We can expect that geneticists will in fact begin to unravel the genetic basis of mesothelioma, and as they do defendants will increasingly ask juries to accept the genetic explanation as the cause of the disease.

These groundbreaking genetic developments have much to offer medicine. But what do they contribute to toxic tort litigation, where the question of cancer causation is often the most important issue in the case?

This article explores the current state of genetic proof in toxic tort cases, with a focus on asbestos cases involving mesothelioma, the chief disease involved in asbestos litigation today.

Genetic discoveries have the potential to turn asbestos litigation upside down. But before that day comes, litigants will face a sea of muddy medical issues and an array of potential expert disputes, all of which could delay any substantial impact on asbestos litigation for some time.

Eventually, scientists will likely fully discover and document the combinations of genetic mutations that produce mesothelioma, without any contribution from low-level asbestos exposures. Research may also determine that some mutations create a propensity for mesothelioma.

Either or both discoveries could clarify asbestos litigation substantially, and possibly drive the litigation to a long-overdue decline or at least a greater focus on cases with a legitimate scientific basis.

Courts should anticipate an increasing use of genetic testimony in asbestos and toxic tort litigation and institute the necessary controls both to reject unscientific guesswork while at the same time encourage the development of legitimate genetic evidence of causation.

**ASBESTOS CAUSATION AND GENETICS**

The focus of much testimony and dispositive motions practice in asbestos litigation today is the question of what causes mesotheliomas in individuals who have very little exposure to asbestos.

The "old" asbestos litigation that dominated for the first two decades focused on insulators, shipyard employees, and factory workers who had extensive exposure to the amphibole form of asbestos fibers, usually from work in Navy shipyards or through installing asbestos fireproofing.

But by the 1990s the litigation had largely turned to focus on a different type of asbestos exposure, to the fiber known as chrysotile, which is much less potent and arguably does not produce mesothelioma at levels experienced by humans.

These later cases also often involved far lower exposures — e.g., a few backyard brake jobs or removal of a handful of gaskets.

Those minute exposures, often approaching or not exceeding general background exposures, have raised serious questions about whether the exposures were sufficient to cause anything at all.

Today's litigation is dominated by these low-dose cases, many involving "take-home" or "bystander" cases of persons who never handled asbestos themselves but were only around someone who did.

Based on both historical epidemiology and current genetics research, a large segment of today's mesothelioma cases consists of persons with no meaningful exposure to asbestos. Most asbestos epidemiology studies have documented that typically from twenty to fifty percent of the identified mesotheliomas were not related to any known, meaningful asbestos exposure.
Most critically, the rate of asbestos-induced mesothelioma in women in particular has always been very low — today some researchers believe that as many as nine out of ten women with mesothelioma in certain age cohorts likely have a disease that is not caused by any asbestos exposure.

Where are these non-asbestos mesotheliomas coming from?

There are a handful of other, known exogenous causes (outside the body), such as radiation therapy and erionite, but the vast majority of non-asbestos mesotheliomas are likely produced by errors occurring in the body’s own natural processes of gene replication and mutation.

These cases are sometimes referred to as spontaneous mesotheliomas — meaning the body needs no help from asbestos or anything else in generating them.

The human body, for all its wonders, produces multiple mutated cells every day, and eventually some of those cells may break through the body’s defenses and produce a cancer.

As Robert Weinberg, author of One Renegade Cell, stated, “[T]he rock-solid stability of the cell’s genetic data base is a mirage. The constancy of our genome is the result of a high-wire balancing act, a permanent struggle in which an ever-vigilant repair apparatus continuously fights off genetic chaos.”

The trend toward non-asbestos induced mesotheliomas is consistent with recent findings regarding all cancers — the human body produces an enormous amount of cancer of all types on its own.

One group of researchers, based on their studies of stem cell replication, estimates that as many as two-thirds of all cancers are spontaneously induced, with no input from exposures or outside influences.

One reality associated with this phenomenon is that the older we get, the more likely we are to have such a spontaneously-induced cancer — our defenses get weaker, and the mutated cells that for most of our lives were killed or controlled instead become a spreading tumor.

