to trial and jurors ultimately considering the evidence in their decision.

There also is a growing list of state and federal cases where courts have approved discovery processes to obtain blood or other tissue samples to perform genomic testing and analyses. However, courts have declined to order certain forms of testing in some circumstances. In our experience, most courts and lawyers will benefit from some expert assistance to better understand and frame legal issues related to the application of genomics in civil litigation. We encourage courts and litigants to more fully appreciate that genomic information and knowledge is growing exponentially, to think broadly, and to work toward best practices that will serve the interests of both science and law. We believe that with adherence to transparent best practices, data generated in litigation could in fact advance scientific research findings and accelerate progress toward understanding and ameliorating diseases and adverse conditions.

How Genomic Information May be Useful in a Toxic Tort Case

The following three examples illustrate cases where genetic analysis may be particularly informative to the court.

Well-Known, Normal Modes of Action: In cases that involve well-established science around a mode of action, it may be that a well-known mechanism of action posits that a disease was caused through a known, thoroughly studied, and well-published molecular progression of events. The following events might fall into this broad category: (a) familial inheritance of mutated genes; (b) spontaneously acquired somatic mutation(s); or (c) somatic mutation(s) that reflect or fail to reflect a signature pattern for mutations induced via exposure to a particular toxicant with a well-documented MOA.

The **Harvey** case (discussed earlier) falls into this category.

Mechanisms of Action: The World Health Organization International Agency for Research on Cancer (IARC), along with the US National Institutes of Health, has tried to define the mechanism of actions (MOAs) for various forms of toxicant damage. However, given the number of toxicants, genetic variations, and other unknown variables, the MOA of toxicant damage is not always clearly defined and presents an opportunity for careful and thoughtful investigation and interpretation of how an outcome came to pass. For example, a theory presented by the plaintiff as to how a toxicant exposure caused a disease

may not be clearly supported in the published scientific literature. In such instances, we may suggest an investigation for a specific genetic signature or a study to be designed with knowledge from the literature (along with the plaintiff's own genetic data) to support or refute the claim(s).

The **Guzman** case (discussed earlier) falls into this category.

Assessment of Contributory Factors: Genomic analysis may reveal multiple factors that may have contributed to an outcome. For example, the parties may agree that a toxicant was a factor involved in the development of the disease, but the plaintiff may also have had a genetic predisposition. A genetic susceptibility may have contributed through other lifestyle choices or exposures unrelated to the exposure at issue (e.g., smoking, diet, or tanning). For example, smoking of conventional tobacco is generally not considered a factor in the development of mesothelioma. However, more recent work suggests that smoking may be a mesothelioma risk factor in a small, genetically susceptible group of individuals.

The **Blackford-Cleeton** (discussed earlier) case falls into this category.

Conclusions

The application of genetic technologies has brought significant benefits to society, and we believe it offers substantial value to the resolution of legal issues. In the toxic tort arena, genomic analysis may be helpful to and argued by plaintiffs or defendants, as illustrated by the four cases described in this paper. Some legal precedents have already been set, and more will emerge as genomics technologies advance. Genetic data and techniques are becoming ever more powerful tools for explaining when and how diseases arise.

Genomic and genetic data and conclusions can have very strong evidentiary value. Depending on the nature of the case, such findings can provide conclusive answers for a judge or jury. These methods and techniques may be limited by the lack of relevant peer-reviewed research publications, genetic signatures of exposure and/or availability of tissue for testing. However, in many instances, genomic testing can be implemented using a powerful suite of tools to enlighten courts on sources of tumorigenesis and other diseases. Our experience can help with determining what cases are appropriate for genomic analysis given the current state of the knowledge base and the costs involved.

ToxicoGenomica provides end-to-end service to counsel involved with toxic tort cases, some of which are outlined below:

- We work with the entire team (including primary and secondary clients as well as medical and

toxicology experts) to review all relevant documents and information that could have a genetic component (e.g., medical records, family histories, and pathology reports).

