THE MORE WE KNOW, THE LESS INTELLIGENT WE ARE? — HOW GENOMIC INFORMATION SHOULD, AND SHOULD NOT, CHANGE TOXIC TORT CAUSATION DOCTRINE

*Steve C. Gold**

Advances in genomic science are rapidly increasing our understanding of disease and toxicity at the most fundamental biological level. Some say this heralds a new era of certainty in linking toxic substances to human illness in the courtroom. Others are skeptical. In this Article I argue that the new sciences of molecular epidemiology and toxicogenomics will evince both remarkable explanatory power and intractable complexity. Therefore, even when these sciences are brought to bear, toxic tort claims will continue to present their familiar jurisprudential problems. Nevertheless, as genomic information is used in toxic tort cases, the scientific developments will offer courts an opportunity to correct mistakes of the past. Courts will miss those opportunities, however, if they simply transfer attitudes from classical epidemiology and toxicology to molecular and genomic knowledge. Using the possible link between trichloroethylene and a type of kidney cancer as an example, I describe several causation issues where courts can, if they choose, improve doctrine by properly understanding and utilizing genomic information.

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* Assistant Professor of Law, Rutgers School of Law — Newark. J.D., Yale Law School; A.B. *cum laude* in Biology, Harvard College. A line in REPO MAN (1984) inspired my title: "The more you drive, the less intelligent you are." This research was partially supported by the Dean's Research Fund of Rutgers School of Law — Newark. I am grateful for helpful suggestions that many of my Rutgers colleagues provided; among these, Adil Haque, Howard Latin, John Leubsdorf, Brandon Paradise, James Pope, and Sabrina Safrin were particularly giving of their time. Thanks to Diane Connolly, Michael Dore, Michael Froomkin, Michael Green, Molly Hall, Andrew Klein, Richard Lewontin, Joseph Sanders, and Wendy Wagner, who were kind enough to offer invaluable comments on earlier drafts. Eric Lander graciously referred me to information on the current state of genomic science. I deeply appreciate the efforts of librarian Susan Lyons and indefatigable research assistants Jamie Delman, Tara Elliott, and Caitlin Stephens. Finally, I owe a debt that can never be repaid to my wife, Jenny Aley, who persistently prodded and patiently put up with the writing process. I thank her for motivating and tolerating me.

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I. Introduction

"Law lags science; it does not lead it."[1] For more than thirty years, the treatment of causation in toxic tort cases has exemplified this dictum, resulting in poorly articulated, poorly implemented doctrine. Today's incredibly rapid increase in the understanding of disease and toxicity at the genetic and molecular level offers the law an opportunity to catch up — or to fall further behind scientific reality.

In this Article I argue that genomic science evinces remarkable explanatory power coupled with intractable complexity. Therefore, despite the vast increase in scientific knowledge, familiar problems of toxic tort causation will remain as courts grapple with seemingly deterministic science that will frequently produce indeterminate results. But this new knowledge nevertheless offers an opportunity to more appropriately apply developing science to developing law. If courts simply transfer prior attitudes and prior mistaken doctrine to the new genomic era, they will miss that opportunity.

Part II reviews how courts responded to the difficulties of proving toxic tort causation, focusing particularly on judicial treatment of evidence derived from classical epidemiology. Part III describes enough of the emerging sciences of toxicogenomics and molecular epidemiology to show their potential usefulness in toxic tort cases and surveys the relatively limited legal scholarship assessing this potential. Part IV analyzes the extent to which these new sciences will or will not ease the toxic tort causation problem, predicts how courts are likely to apply them in the absence of doctrinal

[1] Rosen v. Ciba-Geigy Corp., 78 F.3d 316, 319 (7th Cir. 1996) (Posner, C.J.). An electronic search in June 2009 found twenty-six federal and state court opinions quoting this catchy sentence. One might think the remark expresses a deferential judicial attitude toward science. On the contrary, *Rosen* makes numerous assertions of fact (which may or may not be correct) without citation to scientific evidence, such as: "Quitting smoking is, by inducing stress, more likely to precipitate a heart attack than smoking one more cigarette is likely to do." *Id.*

change, and proposes better ways for courts to respond — ending with a suggestion that new scientific tools may reinvigorate old proposals for legal reform.

II. Causation in Toxic Torts Before Genomics

A. The Problem

Toxic tort causation challenged the legal system because, despite scientific understanding that exposure to certain substances could lead to disease, the diseases themselves provided "no physical evidence of the inducing agent"[2] and occurred also in some people who had no known exposure to an alleged causative agent.[3] The existence of "background" cases of disease not associated with exposure raised the problems of proving, for legal purposes, (1) that the substance in question caused *any* of the incidence of the disease in question (often called "general causation") and (2) that an individual plaintiff's case was distinguishable from the background incidence of disease and therefore could be causally attributed to exposure (often called "specific causation").[4]

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[2] Steve Gold, Note, *Causation in Toxic Torts: Burdens of Proof, Standards of Persuasion, and Statistical Evidence*, 96 Yale L.J. 376, 379 (1986).

[3] Latency — the fact that many diseases that originate in toxic exposure manifest as illness years later — is often cited as a causation problem. *E.g.*, Ayers v. Jackson Twp., 525 A.2d 287, 301 (N.J. 1987); Albert C. Lin, *Beyond Tort: Compensating Victims of Environmental Toxic Injury*, 78 S. Cal. L. Rev. 1439, 1441–42 (2005). To be sure, latency can pose problems for a toxic tort plaintiff: the plaintiff may not recall the exposure or may not imagine it is connected to the disease; passage of time may make it difficult to identify the manufacturer(s) of the product to which plaintiff was exposed; liable parties may become defunct or insolvent. But if the toxic agent left behind a detectable telltale "fingerprint" or caused a disease that occurred only in persons exposed, latency alone would not prevent a plaintiff from proving the causal connection between exposure and illness. *See generally* Michael D. Green, *The Future of Proportional Liability: The Lessons of Toxic Substances Causation*, *in* Exploring Tort Law 352, 372–73 (M. Stuart Madden ed., 2005) ("existence of competing causes and the proportion of disease that they cause," rather than length of latency period, is critical).

[4] The distinction between general and specific causation, and the need to prove both, figures prominently in toxic tort jurisprudence and commentary. *See, e.g.*, Henricksen v. ConocoPhillips Co., 605 F. Supp. 2d 1142, 1176 (E.D. Wash. 2009) (stating that plaintiff must prove both, but "court's ultimate focus" is proof that individual plaintiff's disease was caused by exposure); Gerald W. Boston, *A Mass-Exposure Model of Toxic Causation: the Content of Scientific Proof and the Regulatory Experience*, 18 Colum. J. Envtl. L. 181, 213 (1993). It is not, however, unique to that context. The same distinction could be, but is not, made in many instances of more traditional causation. *See* Restatement (Third) of Torts: Liab. for Physical & Emotional Harm § 28 cmt. c(4) (2010) (citing Joseph Sanders & Julie Machal-Fulks, *The Admissibility of Differential Diagnosis Testimony to Prove Causation in Toxic Tort Cases: The Interplay of Adjective and Substantive Law*, 64 Law & Contemp. Probs. 107 (2001)). Consider, for example, a plane crash in icy weather. If ice was observed on the plane's wings, the causal inquiry will focus on that observed fact, and will typically be framed as whether the ice caused the accident. The inquiry could, however, be framed in two steps: (1) whether ice on an airplane wing can cause a plane to crash (general causation), and (2) whether this airplane crashed because of ice on the wings or for some other reason (specific causation).

The causal relationship between toxic exposures and illness cannot be observed by our ordinary senses nor inferred by reference to our common experience, so resolving the issue inevitably requires scientific evidence.[5] Yet the *ne plus ultra* of scientific hypothesis testing — controlled, reproducible experiments with replicable results — is inherently unavailable. A plaintiff's life cannot be repeatedly re-lived, varying only the exposure to an allegedly toxic substance, to observe whether disease occurs only in the presence of exposure and not in its absence.[6] Given that limitation, courts must decide what other types of scientific evidence will be legally relevant to the causation issue, and what quantum of such evidence will be deemed sufficient for a plaintiff to carry the burden of proving causation.

B. Classical Sources of Causation Evidence

For proof of toxic causation, the tools of medical science that address individuals, such as physical examinations and even chemical analysis, have been of limited use. They help diagnose and classify illness, but generally have been unable to identify the agent that initiated or promoted disease. Differential diagnosis, which relies on systematically ruling out all *other* plausible causes of a condition,[7] must usually be accompanied by some confirmatory evidence (of "general causation") to be persuasive, lest a particular case of disease be attributed to "background" or "unknown etiology."[8] The conventionally available scientific evidence for assessing suspected toxic effects of substances has come from the disciplines of toxicology and epidemiology.[9]

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[5] *See, e.g.*, Allison v. McGhan Med. Corp., 184 F.3d 1300, 1320 (11th Cir. 1999) (holding that expert testimony is essential because the connection between breast implants and systemic disease "is not a natural inference that a juror could make through human experience"); *Henricksen*, 605 F. Supp. 2d at 1177 ("Expert [causation] testimony is necessary . . . since this is a toxic tort lawsuit").

[6] Something a little like this is the "challenge-dechallenge-rechallenge" sequence, in which a doctor observes whether suspected side effects disappear when a drug is withdrawn and reappear when the drug is re-administered. This is not truly a controlled experiment, and its applicability is obviously limited to exposures that can be altered at will and toxicity that manifests and subsides quickly. Courts have given such observations, at best, a mixed reception. *Compare, e.g.*, *In re* Neurontin Marketing, Sales Practices, and Products Liab. Litig., 612 F. Supp. 2d 116, 159 (D. Mass. 2009) (finding challenge-dechallenge data relevant to support inference of causation) *with, e.g.*, Miller v. Pfizer, Inc., 196 F. Supp. 2d 1062, 1077 (D. Kan. 2002) ("Use of a small number of challenge-dechallenge studies to test a hypothesis is inadequate and not generally accepted methodology.").