Epidemiology data in fact demonstrates that mesothelioma cases are holding steady at around 2,500-3,000 cases per year, even though the industrial exposures sufficient to induce asbestos disease largely ended in the early 1970s.

For any dose-response disease — and asbestos-induced mesothelioma is such a disease — the incidence should drop dramatically as the exposures decline.

The reason for this steady state of the disease is that the population is also growing older — spontaneously induced mesotheliomas are rising and replacing the cases that were caused in past years by actual asbestos exposure.

Yet the litigation continues unabated. Today, asbestos litigation (consistent with declining exposures) has shifted focus to low-dose asbestos cases involving often trivial amounts of asbestos exposure.

The tension between such low exposures and genuine causation science often generates significant battles of the experts over causation.

And the genetic test may involve nothing more intrusive for plaintiff than a swab inside the mouth. But for reasons discussed below, the outcome may not be that simple.

The science can be complicated, and juror decisions can depend on often-confusing epidemiology studies and on the persuasiveness and personalities of individual experts.

Genetic discoveries represent a chance to change this confused world dramatically and to reduce or even eliminate most low-dose, chrysotile-based mesothelioma litigation.

If geneticists can clearly identify either single mutations, or clusters of mutations, that are capable by themselves of inducing mesothelioma, the cases should be resolved by a simple genetic test — if the plaintiff has that mutation or set of mutations, then courts should dismiss the cases for lack of sufficient or admissible expert evidence of causation.

Epidemiology data in fact demonstrates that mesothelioma cases are holding steady at around 2,500-3,000 cases per year, even though the industrial exposures sufficient to induce asbestos disease largely ended in the early 1970s.

The discovery of a gene mutation known to cause a specific disease can easily be case dispositive.

If geneticists can clearly identify either single mutations, or clusters of mutations, that are capable by themselves of inducing mesothelioma, the cases should be resolved by a simple genetic test — if the plaintiff has that mutation or set of mutations, then courts should dismiss the cases for lack of sufficient or admissible expert evidence of causation.

And the genetic test may involve nothing more intrusive for plaintiff than a swab inside the mouth. But for reasons discussed below, the outcome may not be that simple.

Thus, we can expect that geneticists will in fact begin to unravel the genetic basis of mesothelioma, and as they do defendants will increasingly ask juries to accept the genetic explanation as the cause of the disease.

THE BASICS OF GENETICALLY-INDUCED DISEASE

Genetics is complicated and this article can only touch on the basics. Human cells reproduce by copying their DNA to new
or “daughter” cells. That process involves millions of copying steps for each new cell that must be correct or a genetic error occurs.

Think of the challenge of copying the Bible by hand many times without making a single transcription error. As noted above, the reality is that spontaneous errors in gene transcription occur all the time.

Most of those errors are harmless, or on a portion of a gene that is inactive, or the mutated cell is eliminated or repaired by the body. On occasion, however, a series of mutation errors occurs that has clear implications for health consequences.

For cancers, those changes usually induce the cell to grow without control — like an accelerating car without brakes and no way to turn the engine off. Other changes destroy the body’s ability to eliminate the danger from such cells.

Mutations from cell copying typically fall into two classes, and both are involved in asbestos disease. The first is a point mutation occurring during the course of a person’s life, and in somatic or non-reproductive cells.

The majority of genetically-induced asbestos cases will involve point mutations. These cancers are not inherited or passed on — they only affect the individual in which they occur.

Point mutations that become cancers are the result of a consequential change in a cell somewhere in the body, e.g., in the lining of the lung where mesothelioma occurs. Most cancers probably require two or more such mutations to develop into actual disease.

The second category of mutation is a germline mutation, or a change in one of the cells associated with reproduction — a female egg or male sperm cell.

If repeated mutations hit those cells, the change can be passed to future generations, possibly creating an inherited tendency toward a certain cancer. As one example, some types of breast cancer today fall into this category.

Many women have undergone testing to see if they have an inherited mutation such as BRCA1 that could increase their chances of a spontaneously induced breast cancer, without any exposure to outside substances.