- We design appropriate steps and scientifically valid methods to build upon this information in the form of a proposal.
- If appropriate, we work with counsel to develop an affidavit to provide the court with information about the reasons behind and methods for genomic testing.
- We perform all necessary lab work, including extracting DNA from blood or tissue.
- We deploy gene-sequencing machines (or other genomic tools) to analyze the DNA libraries using nationally recognized tools and methods, as well as our own bioinformatics and statistical tools.
- We provide comprehensive written reports to address questions about the role of the genetic factors in the development of a disease in that person. Our data and conclusions are often submitted to medical and toxicology experts for their subsequent medical interpretations and conclusions.
- Upon the client's request, we can provide expert or fact witness testimony, attorney assistance, and supporting research during the conduct of a case.

Who We Are



► **ToxicoGenomica as a Genomics Services Provider**

www.ToxicoGenomica.com

ToxicoGenomica is comprised of a multidisciplinary group of scientists and lawyers. We created ToxicoGenomica to provide fully integrated services for using genomic and systems biology data in civil litigation, and to help develop and utilize best practices related to the use of such information in the legal system. Members of ToxicoGenomica have been involved in providing genetics defense in dozens of toxic tort cases, and are dedicated to accelerating the dissemination of information about the applications of genomics to issues involving disease causation. ToxicoGenomica organizes and sponsored workshops on the topic of the use of genomic information in various aspects of civil law, including case law, statutes, and regulations. ToxicoGenomica is a strategic alliance between the following three organizations.



► **ArrayXpress, Inc.**

www.ArrayXpress.com

ArrayXpress is a genomics and genetics service provider. Since 2002, ArrayXpress has built a strong and long track record of using genomic tools to provide information and answers utilized by pharmaceutical companies, energy companies, agriculture companies and many other academic, corporate and governmental researchers and product producers. The company grew out of pioneering work in genomics by Len van Zyl, PhD, who was a professor at North Carolina State University, and now leads the Company. He co-founded the Company with a technology transfer expert, Michael Zapata. The company has now grown into a team of geneticists, biologists, bioinformaticians, chemists, and technology professionals. ArrayXpress was a “spin-off” of the University built on intellectual property around the use genetic data and tools to improve services for producers of products. Over the past five+ years, AX has also focused on the application of Next Generation Sequencing (NGS) technologies in “toxic tort” cases working for a wide range of well known corporate defendants. AX use NGS technologies to reveal previously unseen evidence, such as inherited gene mutations, acquired mutations, and indicators of toxicant exposure that resides within the genetic makeup of an individual. This information is used by decision-makers to assess legal issues, including decisions regarding the “causation” of a condition or disease.



▶ LSP Group

www.lspgrp.com

The LSP Group (Law Science Policy) is led by Kirk Hartley, an experienced “mass tort” lawyer with a deep interest in genetics, cancer and other diseases. Kirk’s career includes working with both plaintiff and defense clients, as well as advising persons who advocate for “future claimants” through a process known as serving as “future claimants representative” . In 2011, Kirk founded LSP to continue and build upon his decades of work for clients and focus on the increasing intersections between molecular science and civil law issues. Hartley’s other endeavors include serving as the chair of the Risk Policy & Law specialty group of the Society for Risk Analysis, providing free legal advice and/or litigation services to persons denied access to life-saving therapies or diagnostics, and serving as an unpaid director for Triage Cancer, a 501(c)(3) entity focused on educating a wide range of professionals, patients and caregivers on the legal rights of persons during and after cancer. In 2008, he created the GlobalTort blog focused on increasing multi-disciplinary intersections such as the intersections between molecular science and civil litigation.



▶ Innovative Science Solutions

www.innovativescience.net

Innovative Science Solutions (ISS) is a leading scientific consulting firm serving the worldwide pharmaceutical, biotechnology, and medical device industries. David Schwartz, PhD, is a neuroscientist and was a co-founder of ISS. Early in his career, Dr. Schwartz sought out practical applications for scientific knowledge, which lead him to work as a scientist assisting lawyers practicing as part of a nationally recognized law firm. Ultimately, Dr. Schwartz took that experience to a larger audience by co-founding and building the ISS team. ISS is composed of a team of scientists, regulatory strategists, and consultants providing a wide range of fully-integrated services to industry and counsel to support services for litigation and product stewardship involving complex scientific or medical issues. ISS provides strategic consulting services designed to ensure that counsel and corporations are prepared and knowledgeable on scientific and technical issues relevant to their cases.