[7] "Differential diagnosis" is something of a misnomer. Diagnosis is the medical art of identifying the condition from which a patient suffers. The medically relevant cause or source of the disease is its "etiology." Mary Sue Henifin et al., *Reference Guide on Medical Testimony*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE 439, 443–44 (Fed. Judicial Ctr. ed., 2d ed. 2000) (noting that some courts have used the term "differential etiology").

[8] *See, e.g.*, *Henricksen*, 605 F. Supp. 2d at 1158 (stating that "differential diagnosis cannot demonstrate general causation" but rather assumes it).

[9] Jean Macchiaroli Eggen, *Toxic Torts and Causation: The Challenge of* Daubert *After the First Decade*, 17 NAT. RESOURCES & ENV'T 213, 213 (2003).

Toxicology uses biochemical studies to evaluate the mechanisms of toxic effects, *in vitro* assays of tissue samples to assess histological toxicity, and *in vivo* studies of effects on animal models. Because this science relies on biological stand-ins for people, toxicological evidence presents a court with the general causation question of whether such evidence can support inferences about a substance's toxic effects in living human beings, as well as with the specific causation question of whether it can support an inference about the particular plaintiff.[10]

Epidemiology searches for associations between disease and suspected causal factors. It takes one of two general approaches: to compare the rate of disease incidence between populations exposed to the suspected causal factor(s) and populations not exposed (a "cohort" study), or to compare the rate of exposure to the factor(s) between populations with the disease and populations without the disease (a "case-control" study).[11] The comparison allows computation of a "relative risk." For example, if 5% of smokers get lung cancer, but only 1% of non-smokers do, the relative risk of smokers for lung cancer would be five, implying that smoking explains four of every five cases of lung cancer in smokers ("attributable risk" of 80%).[12]

Epidemiologic studies test the null hypothesis that there is no difference in disease incidence between those exposed to the suspected toxin and those not exposed, i.e., that the relative risk equals one. Because this science relies on statistical analysis of groups, epidemiologic evidence presents a court with the specific causation question of whether such evidence can support inferences about the origin of disease in a specific individual,[13] as well as with the general causation question of whether an observed increase in risk associated with exposure is coincidental — a result of sampling error[14] or

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[10] *See id.*; Boston, *supra* note 4, at 214–15, 218–25.

[11] MaryFran Sowers, *Design Methods for Occupational and Environmental Epidemiology*, *in* ENVIRONMENTAL EPIDEMIOLOGY 21, 23–25 (William M. Draper ed., 1994).

[12] *See* Gary H. Spivey, *The Epidemiological Method*, *in* ENVIRONMENTAL EPIDEMIOLOGY, *supra* note 11, at 9, 14–16. Strictly speaking, relative risk — "the incidence [of disease] among those exposed to a risk factor . . . divided by the incidence among those not exposed . . ." — is the output of a cohort study. *Id.* at 14–15. In case-control studies, epidemiologists calculate an "odds ratio" — the "odds of exposure among the diseased in comparison to the odds of exposure in the control group . . . ." Sowers, *supra* note 11, at 25. Odds ratio "is considered a surrogate estimate of the relative risk . . . ." *Id.* In the smoking example in the text, the odds are 5:1 that a person with lung cancer had smoked and 95:99 that a person in the control group had smoked. The odds ratio is 5.2. For diseases with relatively low overall incidence, the computed relative risk and odds ratio values are quite similar. *See* Michael D. Green et al., *Reference Guide on Epidemiology*, *in* REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, *supra* note 7 at 333, 351. For ease of reference, I use "relative risk" as shorthand for both types of results.

[13] *See* Eggen, *supra* note 9, at 213.

[14] Because these studies attempt to estimate population ("parametric") values of disease incidence from study of a sample, relative risk estimates are subject to random error. Ideally, the samples are randomly selected such that any relevant traits *except* exposure would be expected to be similarly distributed in the sample of exposed individuals and in the sample of unexposed individuals. But even with such theoretically perfect, unbiased sampling, identical parametric values may, by chance, produce sample measurements that appear to differ. *See* David H. Kaye & David A. Freedman, *Reference Guide on Statistics*, *in* REFERENCE MANUAL

problems with the study design[15] — or is too small to matter even though it is real.[16]

C. The Courts Embrace Epidemiology — Perhaps Too Tightly

In the early years of widespread toxic tort litigation, some questioned the fit between the population-based data of epidemiology and the legal requirement of proof of causation of an individual plaintiff's disease.[17] To a few courts, relying on relative incidence to prove the cause of illness seemed much like relying on the relative number of buses to prove the cause of a traffic accident.[18] For example, in 1991, the Delaware Supreme Court, affirming a directed verdict against five plaintiffs who suffered from asbestos-related diseases, cited with approval an earlier Superior Court ruling that "an epidemiologist's testimony was insufficient . . . to prove that exposure to asbestos products caused the decedent's disease and death[,]" because epidemiology involved "an inference of causation based upon . . . the statistical frequencies of diseases among groups," in contrast to "direct expert medical testimony based upon an individualized diagnosis."[19]

ON SCIENTIFIC EVIDENCE, *supra* note 7, at 83, 121–22. Conventionally, to confidently reject a null hypothesis and declare a result "statistically significant," scientists require no more than a 5% probability that an apparent difference between two populations results from sampling error. *See id.* at 124. Sampling error could also obscure a real difference between parametric values, especially if a study has limited statistical "power" — the ability to produce statistically significant results. Statistical power is low if the number of subjects in the study, and/or the degree of difference between parametric values, is small. *Id.* at 125–26.

[15] Errors in measuring or classifying the study variables, perhaps because researchers used an imperfect proxy to identify exposure or disease, can result in "information bias"; undetected differences in the way in which sampled members of the exposed and unexposed populations are chosen can result in "selection bias"; undetected differences in some potentially causal variable that the study does not adequately control can result in "confounding." George Maldonado, *Interpreting Epidemiological Studies*, *in* ENVIRONMENTAL EPIDEMIOLOGY, *supra* note 11, at 29, 30–37 (William M. Draper ed., 1994). All these potential errors can cut both ways. Depending on the nature of the bias or confounding, they can create the appearance of a statistical association without true causation, or create the appearance of no statistical association despite the existence of a real causal relationship. *See id.* Statistical significance testing does not detect such biases or confounding. Kaye & Freedman, *supra* note 14, at 121.

[16] Whether an established increase in risk is "too small to matter" is, of course, a policy question, rather than a scientific one.

[17] *See, e.g.*, Michael Dore, *A Commentary on the Use of Epidemiological Evidence in Demonstrating Cause-In-Fact*, 7 HARV. ENVTL. L. REV. 429, 431–35 (1983) (arguing epidemiologic evidence inappropriate as proof of causation in individual cases); Junius C. McElveen Jr. & Pamela S. Eddy, *Cancer and Toxic Substances: The Problem of Causation and the Use of Epidemiology*, 33 CLEV. ST. L. REV. 29, 36–47 (1984–1985).

[18] Smith v. Rapid Transit, 58 N.E.2d 754 (Mass. 1945) (finding statistical likelihood alone insufficient to support finding that bus that injured Smith was defendant's).

[19] Money v. Manville Corp. Asbestos Disease Comp. Trust Fund, 596 A.2d 1372, 1376 n.6 (Del. 1991) (citing Lee v. A.C. & S. Co., 542 A.2d 352, 355 (Del. Super. Ct. 1987)). Each plaintiff proved he had been exposed to various asbestos-containing products, but offered no medical testimony that each defendant's particular product caused his disease. *Id.* at 1374–75; *see also, e.g.*, Szczepaniak v. United States, No. 80-990-MA, 1983 U.S. Dist. LEXIS 18875, at *12 (D. Mass. Mar. 2, 1983) (finding epidemiology not probative of causation); Sulesky v. United States, 545 F. Supp. 426, 430 (S.D. W. Va. 1982) (finding epidemiology "not determinative").

But courts were also reluctant to infer causation from *in vitro* or animal studies.[20] As courts came to understand that toxic tort cases would rarely if ever involve "direct expert medical testimony"[21] on specific causation, epidemiologic proof gained more and more acceptance.[22]

Judge Jack Weinstein's influential opinions in the Agent Orange cases in the 1980s exemplified courts' increasing willingness not just to accept epidemiologic evidence as proof of causation, but to require it. After approving a massive settlement with a class of veterans exposed to Agent Orange,[23] Judge Weinstein dismissed all claims of individual plaintiffs who had opted out of the class, for failure to prove causation.[24] The decision systematically rejected all other forms of causation evidence these plaintiffs tried to present, holding that epidemiologic studies of exposed human populations were the "only useful studies having any bearing on causation."[25] Many

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[20] *See, e.g.*, Bell v. Swift Adhesives, Inc., 804 F. Supp. 1577, 1579–81 (S.D. Ga. 1992) ("[courts] have tended to view [animal] studies with suspicion . . . . Nothing in the record persuades this Court to depart from . . . precedent . . . by viewing animal studies favorably;" ruling that expert opinion based predominantly on animal studies cannot satisfy "reasonable degree of medical certainty" standard); *see also* Lynch v. Merrell-Nat'l Labs., 830 F.2d 1190, 1194 (1st Cir. 1987) ("[s]tudies of this sort, singly or in combination, do not have the capability of proving causation in human beings in the absence of any confirmatory epidemiological data"); Boston, *supra* note 4, at 282 (citing *In re* "Agent Orange" Prod. Liab. Litig., 611 F. Supp. 1223, 1241 (E.D.N.Y. 1985) [hereinafter *Agent Orange Opt Out*]) (giving examples of judicial rejection of opinions based on toxicological data unconfirmed by epidemiologic studies).

[21] *Money*, 596 A.2d at 1376.