Scientists used to adhere to a “one-hit” theory for mutations, a theory that requires only a single mutation in a particular cell to produce cancer.

But that theory is largely discredited. Today’s geneticists instead understand that the same cell would have to undergo multiple changes to become a cancerous cell.

Even then, that cell will not turn into a malignant tumor unless it can evade or defeat the many ways our bodies kill, repair, or remove these aberrant cells.

By one estimate, the body produces about 100 mutated cells a day, and our bodies are ordinarily quite good at controlling or eliminating the danger from those cells.

For asbestos-induced disease, the risk comes from overwhelming exposures that create many mutated cells or overwhelm the body’s defenses.

That is believed to be the case, for instance, with the insulator and shipyard type of asbestos exposure — the extensive exposures of those workers prevented the workers’ bodies from processing the invading fibers or mutated cells to avoid disease.

For younger plaintiffs or non-asbestos workers who rarely had sufficient exposure to cause disease, a genetic, spontaneously caused cancer is much more likely, and proving that reality may be the key to a defense verdict.

Some cancers are believed to be caused by a single mutated genetic segment, but that phenomenon is rather rare. Instead, most cancers, including mesothelioma, appear to involve a cluster of mutations at different points in the genetic code (known as alleles) rather than just one.

In addition, that cluster of mutations could produce any of a set of specific cancers. Thus, a group of several mutations could appear connected to a specific set of cancers, e.g., one of which is mesothelioma.

With a few possible exceptions, a single genetic modification is not likely to explain mesothelioma — most instances of mesothelioma appear instead to be induced by a set of mutations on various genes.

That complication makes the defense case and genetic testing more difficult.

As one example, a mutation on the ALK gene is now identified as a cause of peritoneal mesothelioma in women as reported in some articles.¹¹

This mutation is rare and accounts for a small percentage of such cases. One particular mutation known as BAP1 also may be a single point mutation that by itself can explain a case of mesothelioma.¹²

BAP1, however, is related to several other cancers, including melanoma, so there is not a one-to-one correspondence between a person with a BAP1 error and mesothelioma as the outcome.

Some asbestos defendants have presented a BAP1 defense in some litigation, but with unclear results to date. As of 2018,
one set of authors had identified two trials that proceeded with testimony on both sides of BAP1 sole causation.\textsuperscript{11}

One interesting twist in the first trial is that one of the defendants intended to argue in part that given the very recent nature of the BAP1 discovery, the defendant could not possibly have known that plaintiff was an “eggshell skull” victim susceptible to extremely small exposures at the time the exposures occurred — a potential state-of-the-art usage of genetic testing.

Another set of cases where genetic defenses are viable are those involving multiple family members. These families typically have inherited mutations that lead to certain cancers occurring in more than one family member.

In one such instance, the defense expert identified a CDKN2A error in plaintiff, and her mother had the same error. The family had an extensive history of cancers, including mesothelioma.\textsuperscript{11}

The presence of this hereditary error plus multiple cancers created a strong jury argument that the disease was entirely inherited. Such a case is a prime candidate for a defense genetic explanation, even if the specific mutation underlying the set of cancers is not yet known.

The ongoing research continues to identify mutations linked to mesothelioma, any of which could end up being keys to litigation. For example, a number of known hereditary syndromes can produce cancers, without outside influence, and some of those syndromes appear to include mesothelioma.

One example is the Li-Fraumeni Syndrome (LFS), a rare inherited disorder involving the TP53 enzyme that can affect almost any organ system.

A large number of other sections of the genetic code are under investigation (e.g., the NF2 segment involving inherited errors reported in significant number of mesothelioma cases).

Defense experts will likely need to see fairly strong evidence of a correlation, however, before asserting these mutations as a defense in litigation.

The science of mesothelioma causation and genetics at present is still in its infancy.

Even without a specifically-identified genetic mutation in a plaintiff, however, defendants can always present a generic defense that a mesothelioma is much more likely to be genetic than caused by minimal asbestos exposure.

There is a wealth of literature and material to support such a defense.

The cases most likely to support such a defense include younger plaintiffs (born too late for significant asbestos exposure) and women, whose disease rate has historically been mostly spontaneously-induced.

But the next step — detecting a specific set of mutations in a plaintiff and proving those as the sole cause of mesothelioma — is still in development and will only slowly be incorporated into litigation.

**PLAINTIFF EXPERT RESPONSE**

The discovery of a genetic basis to mesothelioma is obviously a threat to the ongoing litigation.

Plaintiff-supporting experts are not yet ready to yield the floor to genetic cause, however, and instead have mounted a “susceptibility” approach that allows them to buy into any genetic errors instead of trying to discount the genetic testing.

That approach claims that the disease is allegedly “multifactorial,” meaning a combined cause — the genetic error simply made the plaintiff more vulnerable to even the smallest of asbestos exposures.

This testimony is an attempt to fold these cases into the category of “eggshell skull victims,” a tort doctrine that is familiar to first-year law students from their torts classes.\textsuperscript{11}

Multifactorial cause of cancers is in fact a well-known phenomenon, and a fair number of cancers are presumed to be the result of both a genetic error and the influence of an outside influence (e.g., smoking) that puts the patient over the edge into cancer.

But recent research by Tomasetti and his colleagues has demonstrated that two-thirds of all cancers are likely caused solely by point mutations and thus are not multifactorial. The other one-third are produced by inherited mutations or by environmental factors.

Thus, environmental causes, including multifactorial causes, account for less than 1/3 of all cancers. The rest are produced by the body’s own mutation errors.

The burden should be on plaintiffs in asbestos and toxic tort cases to not merely speculate that mesothelioma is multifactorial, but to prove it with competent epidemiology studies.

That proof is almost always lacking. Without it, the principle of Occam’s Razor should apply — the simplest explanation is the correct one.

Notwithstanding, the fight over multifactorial cause will be the source of a great deal of expert dispute and motions practice for the near future.

Plaintiffs may also actually benefit from another development in the genetics world, although it is too early to tell. Some researchers are developing genetic evidence of the impact from specific toxins and carcinogens.

If that form of tracing proves successful, the testing might indicate, for instance, mutations or other cellular injury...
induced by specific forms of asbestos present in the plaintiff’s body.

Such a finding might contribute to a plaintiff’s case. Conversely, the absence of such harm might contribute strongly to a defense theory that the disease was genetically induced. How concrete and conclusive these genetic marker studies will turn out to be is unclear.

**PRACTICE POINTERS FOR THE NEXT TEN YEARS**

So, if you are a defense practitioner in toxic tort or asbestos litigation, where do you go with this information to handle your matters in the near future?

Genetic causation articles and science are incredibly complex, including an entire language that most of us have no familiarity with. Lawyers will need considerable expert help to understand when and how to assert a genetic defense.

Here are a few practice pointers.

- **Consider the genetic basis for latent diseases or injuries as an alternative to toxic exposure.** Many disease endpoints in litigation today likely have their source in spontaneous mutations rather than the minute exposures involved in today’s environment and workplace. Check the literature, talk to a geneticist — find out if you have an argument and what the state of the science is for that particular endpoint.

- **Look for plaintiffs whose disease is likely genetic.** For mesothelioma, genetic defenses will likely not completely eliminate any remaining “old” litigation involving significantly exposed insulators and shipyard workers. The epidemiology supporting amphibole asbestos causation, at least, is usually compelling, if the lifetime dose is high enough. But for younger plaintiffs or non-asbestos workers who rarely had sufficient exposure to cause disease, a genetic, spontaneously-caused cancer is much more likely, and proving that reality may be the key to a defense verdict. The same is likely true of most chrysotile-based exposures, given the at best limited propensity of chrysotile to produce mesothelioma at all in humans. Most of those cases will also involve no meaningful alternative asbestos exposure (e.g., insulation work), and thus the genetic cause is a necessary component for the jury to understand how, if not asbestos, plaintiff incurred the disease.