[22] Early instances included, for example, *Lynch*, 830 F.2d at 1193–94 (permitting defendant to rely on epidemiologic evidence showing lack of association between Bendectin and birth defects); *Ellis v. Int'l Playtex, Inc*., 745 F.2d 292, 299–305 (4th Cir. 1984) (permitting plaintiff to rely on epidemiologic evidence); *Kehm v. Procter & Gamble*, 580 F. Supp. 890, 898–902 (N.D. Iowa 1982) (same), *aff'd* 724 F.2d 613 (8th Cir. 1983); *Cook v. United States*, 545 F. Supp. 306 (N.D. Cal. 1982) (same). Today, few courts question that evidence or expert opinion derived from applicable epidemiologic studies can help prove or disprove a causal connection between an exposure and a disease. RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYSICAL & EMOTIONAL HARM § 28 cmt. c(3) (2010) ("Cases accepting the proposition that relevant epidemiologic studies are acceptable evidence to support proof of general causation are legion.").

[23] *In re* "Agent Orange" Prod. Liab. Litig., 597 F. Supp. 740 (E.D.N.Y. 1984), *aff'd*, 818 F.2d 145 (2d Cir. 1987) [hereinafter *Agent Orange Fairness*].

[24] *Agent Orange Opt Out*, 611 F. Supp. 1223, 1229 (E.D.N.Y. 1985), *aff'd*, 818 F.2d 187 (2d Cir. 1987). Gerald Boston persuasively observed that the "real reason" the opt-out cases *had* to be dismissed was that "a favorable outcome to the plaintiffs would be intolerable and inconsistent with the class-wide treatment" afforded by the just-approved settlement. Boston, *supra* note 4, at 191. Judge Weinstein later allowed dismissed opt-out plaintiffs to rejoin the class and share in the settlement proceeds. *In re* "Agent Orange" Prod. Liab. Litig., 689 F. Supp. 1250 (E.D.N.Y. 1988).

[25] *Agent Orange Opt Out*, 611 F. Supp. at 1231. Even courts holding that causation might be proved without epidemiologic evidence frequently characterize epidemiology as the "best" evidence. *E.g.*, Beck v. Koppers, Inc., No. 3:03CV60-P-D, 2006 U.S. Dist. LEXIS 25519, at *10 (N.D. Miss. Feb. 2, 2006); *see also, e.g.*, Norris v. Baxter Healthcare Corp., 397 F.3d 878, 882 (10th Cir. 2005); Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1198 (11th Cir. 2002); Lakie v. Smithkline Beecham, 965 F. Supp. 49, 56 (D.D.C. 1997) (calling lack of epidemiologic evidence "important" yet admitting plaintiff's expert causation testimony).

other courts — though by no means all — have expressly or effectively held that epidemiologic evidence is necessary to prove causation.[26]

Agent Orange also provided an early illustration of a court marrying the probabilistic language of epidemiology and the requirement of proof by a preponderance of the evidence to create a new substantive requirement for what must be proven to establish causation in toxic tort cases.[27] When an epidemiologic study finds a relative risk of two, the incidence of disease in an exposed population is double the incidence in an unexposed population. In the exposed population, therefore, half of the cases of disease would be "background" cases, and the other half would be considered attributable to the exposure. Pick a case at random, and it is equally likely to be a background case or a case that would not have occurred but for the exposure (although one cannot tell which it actually is). Judge Weinstein, and many judges before and since, reasoned that a plaintiff would have to prove a relative risk greater than two in order to prove that it was "more likely than not" that exposure to the toxic substance caused a particular case of disease.[28] By this substantive standard, proving the required level of relative risk for the exposed population becomes equivalent to meeting the preponderance standard in an individual case. Conversely, failing to prove it becomes equivalent to being unable to prove causation in an individual case.

In 1986, I predicted that this convenient but misleading conflation of probabilistic expressions of relative risk with probabilistic formulations of the preponderance standard would spread, leading to fixation on the numerical output of epidemiologic studies.[29] In 1993, Gerald Boston surveyed case law and concluded that even in mass tort cases involving large exposed populations, "the decisions have largely rejected defendants' arguments that

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[26] *E.g.*, Brock v. Merrell Dow Pharm. Inc., 874 F.2d 307, 315 (5th Cir. 1997), *modified on reh'g*, 884 F.2d 166 (5th Cir. 1989) ("speculation unconfirmed by epidemiologic proof cannot form the basis for causation in a court of law"); Raynor v. Merrell Pharm. Inc., 104 F.3d 1371, 1374 (D.C. Cir. 1997) ("[non-epidemiologic studies,] singly or in combination, are not capable of proving causation in human beings in the face of the overwhelming body of contradictory epidemiological evidence" (citations omitted)). *But see* Pick v. American Medical Systems, Inc., 958 F. Supp. 1151, 1158 (E.D. La. 1997) (stating that *Brock* did not hold that epidemiologic evidence always is required); Longmore v. Merrell Dow Pharm., Inc., 737 F. Supp. 1117 (D. Idaho 1990) (holding that under Idaho law, animal studies and chemical analysis allowed plaintiff to avoid summary judgment despite the large number of contrary epidemiologic studies).

[27] *Agent Orange Fairness*, 597 F. Supp. at 836; *see* Gold, *supra* note 2, at 384–86.

[28] *Agent Orange Fairness*, 597 F. Supp. at 836; *accord, e.g.*, Daubert v. Merrell Dow Pharm., Inc., 43 F.3d 1311, 1320–21 (9th Cir. 1995); DeLuca v. Merrell Dow Pharm., Inc., 911 F.2d 941, 958 (3d Cir. 1990); Hall v. Baxter Healthcare Corp., 947 F. Supp. 1387, 1403 (D. Or. 1996); Marder v. G.D. Searle & Co., 630 F. Supp. 1087, 1092 (D. Md. 1986), *aff'd* 814 F.2d 655 (4th Cir. 1987); Cook v. United States, 545 F. Supp. 306, 308 (N.D. Cal. 1982). This reasoning, based on the "statistical symmetry" of the preponderance rule and a relative risk equal to two, Andrew R. Klein, *Causation and Uncertainty: Making Connections in a Time of Change*, 49 JURIMETRICS J. 5, 27 (2008), has been criticized, Richard Scheines, *What's the Law to Do?: Causation, Truth, and the Law*, 73 BROOK. L. REV. 959, 970 (2008) ("high probability of causation . . . might be what the law must resort to . . . but it should not be confused with assenting to the truth of a but-for claim").

[29] Gold, *supra* note 2, at 389–92.

such studies must demonstrate a threshold relative risk of 2.0 . . . ."[30] But Russelyn Carruth and Bernard Goldstein soon documented a slow but steady increase in the number of judicial decisions referring to this threshold in discussions of toxic tort causation.[31] They found that between 1982 and early 1999, just about half of the decisions that considered the issue held that proof of relative risk greater than two was required to sustain a plaintiff's burden on causation, or to support an expert opinion of causation, or both.[32] The trend, although not universal, has continued in the last decade.[33]

A striking example is the Texas Supreme Court's decision in *Merrell Dow Pharmaceuticals v. Havner*.[34] The *Havner* court effectively made proof of relative risk greater than two a substantive element of a toxic tort plaintiff's prima facie case.[35] The decision also imposed several stringent credi-

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[30] Boston, *supra* note 4, at 327.

[31] Russelyn S. Carruth & Bernard D. Goldstein, *Relative Risk Greater than Two in Proof of Causation in Toxic Tort Litigation*, 41 JURIMETRICS J. 195 (2001).

[32] *Id.* at 200–01.

[33] In my review of decisions, excluding statutory vaccine cases, issued since early 1999, slightly less than half adhered to the view that proof of relative risk greater than two is required (list on file with author). *Compare In re* W.R. Grace & Co., 355 B.R. 462, 483 (Bankr. D. Del. 2006) (expressing approval of equating relative risk greater than two and preponderance rule, and holding proof of such relative risk needed to establish that product is unreasonably dangerous) *and* Graham v. Lautrec, Ltd., No. 01-031717 CE, 2003 WL 23512133, at *1 (Mich. Cir. Ct. July 24, 2003) (noting that relative risk greater than two is needed to prove causation), *with* King v. Burlington Northern Santa Fe Ry. Co., 762 N.W.2d 24, 46 (Neb. 2009) ("[W]e decline to set a minimum threshold for relative risk . . . above the minimum requirement that the study show a relative risk greater than 1.0") *and In re* Hanford Nuclear Reservation Litig., 292 F.3d 1124, 1136–37 (9th Cir. 2002) (holding that plaintiffs need not prove they received "doubling dose" of radiation, because radiation-disease link was already established, distinguishing case from other toxic torts and making relative risk threshold inappropriate); *see also* Estate of George v. Vermont League of Cities and Towns, 2010 VT 1, ¶ 28, No. 08-374, 2010 WL 144023 (Vt. Jan. 15, 2010) (concluding, in worker's compensation case, that "trial court did not abuse its discretion in considering a relative risk greater than 2.0 as a reasonable and helpful benchmark" tying into preponderance standard). *But see* Klein, *supra* note 28, at 27 ("weight of opinion today . . . is decidedly against" requiring threshold relative risk to prove specific causation); *id.* at 27 n.136 ("quite substantial body of case law and commentary rejects an epidemiologic threshold for sufficient proof of general causation" (quoting RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYSICAL & EMOTIONAL HARM § 28 cmt. c (2010))). Professor Klein's text discusses specific causation, while the Restatement Reporters' Note addresses general causation. Moreover, the cases cited in the Reporters' Note address the subtly different question of whether general causation can be proven in the *absence* of epidemiologic evidence. That many courts are (at least in principle) willing to consider a claim of toxic causation without epidemiologic evidence does not contradict the claim that for many courts, *if* epidemiologic evidence is presented, the relative risk must be greater than two in order to satisfy the preponderance standard.

[34] 953 S.W.2d 706 (Tex. 1997).