- **Target cases involving familial cancers, including mesothelioma.** Discovery should include a family cancer history to determine whether the family may have a set of genetic mutations that creates the pathway for spontaneously-induced cancers. Genetic testing may be appropriate for one or more family members, but a court order may be needed to accomplish this. The current literature will also be critical, as it appears mutations will produce a discrete set of cancers, not just a single type. Defense counsel need to elicit the type of cancers in the family cluster during discovery.

  - **Watch the medical records for genetic testing.** Many treating physicians today are ordering genetic testing for patients with cancer to help type the cancer and identify possible immunotherapy treatments. This information may be critical for the defense. Defense counsel should ensure that all such records are produced.

  - **Consider genetic testing but be aware of the limitations.** If there is no family history, and the exposures are not sufficient to explain the disease, then genetic point mutations are likely at fault. A genetic test could screen for the known mutations that are related to mesothelioma (or another cancer). But only a few mutations today are clearly linked to mesothelioma, so the odds of proving one of those may be relatively small for the present. Other mutations will fall into the “may be linked” category, for now — possibly worth trial testimony by a defense expert to help explain the role of genes in disease, if a judge will let that testimony in.

It is easy to see how the next ten years is likely to consist of defendants, mostly at least, aggressively pursuing the latest genetic testing theories and applying them to plaintiffs in any given case.

Plaintiffs’ counsel and their experts, in turn, will respond by muddying the waters with multifactorial theory, fighting off the requested genetic testing, and challenging the defense genetic testimony.

Regardless, the future of asbestos litigation is increasingly going to involve genetics — practitioners in this area would do well to get a primer in genetic causation of disease and begin to watch the literature and cases for relevant developments.

**Notes**

2. John E. Craighead, *Epidemiology of Mesothelioma and Historical Background*, in Malignant Mesothelioma (Andrea Tannapfel ed. 2011) (“[M]any cases of mesothelioma are idiopathic, while some are caused by therapeutic irradiation or chronic inflammation in body cavities.”); Mary Jane Teta et al., *U.S. Mesothelioma Patterns 1973-2002: Indicators of Change and Insights into Background Rates*, 17 Eur. J. Cancer Prevention 525, 526 (2008) (“[S]cientific evidence suggests that a portion of cases occurred with no apparent history of asbestos exposure .... it is generally well accepted, therefore, that there is a background rate of mesothelioma, unrelated to asbestos exposure.”).
flurry of research activity over the last 5-6 years, the BAP1 gene is now firmly linked causally to a novel tumor predisposition syndrome (TPDS) characterized by increased susceptibility to mesothelioma, UM, cutaneous melanoma (CM) and benign melanocytic tumors, as well as several other cancer types.”).


13 See, e.g., Genetic Risk Factors for Mesothelioma, on Asbestos.com, a plaintiff-focused website, https://bit.ly/34VnHC9 (arguing that “[t]he BAP1 gene regulates a channel that moves calcium inside cells. When the gene is damaged or mutated, calcium levels drop, making it more likely to become malignant when exposed to carcinogens such as asbestos.”).

This article was published on Westlaw Today on November 9, 2020.

ABOUT THE AUTHORS

William L. Anderson (L) is a partner in Crowell & Moring’s Mass Tort, Product, and Consumer Litigation Group. He has practiced for 32 years in product liability, toxic tort and environmental matters, which typically involve significant and complex medical and scientific issues and national coordination roles. He can be reached at wanderson@crowell.com. Peter C. Condon (C), also a partner in the firm’s Mass Tort, Product, and Consumer Litigation Group, is a veteran litigator who focuses his practice on toxic tort, product liability and commercial matters. He may be reached at pcondon@crowell.com. Kieran J. Tuckley (R) is an associate in the Mass Tort, Product, and Consumer Litigation Group. He represents product manufacturers and property owners in complex product liability and toxic tort litigation pending in courts across the country. He may be reached at ktuckley@crowell.com. All of the authors are based in the firm’s office in Washington, D.C.

Thomson Reuters develops and delivers intelligent information and solutions for professionals, connecting and empowering global markets. We enable professionals to make the decisions that matter most, all powered by the world’s most trusted news organization.