[35] *Id.* at 717–18 (referring to "requirement of more than a 'doubling of the risk'"). One federal court, obliged to apply Texas law, stated that *Havner* "hedges this requirement with qualifiers." Cotroneo v. Shaw Envtl. & Infrastructure, Inc., No. H-05-1250, 2007 U.S. Dist. LEXIS 79139, at *8 n.5 (S.D. Tex. 2007). But the qualifiers, in context, serve primarily to leave open the possibility that *even* epidemiologic evidence of relative risk greater than two might not suffice. *See Havner*, 953 S.W.2d at 718 ("We do not hold . . . that a relative risk of more than 2.0 is a litmus test *or that a single epidemiological test is legally sufficient* evidence of causation.") (emphasis added). Overall, except possibly in unusual circumstances, proof of causation in toxic tort cases in Texas after *Havner* would seem to require at least one epidemi-

bility requirements on the mandatory epidemiologic evidence, considerably stiffening the standard of persuasion as well.

Havner established as a matter of law that even epidemiologic evidence showing high relative risks would be insufficient unless the plaintiff can "show that he or she is similar to those in the studies,"[36] including that the plaintiff's "exposure or dose levels were comparable to or greater than those in the studies" relied upon.[37] This suggests that a plaintiff exposed to a dose slightly below the dose featured in an epidemiologic study could not survive summary judgment, even if the study found that exposure at the studied dose more than doubled the relative risk and a toxicologist would testify to an established dose-response relationship in support of an inference of causation.

Similarly, the *Havner* court imposed its view of statistical significance as a per se rule.[38] Because the relative risk value reported in any epidemiologic study is an estimate subject to sampling error, epidemiologists usually report a confidence interval associated with the computed relative risk.[39] The court observed that a relative risk of one implied no increase in risk (and therefore no basis to reject the null hypothesis).[40] Applying the statistical significance convention[41] to this understanding, the court went on to hold that even an observed relative risk greater than two would be insufficient if the reported 95% confidence interval[42] were wide enough to include a relative risk of one.[43] This suggests that a case supported by epidemiologic stud-

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ologic study that both shows a relative risk greater than two *and* satisfies the requirements the *Havner* court set for finding that the study is probative. *See, e.g.*, Exxon Corp. v. Makofski, 116 S.W.3d 176, 182–83, 188 (Tex. App. 2003) (stating that relative risk greater than two is required after *Havner*); Wells v. SmithKline Beecham Corp., No. A-06-CA-126-LY, 2009 WL 564303, at *8 (W.D. Tex. Feb. 19, 2009) (concluding that "*Havner* establishes substantive Texas law on a plaintiff's causation burden of proof"; finding proffered testimony insufficient). *But see* Merck & Co., Inc. v. Garza, 277 S.W.3d 430, 435 (Tex. App. 2008) (holding that *Havner* did not establish bright-line rule requiring relative risk greater than two).

[36] 953 S.W.2d at 720.

[37] *Id.* at 721.

[38] *Id.* at 722–24.

[39] A confidence interval is an estimate of the parametric value, *see supra* note 14, expressed as a range rather than a single measured sample value. Kaye & Freedman, *supra* note 14, at 161.

[40] 953 S.W.2d at 723.

[41] *See supra* note 14.

[42] An "*x*% confidence interval" (CI) indicates that, barring bias or confounding, "[i]ntervals obtained this way cover the true value" *x*% of the time. Kaye & Freedman, *supra* note 14, at 161. Thus, for example, a study found that the relative risk for fibrocystic breast disease, among postmenopausal women who used oral contraceptives for less than two years, was 2.29, with a 95% CI of 1.09 to 4.83. Gertrude S. Berkowitz et al., *Oral Contraceptive Use and Fibrocystic Breast Disease Among Pre- and Postmenopausal Women*, 120 AM. J. EPIDEMIOLOGY 87, 91 (1984). A confidence interval can be computed for any arbitrarily chosen *x*. For a given study, confidence intervals widen as *x* increases. Kaye & Freedman, *supra* note 14, at 119. For a given value of *x*, larger sample sizes produce narrower confidence intervals than smaller sample sizes, because having more data points reduces the likelihood that random chance skewed the result. *Id.* at 118 n.116. A narrow interval with a high *x* reflects a measurement with small random error. *Id.* at 119.

[43] 953 S.W.2d at 723–25.

ies of low statistical power[44] could not succeed, even if the reported relative risk were high[45] and a toxicologist would testify that other data supported the inference of causation.

Havner's requirements are more than a routine caution that scientific evidence must be reliable and relevant. Taken together, they present substantial obstacles for cases that require any meaningful degree of inference from existing data, regardless of whether a qualified expert would reliably opine that the inference were reasonable.

D. Evidence Meets Substance: Keepers of the Gate

Decisions holding that only certain types of evidence could be sufficient to establish causation limit the types of inference that are permitted to a legal fact finder. A more fundamental question is whether the evidence, and thus the opportunity to make the inference, gets before the fact finder at all. After *Daubert v. Merrell Dow Pharmaceuticals*,[46] *General Electric Co. v. Joiner*,[47] *Kumho Tire Co., Ltd. v. Carmichael*,[48] and similar state cases[49] which cast the court as gatekeeper for the reliability and fit of expert testimony, the answer has frequently been no.

Daubert and its ilk have often been criticized for promoting judicial weighing of the evidence in the guise of determining reliability and relevance.[50] In toxic tort causation, where substantive doctrine of what it *means* to prove causation is already dressed in evidentiary clothing purporting to

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[44] *Havner* did not acknowledge the possibility that limitations in statistical power of a study could make it difficult to obtain statistically significant results (especially for relatively small differences in risk of relatively rare diseases), nor did it recognize that other evidence could be persuasive in confirming a result in which, say, only the 94% or 92% confidence interval were narrow enough to exclude one.

[45] The *Havner* court correctly recognized that seemingly precise relative risk values are uncertain (as reflected by confidence intervals), but nevertheless created a bright-line threshold of relative risk greater than two. Thus a study with relative risk greater than two but a 95% CI that includes one would fail the test, because the true relative risk might be one; but a study with a relative risk just under two would not be credited for the possibility that the true relative risk might exceed two. Moreover, *any* 95% CI that includes one would fail the test: a relative risk of two with 95% CI of 0.99 to 3.01 fails just as badly as a relative risk of three with 95% CI of 0.5 to 18. The *Havner* rule would treat both as though a relative risk of one is as likely as a relative risk greater than one. *Cf.* DeLuca v. Merrell Dow Pharm., Inc., 911 F.2d 941, 946–48 (3d Cir. 1990) (discussing epidemiology text relied on by plaintiff's expert that asserts parametric value more likely to be near center of confidence interval than edge).

[46] 509 U.S. 579 (1993).

[47] 522 U.S. 136 (1997).

[48] 526 U.S. 137 (1999).

[49] *E.g.*, E.I. du Pont de Nemours & Co. v. Robinson, 923 S.W.2d 549 (Tex. 1995).

[50] *See, e.g.*, Lucinda M. Finley, *Guarding the Gate to the Courthouse: How Trial Judges are Using Their Evidentiary Screening Role to Remake Tort Causation Rules*, 49 DEPAUL L. REV. 335 (1999); Wendy Wagner, *The Perils of Relying on Interested Parties to Evaluate Scientific Quality*, 95 AM. J. PUB. HEALTH 599, S101–103 (Supp. 1 2005); Eggen, *supra* note 9, at 213 ("Far from embodying a simple evidentiary rule, *Daubert* has exerted significant substantive influence . . . .").

state *how* one proves causation, this mixture is almost inevitable.[51] For a trial court, assessing admissibility rather than sufficiency of expert testimony may be the path of least resistance; "when in doubt, keep it out" costs a *Daubert* hearing but saves days of trial and reduces the likelihood of reversal.[52] Very often, toxic tort causation cases are decided by the exclusion of proffered evidence, and when that happens, the absence of what the court deems to be an acceptable study showing relative risk greater than two is frequently decisive.[53]

Dunn v. Sandoz Pharmaceuticals Corp.[54] illustrates how the effective imposition of a "relative risk greater than two" substantive rule interacts with expert testimony gatekeeping. In *Dunn*, the plaintiff's decedent took Parlodel to inhibit lactation after giving birth and subsequently suffered a stroke. Strokes are extremely rare among recently postpartum women, but epidemiologic studies showed the relative risk for those who had taken

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[51] *See* Boston, *supra* note 4, at 209 ("tort causation has been intertwined in the judicial decisions . . . with the rules of evidence governing the admissibility of expert testimony" but "rules of evidence should not drive the law of torts"); RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYSICAL & EMOTIONAL HARM § 28 cmt. c (2010) (explaining how standards for admissibility and sufficiency are technically distinct); *id.* § 28 cmt. c(1) (listing cases supporting the contention that courts often refuse to admit expert testimony that would not be sufficient).

[52] *In re Joint S. and E. Dist. Asbestos Litig.*, 827 F. Supp. 1029 (S.D.N.Y. 1993), *rev'd in pertinent part*, 52 F.3d 1124 (2d Cir. 1995), illustrates this principle. The district court granted judgment n.o.v., explaining, in a long opinion replete with scholarly references, that plaintiff's expert testimony (which had been presented to the jury) was insufficient to establish causation. The Second Circuit reversed, holding that the district court, having admitted the testimony under *Daubert*, erred by weighing its credibility, thereby invading the province of the jury. A district judge might well conclude that the best way to express skepticism of expert testimony is to refuse to admit it in the first instance. *See Joiner*, 522 U.S. at 519 (holding that abuse of discretion is standard of review for exclusion of expert testimony); *In re* TMI Litig., 193 F.3d 613, 666 n.92 (3d Cir. 1999) (noting that *Joiner* left no basis for "heightened" or "stringent" review of exclusion of expert testimony); *cf.* Zuchowicz v. United States, 140 F.3d 381, 387 (2d Cir. 1998) (noting that the appellate court is "reluctant to upset" a decision to admit expert causation testimony as an abuse of discretion).

[53] *See, e.g.*, Henricksen v. ConocoPhillips Co., 605 F. Supp. 2d 1142, 1158, 1171, 1175 (E.D. Wash. 2009); Ashburn v. General Nutrition Centers, Inc., 533 F. Supp. 2d 770 (N.D. Ohio 2008) (excluding testimony for failure to explain choice of another methodology in light of primacy of epidemiology); Pozefsky v. Baxter Healthcare Corp., No. 92-CV-0314, 2001 WL 967608, at *3 (N.D.N.Y. August 16, 2001) (excluding testimony in light of negative epidemiology; sufficient epidemiologic proof requires relative risk greater than two); Watts v. Radiator Specialty Co., 990 So. 2d 143 (Miss. 2008) (affirming exclusion of testimony based in part on lack of statistically significant epidemiology); Kerns v. Hobart Bros. Co., No. 2007 CA 32, 2008 WL 1991909 (Ohio App. 2 Dist. May 9, 2008) (affirming exclusion of testimony for lack of epidemiologic study of plaintiff's industry, despite *in vitro* studies and epidemiologic studies of workers in other industries); *cf.* City of San Antonio v. Pollock, 284 S.W.3d 809 (Tex. 2009) (holding that testimony admitted without objection was insufficient as a matter of law). *But see* King v. Burlington Northern Santa Fe Ry. Co., 762 N.W.2d 24, 46–47 (Neb. 2009) ("significance of epidemiological studies with weak positive associations is a question of weight, not admissibility"); Allen v. Martin Surfacing, 263 F.R.D. 47, 56 (D. Mass. Sept. 24, 2008) (holding that causation testimony will be admitted and tested by the adversary process, rather than excluded altogether, despite paucity of epidemiologic evidence). Of the thirty-one cases Carruth and Goldstein examined, twenty-one addressed whether relative risk greater than two is a threshold for admissibility of an expert opinion on causation, and ten held that it is. Carruth & Goldstein, *supra* note 31, at 201.

[54] 275 F. Supp. 2d 672 (M.D.N.C. 2003).

Parlodel was 8.4. There were so few cases in both the exposed and unexposed population, however, that the 95% confidence interval for the relative risk was extraordinarily wide and the result was not statistically significant. The plaintiff's expert was prepared to testify that the exposure and disease satisfied all the confirmatory factors epidemiologists usually rely on to check that an observed association is really causative and not coincidental. The court held that those factors were irrelevant absent a statistically significant epidemiologic result and excluded the testimony — even though the court also stated that epidemiologic proof is not required to prove causation.[55]

If epidemiologic evidence does appear to demonstrate a relative risk greater than two, courts tend to scrutinize the study closely for exact congruence with the substance and dose to which the plaintiff was exposed, and the disease with which the plaintiff has been diagnosed.[56] Many courts have rejected proffered expert causation evidence not only because they have deemed it "unreliable" but also for its failure to "fit" the case.[57]

By contrast, numerous courts have treated epidemiologic studies that fail to show increased risk associated with exposure as if those studies conclusively disprove causation.[58] Scientifically, that is simply not so: failing to find evidence to support a hypothesis is not the same as disproving it.[59] Just as epidemiology might find associations that are coincidental rather than causal, it might fail to find a real causal connection because of confounding, methodological limitations, or other sources of error.[60] Courts have been vigilant against spurious associations. Few have even acknowledged the

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[55] *Id.* at 677–81, 684.

[56] *See, e.g.*, Merrell Dow Pharm. Inc. v. Havner, 953 S.W.2d 706, 719–24 (Tex. 1997).

[57] Daubert v. Merrell Dow Pharm. Inc., 509 U.S. 579, 591 (1993); *see also Joiner*, 522 U.S. at 152–53 (Stevens, J. concurring in part and dissenting in part) (agreeing that proferred evidence did not "fit" but disagreeing that it was unreliable). "Fit" provided the basis for exclusion in, for example, *Allison v. McGhan Med. Corp.*, 184 F.3d 1300, 1317 (11th Cir. 1999); *Porter v. Whitehall Labs.*, 9 F.3d 607, 616 (7th Cir. 1993); and *Soldo v. Sandoz Pharm. Corp.*, 244 F. Supp. 2d 434, 568, 572 (W.D. Pa. 2003) (rejecting studies of related chemicals, animal models, or different diseases). *Havner*'s "similarity" requirement, 952 S.W.2d at 720, though cast as a matter of reliability, seems related to the concept of "fit."

[58] *See, e.g.*, *In re* Hanford Nuclear Reservation Litig., 534 F.3d 986, 1011, 1013–14 (9th Cir. 2008) (affirming exclusion of expert's proffered testimony that epidemiologic studies failing to show causation do not preclude causation); Brown v. Am. Home Prods. Corp., No. 99-20593, 2000 U.S. Dist. LEXIS 12275 (E.D. Pa. Aug. 28, 2000); *Agent Orange Opt Out*, 611 F. Supp. 1223, 1231–32 (E.D.N.Y. 1985), *aff'd*, 818 F.2d 187 (2d Cir. 1987).

[59] *See, e.g.*, Michael Shermer, *I Want to Believe*, SCI. AM., July, 2009, at 33, 33 ("Failure to reject the null hypothesis does not make the claim false, and, conversely, rejecting the null hypothesis is not a warranty on truth."). Of course, a consistent body of well-designed epidemiologic studies that fail to find an association can be very powerful evidence of no causation, especially in the absence of contrary toxicological evidence.

[60] *See* Raymond Richard Neutra, *The Successes and Failures of Environmental Epidemiology*, *in* ENVIRONMENTAL EPIDEMIOLOGY, *supra* note 11, at 245, 249 (describing saccharine controversy as possible example of a real effect undetectable by epidemiology); *see also supra* note 14 and *infra* notes 254–57 and accompanying text. Genetic diversity conferring varying degrees of resistance or susceptibility to the effect of particular toxins, for example, could make the toxicity invisible to an epidemiologic study that did not take genetics into account. *See infra* Parts III.B, IV.C.2.

possibility that negative epidemiologic results may mask real causal associations.[61]

E. The Opposing Tendency

Some courts have taken a more flexible and inclusive approach to proof of toxic tort causation. The New Jersey Supreme Court, two years before *Daubert*, also faced a toxic tort case that challenged the "general acceptance" test for scientific expert testimony.[62] The trial court had applied the general acceptance test to exclude testimony by an expert who would have opined that exposure to polychlorinated biphenyls ("PCBs") had caused plaintiffs' decedents' fatal colon cancers, based on scientific (mainly animal) studies, circumstantial evidence, and facts specific to each decedent.[63] The New Jersey Supreme Court found the test unduly stringent for the claim at hand: "[I]n toxic-tort litigation, a scientific theory of causation that has not yet reached general acceptance may be found to be sufficiently reliable if it is based on a sound, adequately-founded scientific methodology involving data and information of the type reasonably relied on by experts in the scientific field."[64] The court remanded for reconsideration of the expert's testimony under this "broadened" standard for admissibility.[65]

More recently, the Kentucky Supreme Court also declined to impose narrow limits on the type of evidence that would be admissible and could be sufficient to prove toxic tort causation. In a Parlodel case, that court upheld the trial judge's decision to admit expert testimony that relied significantly on case reports, animal studies, and chemical structure analysis. "[W]e view [*Dunn* and other cases that had excluded similar testimony] . . . as incorrectly requiring scientific certainty, which was not intended by *Daubert*," the Kentucky Supreme Court wrote.[66] "Science, like many other

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[61] One might think this merely reflects the law's allocation of the burden of proof to the plaintiff. If, however, the burden of proving causation is changed to a requirement to prove relative risk greater than two, then any available "particularistic" evidence becomes a sword that can cut in only one direction. A defendant can use it to discredit the reliability or relevance of epidemiologic evidence that a plaintiff might present. But a plaintiff who lacks epidemiologic evidence to satisfy a particular court's standards cannot rely on particularistic evidence to overcome that lack. *But see* Cooley v. Lincoln Elec. Co., No. 1:05-CV-17734, 2010 WL 910049, at *2 (N.D. Ohio Mar. 10, 2010) (noting that court would admit testimony that epidemiologic studies had not found statistically significant associations, but "will not allow any witness to opine that epidemiological studies . . . are evidence of an absence of an association . . . unless the witness has performed a methodologically reliable analysis" of the studies' statistical power to support that conclusion).

[62] Rubanick v. Witco Chem. Corp., 593 A.2d 733 (N.J. 1991).

[63] *Id.* at 735–36, 748. The defendant's expert witnesses testified, inter alia, that inference of human causation from animal studies is invalid and human studies, overall, showed little or no increased cancer risk from PCB exposure. *Id.* at 736–37.

[64] *Id.* at 747–48.

[65] *Id.* at 750. The opinion repudiated *Agent Orange Opt Out* and other decisions that demanded epidemiologic evidence or that established relative risk thresholds. *Id.* at 741, 744–45.

[66] Hyman & Armstrong, P.S.C. v. Gunderson, 279 S.W.3d 93, 104 (Ky. 2008).

human endeavors, draws conclusions from circumstantial evidence when other, better forms of evidence are not available."[67]

Scientific concepts of evidence and inference, however, have coexisted uneasily at best with their legal counterparts when it comes to proof of toxic tort causation.[68] In part this is because science has remained fundamentally uncertain about the chain of events leading from exposure to illness.[69] Advances in our ability to understand and detect disease processes at the molecular level have begun to reduce that uncertainty. Can the new science that marries genetic understanding to epidemiologic methods provide a better fit between the probabilistic nature of toxic causation and the law's traditional, intuitive, deterministic concept of cause?

III. Genomics, Toxicogenomics, and Molecular Epidemiology: The More We Know

Soon after the turn of the century, biologists sequenced the human genome[70] and ever since have been engaged in a more or less systematic effort to figure out how the genome works.[71] A gene is a segment of DNA, found at a particular location ("locus") on a chromosome, which codes for a particular sequence of amino acids as determined by the arrangement of the four nucleotide bases of which DNA is made.[72] A protein forms when one or more of these amino acid sequences folds into three-dimensional shape under the influence of other biochemical constituents. The sequence of amino acids, together with any other chemical controls on how the protein folds, determines the protein's structure and function.[73]

A gene is said to be "expressed" if the cell, tissue, or organism under study is actively manufacturing the amino acid sequence associated with that gene. Gene expression is controlled not only by genes themselves but by "epigenetic" factors: "an extra layer of instructions that influences gene ac-

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[67] *Id.* (quoting Globetti v. Sandoz Pharm. Corp., 111 F. Supp. 2d 1174, 1180 (N.D. Ala. 2000)).

[68] Troyen A. Brennan, *Causal Chains and Statistical Links: The Role of Scientific Uncertainty in Hazardous-Substance Litigation*, 73 Cornell L.R. 469, 471 (1988).

[69] *Id.* at 474–75.

[70] Int'l Hum. Genome Sequencing Consortium, *Initial Sequencing and Analysis of the Human Genome*, 409 Nature 860 (2001); Press Release, Nat'l Hum. Genome Res. Inst., International Consortium Completes Human Genome Project (Apr. 14, 2003), *available at* http://www.genome.gov/11006929.

[71] *See* Charles C. Chung et al., *Genome-wide Association Studies in Cancer — Current and Future Directions*, 31 Carcinogenesis 111, 111 (2010); Francis S. Collins et al., *The Human Genome Project: Lessons from Large-Scale Biology*, 300 Sci. 286, 287 (Apr. 11, 2003).

[72] The intermediary molecule, RNA, can read a gene's nucleotide bases three at a time and translate each triplet into one of 23 amino acids. There are also genes that function without being translated into amino acid sequences, for example by producing RNA sequences that regulate aspects of the cellular machinery.

[73] J.V. Chamary & Laurence D. Hurst, *The Price of Silent Mutations*, Sci. Am., June 2009, at 46, 48.

tivity."[74] These biochemical instructions involve proteins and other chemical groups associated with genes,[75] non-coding DNA sequences,[76] RNA,[77] and other aspects of the chemical environment of the cell.[78]

Genes vary from person to person, of course. In the human population, a given gene may occur in a number of variable forms, which geneticists call polymorphisms. Each particular form in which a polymorphic gene appears is an allele.[79] For any given gene, each individual ordinarily possesses two alleles, one inherited from each parent. Some polymorphisms affect the expression of the gene (whether its protein manufacturing machinery is turned on or off) or the activity of the resulting protein (whether or how well it does its biochemical job, which can include the job of turning other genes on or off).[80] Because our health depends on having the right amount of properly formed and functioning proteins in the right places in our bodies,[81] those effects may sometimes lead to the development of clinical disease.[82]

A. Genetic Variability and "Background" Risk

The observation that some diseases seem to run in families long predates scientific understanding of the cellular, much less molecular, bases of inheritance.[83] Discovery of the genetic code demystified a number of these observed patterns. A famous dramatic example is the sickle-cell trait, in

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[74] Gail P. A. Kauwell, *Epigenetics: What It Is and How It Can Affect Dietetics Practice*, 108 J. AM. DIETETIC ASS'N 1056, 1056 (2008). Kauwell vividly described genes as instructions written in "indelible ink" while the epigenetic code is "written in pencil in the margins." *Id.*

[75] *Id.*

[76] Only about 2% of human DNA consists of genes that encode proteins. Elliott H. Margulies et al., *An Initial Strategy for the Systematic Identification of Functional Elements in the Human Genome by Low-Redundancy Comparative Sequencing*, 102 PROC. NAT'L ACAD. SCI. 4795, 4795 (2005).

[77] *See* Nelson C. Lau & David P. Bartel, *Censors of the Genome*, SCI. AM., Aug. 2003, at 34 (noting that short interfering RNA affects gene expression); Jeremy E. Wilusz et al., *Long Noncoding RNAs: Functional Surprises from the RNA World*, 23 GENES & DEV. 1494, 1494 (2009).

[78] *See* Chamary & Hurst, *supra* note 73, at 52–53; Philipp Kapranov, *From Transcription Start Site to Cell Biology*, 10 GENOME BIOLOGY 217 (2009); Fabio Mohn & Dirk Schübeler, *Genetics and Epigenetics: Stability and Plasticity During Cellular Differentiation*, 25 TRENDS GENETICS 129 (2009); George P. Rédei et al., *Changing Images of the Gene*, 56 ADVANCES GENETICS 53 (2006).

[79] *See* Lynnette R. Ferguson, *Nutrigenomics Approaches to Functional Foods*, 109 J. AM. DIETETIC ASS'N 452, 453 (2009) (providing concise definitions of these terms).

[80] *See* Stephen Barnes, *Nutritional Genomics, Polyphenols, Diets, and Their Impact on Dietetics*, 108 J. AM. DIETETIC ASS'N 1888, 1890–91 (2008).

[81] *See generally* James R. Heath et al., *Nanomedicine Targets Cancer*, SCI. AM., Feb. 2009, at 46–47.

[82] *See generally* David Altshuler et al., *Genetic Mapping in Human Disease*, 322 SCI. 881, 881 (2008) (discussing the connection between disease and genes).

[83] *See* Alan E. Guttmacher & Francis S. Collins, *Genomic Medicine — A Primer*, 347 NEW ENG. J. MED. 1512, 1512 (2002); *see also* Eric S. Lander & Robert A. Weinberg, *Genomics: Journey to the Center of Biology*, 287 SCI. 1777 (2000) (describing the history of understanding of the basis of inheritance).

which alteration of just one DNA nucleotide base in the gene that codes for hemoglobin causes a substitution of a single amino acid that changes the shape of the protein and reduces its ability to carry oxygen in the blood.[84] "High penetrance" genes like this lead directly (and essentially invariably) to unique diseases.[85]

Biomedical investigation of the genome, however, "is rapidly expanding beyond the boundaries of single gene disorders that traditionally have been associated with individually uncommon specific" hereditary diseases and conditions "to the realm of chronic diseases including cancer."[86] Researchers are finding more subtle connections between genetic variations and disease, including "complex traits" that exhibit "non-Mendelian" inheritance, i.e., that do not appear to result from the inheritance of a specific form of a single gene.[87] With respect to biologically complex diseases such as cancer, genetic variations are typically "low penetrance" — they do not invariably produce disease, but they affect the likelihood of developing disease.[88]

For example, certain rare variations in the *BRCA1* and *BRCA2* genes, termed susceptibility alleles, significantly increase a woman's risk of developing breast cancer.[89] These alleles, and susceptibility alleles of some other genes that are also associated with increased risk of breast cancer, were discovered by genetic studies of families that had unusually high incidence of the disease.[90] The availability of new genomic techniques allowed research-

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[84] *See* Muin J. Khoury & Janice S. Dorman, *Genetic Disease, in* MOLECULAR EPIDEMIOLOGY 365, 370 (Paul A. Schulte & Frederica P. Perera eds., 1993).

[85] Many other changes in single genes cause specific genetic diseases such as Huntington's disease and cystic fibrosis. Lander & Weinberg, *supra* note 83, at 1777, 1780. More than 600 different disease-causing mutations of the gene responsible for cystic fibrosis have been reported, and even they do not account for all cases of the illness. Neil A. Holtzman & Lori B. Andrews, *Ethical and Legal Issues in Genetic Epidemiology*, 19 EPIDEMIOLOGIC REVS. 163, 167 (1997).

[86] Muin J. Khoury, *Genetic Epidemiology and the Future of Disease Prevention and Public Health*, 19 EPIDEMIOLOGIC REVS. 175, 175 (1997).

[87] Stephanie L. Sherman, *Evolving Methods in Genetic Epidemiology. IV. Approaches to Non-Mendelian Inheritance*, 19 EPIDEMIOLOGIC REVS. 44, 44 (1997); *see also* Francis S. Collins, Mark S. Guyer & Aravinda Chakravarti, *Variations on a Theme: Cataloging Human DNA Sequence Variation*, 278 SCI. 1580, 1580 (Nov. 28, 1997) (noting that "progress in analyzing complex genetic disorders" has been slower than on Mendelian disorders and "is likely to be much more difficult than some had originally envisaged").

[88] High and low penetrance are relative terms. *See* Evgeny N. Imyanitov, Alexandr V. Togo, & Kaido P. Hanson, *Searching for Cancer-Associated Gene Polymorphisms: Promises and Obstacles*, 204 CANCER LETTERS 3, 8 (2004) ("[L]ow penetrance is often exemplified as something like 1.5-fold risk elevation").

[89] *See, e.g.*, Athina Christopoulou & John Spiliotis, *The Role of BRCA1 and BRCA2 in Hereditary Breast Cancer*, 10 GENE THERAPY & MOLECULAR BIOLOGY 95, 96 (2006) (women carrying mutations have a 40% to 85% lifetime risk, versus 12.5% in general population); Jaya M. Satagopan et al., *The Lifetime Risks of Breast Cancer in Ashkenazi Jewish Carriers of BRCA1 and BRCA2 Mutations*, 10 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 467, 469–70 (2001) (finding particular alleles of these genes conferred relative risks of 3.3 to 21.6 for developing breast cancer by various ages).

[90] *See* Paul D.P. Pharoah et al., *Polygenes, Risk Prediction, and Targeted Prevention of Breast Cancer*, 358 NEW ENG. J. MED. 2796, 2797 (2008). Other genetic association methods

ers to identify half a dozen new susceptibility alleles that occur at relatively high frequency in the population.[91] Individually, these alleles confer small increments of risk.[92] Their collective impact can be significant, however: an unfortunate woman with two copies of all the common higher-risk alleles would face six times the lifetime risk of breast cancer as would a woman with none of them.[93]

Polymorphisms in many other genes have also been linked to heightened risk of cancer and other diseases. For example, human cancers often display mutations in the tumor suppressor gene *p53*. The many variations of this gene have been likened to a spectrum.[94] Diverse *p53* alleles appear to have substantial effects on overall susceptibility to numerous forms of cancer.[95] "Oncogenes" associated with the genesis or promotion of particular cancers have also been identified.[96] Researchers have found other genes with alleles that are associated with forms of hypertension, diabetes, Alzheimer's disease, osteoporosis, and other conditions.[97]

The ambitious overall goal of genomic research is to "comprehensively annotate the genome,"[98] which would allow the "genetic dissection of complex biological phenomena."[99] The leaders of the Human Genome Project predicted that "these genetic tools should make it possible . . . to identify the genes that confer even relatively modest risk for common diseases."[100] The concept, in essence, is to develop a giant matrix with human genotypes on one axis of the array, diseases on the other, and at each intersection, a value for the risk of that disease associated with that genotype.[101] In principle, this

located several additional genes with (fortunately rare) susceptibility alleles that confer relative risk of breast cancer ranging from 2 to 2.5. *Id.* at 2797–98.

[91] *See id.* at 2797–99. The risk allele frequencies range from 0.25 to 0.5. A frequency of 0.5 implies that 75% of the population has at least one copy and 25% has two copies; a frequency of 0.25 implies that 43.75% of the population has at least one copy.

[92] *See id.* at 2799 (noting that the relative risks per allele range from 1.07 to 1.26).

[93] Fortunately, the probability of having the full possible complement of higher-risk alleles is low, because the genes assort independently of one another. Based on the estimated frequency of each allele, only seven in ten million women would have such a genotype. The risk comparison is based on an assumption that the interaction between the genes' contribution to risk is multiplicative. *Id.* at 2799.

[94] *See, e.g.*, William P. Bennett et al., *Molecular Epidemiology of Human Cancer Risk: Gene-Environment Interactions and p53 Mutation Spectrum in Human Lung Cancer*, 187 J. PATHOLOGY 8 (1999).

[95] *See generally* S. Perwez Hussain & Curtis C. Harris, *Molecular Epidemiology of Human Cancer: Contribution of Mutation Spectra Studies of Tumor Suppressor Genes*, 58 CANCER RES. 4023 (1998).

[96] Lander & Weinberg, *supra* note 83, at 1780.

[97] Collins et al., *supra* note 87, at 1581 nn.2 & 7; *see also* Altshuler et al., *supra* note 82, at 883.

[98] Chung et al., *supra* note 71, at 111.

[99] Collins et al., *supra* note 87, at 1581.

[100] Int'l Hum. Genome Sequencing Consortium, *supra* note 70, at 914.

[101] Eric S. Lander, *The New Genomics: Global Views of Biology*, 274 SCI. 536, 537 (1996); s*ee also* Altshuler et al., *supra* note 82, at 881–82 (noting that genome-wide association studies seek "to develop a catalog of common human genetic variants and test the variants for association to disease risk"); Khoury, *supra* note 86, at 178.

information would support the computation of highly individualized assessments of risk.[102]

Despite the promise of genomic susceptibility analysis, realizing the vision of a comprehensive genetic risk profile is far from certain. The numbers alone are daunting: within the 30,000 to 40,000 genes in the human genome,[103] researchers have identified more than ten million single nucleotide polymorphisms ("SNPs"), and millions more may exist.[104] But the difficulties go beyond the sheer numbers of genes, alleles, diseases, and combinations thereof.[105]

Even with technological advances, it has been argued that "[m]ost reported genetic associations have been false positive results,"[106] and others have been valid but overstated.[107] For many genetic polymorphisms, whether the high-risk allele leads to disease depends on other genes.[108] The breast cancer susceptibility alleles *BRCA1* and *BRCA2*, for example, have effects modified by other genes that alter the body's response to environmen-

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[102] *See* Pharoah et al., *supra* note 90, at 2798–99 (discussing the possibility of multi-gene genetic screening for breast cancer risk).

[103] Int'l Hum. Genome Sequencing Consortium, *supra* note 70, at 860.

[104] Altshuler et al., *supra* note 82, at 883. Moreover, "SNPs are only one type of genetic variation." *Id.*

[105] Technological advance has rapidly increased the speed and reduced the unit cost of genetic sequencing. Genetic variants identified so far nevertheless explain only "a small fraction" of such conditions as diabetes and Crohn's disease. *Id.* at 885. That percentage will increase but is "unlikely" to approach 100%. *Id.* at 886. "There may be inherent limits to our ability to relate phenotypic variation and genotypic variation. To the extent that disease is influenced by tiny effects at hundreds of loci or highly heterogeneous rare mutations, it may be impractical to assemble sufficiently large samples to give a complete accounting." *Id.* at 887. ("Phenotype" refers to "the visible properties of an organism that are produced by the interaction of the genotype and the environment." Elaine Trujillo, Cindy Davis & John Milner, *Nutrigenomics, Proteomics, Metabolomics, and the Practice of Dietetics*, 106 J. Am. Dietetic Ass'n 403, 404 (2006)).

[106] Pharoah et al., *supra* note 90, at 2802; *see also* Samuel P. Dickson et al., *Rare Variants Create Synthetic Genome-Wide Associations*, PLoS Biology, Jan. 2010, at 5–7 (demonstrating that 179 SNPs could be statistically significantly associated with sickle-cell anemia, which is caused by a known variant of a known gene); Margaret R. Spitz & Melissa L. Bondy, *The Evolving Discipline of Molecular Epidemiology of Cancer*, 31 Carcinogenesis 127, 130 (2010) (stating that because genome-wide association studies do not identify specific genes, after such a study is performed much further research is needed to establish genetic causes of risk). *But cf.* Chung et al., *supra* note 71, at 111–12 (noting that the older candidate gene approach yielded mostly false positives but genome-wide association studies are more successful).

[107] *See, e.g.*, Holtzman & Andrews, *supra* note 85, at 167 (noting that incidence of breast cancer in Ashkenazi Jewish women was lower than early studies' predictions that were based on frequency of *BRCA1* mutations in that population).

[108] *Id.*; *see also* Frederica P. Perera, *Molecular Epidemiology: On the Path to Prevention?*, 92 J. Nat'l Cancer Inst. 602, 608 (2000) ("many different common polymorphisms are likely to be involved in individual risk of cancer"); Christopher A. Maxwell et al., *Genetic Interactions: the Missing Links for a Better Understanding of Cancer Susceptibility, Progression and Treatment*, 7 Molecular Cancer 4, *8 (2008), http://www.molecular-cancer.com/content/pdf/1476-4598-7-4.pdf ("Interactions between human genes are largely unknown. . . . The detection of these interactions will be invaluable to our understanding of cancer risk").

tal insults such as radiation.[109] Similarly, many genes influence the genetic component of asthma, some synergistically.[110] Epigenetic factors modulate the extent to which a particular genotype confers risk as well.[111]

Some relevant genes and genetic interactions may be extremely difficult to identify.[112] Epigenetic factors may be complex and are not yet well understood.[113] Fully delineating the degree of susceptibility produced by a genetic variation itself will depend on controlling, or at least comprehending, how the polymorphic gene interacts with other genes and epigenetic factors.

To the extent that genetic factors themselves confer risk of disease, they may help to explain a paradox that has plagued the assessment of causation in toxic tort cases: the existence of "background" risk, or the incidence of disease absent known exposure. Genetic factors, however, "by themselves are thought to explain only about 5%" of the incidence of cancer.[114] Beyond the interaction of susceptibility genes with an individual's other genes and epigenetics, a further interaction, exogenous to the individual, is also critical: interaction with the environment,[115] which affects both genes[116] and epige-

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[109] Logan C. Walker et al., *Use of Expression Data and the CGEMS Genome-Wide Breast Cancer Association Study to Identify Genes that May Modify Risk in BRCA1/2 Mutation Carriers*, 112 BREAST CANCER RES. & TREATMENT 229, 229, 233 (2008); *see also* Imyanitov et al., *supra* note 88, at 8.

[110] Leonardo A. Pinto, Renato T. Stein & Michael Kalesch, *Impact of Genetics in Childhood Asthma*, 84 JORNAL DE PEDIATRIA S68, S68, S72 (2008) (noting also that asthma is not entirely genetic and results from "the interaction between genetic and environmental factors"); *see also* Mark A. Rothstein, Yu Cai & Gary E. Marchant, *The Ghost in Our Genes: Legal and Ethical Implications of Epigenetics*, 19 HEALTH MATRIX 1, 16 (2009) (noting that pollution-caused epigenetic changes are implicated in asthma etiology).

[111] *See* Pauline A. Callinan & Andrew P. Feinberg, *The Emerging Science of Epigenomics*, 15 HUMAN MOLECULAR GENETICS R95, R95–R99 (2006); Spitz & Bondy, *supra* note 106, at 127, 131.

[112] *See* Altshuler et al., *supra* note 82, at 885 (stating that current models of gene-gene interactions are simplified); Christopher S. Carlson et al., *Mapping Complex Disease Loci in Whole-genome Association Studies*, 429 NATURE 446, 450 (2004) (noting that there is "little doubt" that interactions exist where "risk associated with a genotype at a locus is dependent on a genotype at another locus" but "sheer number of potential interactions practically guarantees that a comprehensive search has no power to detect them"); Olivia Fletcher, et al., *Association of Genetic Variants at 8q24 with Breast Cancer Risk*, 17 CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION 702, 705 (2008) (explaining that a study, although statistically equivalent to 12,000 samples, had insufficient statistical power to detect modest gene-gene interactions); P. Andrew Futreal et al., *Cancer and Genomics*, 409 NATURE 850, 850–52 (2001).

[113] *See* Callinan & Feinberg, *supra* note 111, at R95–R99 (describing various ways in which epigenetic factors can influence gene expression and disease susceptibility).

[114] Frederica P. Perera, *Environment and Cancer: Who Are Susceptible?*, 278 SCI. 1068, 1068 (1997); *see also* SUZANNE H. REUBEN, PRESIDENT'S CANCER PANEL, REDUCING ENVIRONMENTAL CANCER RISK: WHAT WE CAN DO NOW 1 (2010) ("Single-gene inherited cancer syndromes are believed to account for less than 5 percent of malignancies in the United States.").

[115] "Environment" in this context broadly includes exposures whether voluntary (foods, drugs, cigarette smoking, medical X-rays) or involuntary (pesticides, household and workplace chemicals, pollutants, secondhand smoke, nuclear test fallout, pathogens), irrespective of whether their origin is anthropogenic or not.

[116] Altshuler et al., *supra* note 82, at 885 ("gene-environment interactions play important roles in disease risk"); Francis S. Collins, *The Case for a US Prospective Cohort Study of*

netic factors.[117] For instance, even when an inherited allele increases cancer susceptibility, somatic mutations in other genes "are needed for malignant transformation" of a normal cell into a cancer cell.[118] Such mutations are believed to result from exposure to some kind of mutagenic agent.[119]

B. Genetic Variability and Exposure Risk

Toxicogenomics studies how exposure to suspected toxins interacts with variable genetic material to produce, or not produce, toxic effects, including the development of diseases such as cancer that occur after a latency period. New technologies enable these studies, at least in principle, to be carried out on a large number of genes simultaneously, instead of relying on long, slow, seriatim testing. Broadly speaking, toxicogenomic investigation proceeds in one of two ways that are analogous to the basic methods of epidemiology.[120]

The first approach is to examine genetic material that contains a range of variations and has been exposed to the suspected toxin (either experimentally *in vitro* or in human populations studied after the exposure) to determine whether the variation in genes is reflected in variable toxic effect. If it is, the investigation yields a so-called biomarker of susceptibility — a genetic variation that increases or decreases the likelihood that exposure to the substance will result in harm.[121]

The second approach is to examine exposed and non-exposed biological material for differences in gene mutations, changes in gene expression, or other biochemical indicators. Any differences found may yield bi-

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Genes and Environment, 429 NATURE 475, 475 (2004) ("There is growing recognition that a change in the environment, in combination with genetic disposition, has produced most recent epidemics of chronic disease . . . .").

[117] Kauwell, *supra* note 74, at 1056 (explaining that because environmental factors cause epigenetic changes, "the same exact DNA sequence for a particular gene may give rise to different outcomes"); Trujillo et al., *supra* note 105, at 408–09; *see* J.R. Minkel, *Putting Madness in Its Place*, SCI. AM., Nov. 2009, at 16, 19 (speculating that the urban environment imparts epigenetic changes, which may explain why schizophrenia appears heritable despite lack of identified strong genetic risk markers).

[118] Holtzman & Andrews, *supra* note 85, at 167. "Somatic" refers to a body cell other than a reproductive ("germ") cell. A somatic mutation occurs during an individual's fetal development or lifetime rather than being inherited from a parent's egg or sperm cell (or transmitted to that individual's offspring). STEDMAN'S MEDICAL DICTIONARY 1264–65 (28th ed. 2006).

[119] Futreal et al., *supra* note 112, at 850 ("Throughout life, the DNA in human cells is exposed to mutagens and suffers mistakes in replication, resulting in progressive, subtle changes in the DNA sequence in each cell. Occasionally, one of these somatic mutations alters the function of a critical gene" and results in cancer.).

[120] *See* Quanhe Yang & Muin J. Khoury, *Evolving Methods in Genetic Epidemiology. III. Gene-Environment Interaction in Epidemiologic Research*, 19 EPIDEMIOLOGIC REVS. 33, 35 (1997) ("If one views the gene-environment interaction as the genetic control of sensitivity to the environmental exposure, and genetic factors are regarded as one of the host characteristics, then gene-environment interaction can be analyzed through the use of traditional epidemiologic study designs.").

[121] *See* Jamie A. Grodsky, *Genomics and Toxic Torts*: *Dismantling the Risk-Injury Divide*, 59 STAN. L. REV. 1671, 1688–89 n.66 (2007) [hereinafter Grodsky, *Risk-Injury Divide*].

omarkers of exposure, which could conceivably be quantitative if the degree of biochemical change is proportional to the dose.[122] If the changes caused by exposure relate directly to a disease process such as an early step in carcinogenesis, they could be biomarkers of effect.[123]

Molecular epidemiology links this genomic knowledge to the incidence of disease in human populations.[124] It has already produced important results.

For example, repeated epidemiologic studies failed to identify any association between cigarette smoking and increased risk of breast cancer. Scientists were mystified, because a number of carcinogens in tobacco smoke were strongly linked to mammary tumors in animals, and the biochemical processes in the test animals were very similar to human biology.[125] Then genomics identified a polymorphic gene that codes for an enzyme that neutralizes certain of these carcinogens. When an epidemiologic study grouped its subjects by genotype as well as by smoking status, it revealed that the genes made a vital difference. Women whose genes coded for the most protective form of the enzyme had no increased risk of breast cancer even if they smoked. Women with less protective forms, on the other hand, had a relative risk of eight for breast cancer if they smoked, compared to women with the same genes who did not smoke.[126]

Genetic variability in susceptibility to toxins has clarified other epidemiologic results as well. As long ago as the nineteenth century, aromatic amino compounds used in the dye and leather industries were suspected of causing bladder cancer. Epidemiologic reports of relative risk, however, although all very high, varied by a factor of two.[127] It turns out that some workers have an allele that produces a protective neutralizing enzyme, and

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[122] *See* Jamie A. Grodsky, *Genetics and Environmental Law: Redefining Public Health*, 93 CALIF. L. REV. 171, 186 (2005) [hereinafter Grodsky, *Public Health*].

[123] *Id.*

[124] *See* Margaret R. Spitz & Melissa L. Bondy, *supra* note 106, at 127 (explaining that molecular epidemiology is an extension of classical epidemiology using biomarkers).

[125] *See* David H. Phillips & Seymour Garte, *Smoking and Breast Cancer: Is There Really a Link?*, 17 CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION 1, 1 (2008) (explaining that epidemiologic associations are lacking despite both evidence of mammary carcinogenicity in rodents and the presence of activating enzymes and DNA adducts in human breast tissue); Rick Weiss, *What's Your Cancer Profile?, Scientists Focus on an Overlooked Class of Genes that May Determine Your Odds*, WASH. POST, Sept. 19, 1995, at Z12.

[126] Weiss, *supra* note 125, at Z12; *see* Christine B. Ambrosone et al., *Cigarette Smoking, N-Acetyltransferase 2 Genotypes, and Breast Cancer Risk: Pooled Analysis and Meta-analysis*, 17 CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION 15, 21, 25 (2008) (explaining that "smoking status, but not NAT2 genotype status, was independently associated with breast cancer risk" and that "cigarette smoking is associated with an increase in breast cancer risk among women with NAT2 slow acetylator genotypes"); Perera, *supra* note 108, at 604 (indicating that "individual variations in metabolic pathways and DNA repair mechanisms play an important role in breast cancer risk" among women exposed to carcinogens).

[127] Reported relative risks ranged from 30 to 47 in earlier studies and 8.7 to 17 in later studies (after production methods were changed to reduce workers' exposure). *See* W. C. HUEPER, OCCUPATIONAL AND ENVIRONMENTAL CANCERS OF THE URINARY SYSTEM 119, 156 (1969).

their relative risk is lower.[128] The variation in the earlier epidemiologic results, in studies that could not control for genotype, might have resulted at least in part from random variation in the gene distribution across the study samples or among the different populations from which different studies drew their samples.[129]

Molecular analysis has also detected biomarkers of exposure and/or effect. For instance, polycyclic aromatic hydrocarbons ("PAHs"), a component of cigarette smoke,[130] may explain the apparent link between tobacco smoke and breast cancer; *in vitro* bioassays have found PAHs to be potent mammary carcinogens.[131] Research has shown that PAHs bind to DNA to form addition products, or "adducts," with DNA.[132] Adducts can support inferences of causation in at least two ways: first, by providing evidence of the mechanism by which substances such as PAHs can cause disease,[133] and second, by providing tangible evidence that a person's affected tissue was exposed to the substance.[134] Linking the biochemistry to epidemiology can further support the inference: a study comparing breast cancer patients to subjects with benign breast disease found statistically significant higher levels of PAH-DNA adducts in the cancer patients.[135] As another example, high occupational exposure to benzene has been found to increase the frequency of chromosomal aberrations that are also frequently seen in acute myeloid leukemia and pre-leukemic conditions.[136] Classical epidemiology

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[128] Weiss, *supra* note 125; *see* Imyanitov et al., *supra* note 88, at 8–9 (noting that *NAT2* slow acetylator status is "unfavorable for bladder cancer risk" only in persons exposed to arylamines, and neutral for everybody else).

[129] Different ancestry groups may have different frequencies of various polymorphisms. Altshuler et al., *supra* note 82, at 887 (noting that most previous genomic studies have examined groups of European ancestry); s*ee* Chung et al., *supra* note 71, at 112.

[130] PAHs are a product of incomplete combustion. Human exposure to PAHs comes from many sources, including vehicle exhaust, food, and hazardous waste sites. AGENCY FOR TOXIC SUBSTANCES & DISEASE REGISTRY, PUBLIC HEALTH STATEMENT FOR POLYCYCLIC AROMATIC HYDROCARBONS (PAHs) §§ 1.1, 1.3 (Aug. 1995), *available at* http://www.atsdr.cdc.gov/toxprofiles/tp69-c1.pdf.

[131] *See* Perera, *supra* note 108, at 603.

[132] Perera, *supra* note 108, at 604; *see* Melvyn S. Tockman et al., *Biomarkers of Pulmonary Disease*, *in* MOLECULAR EPIDEMIOLOGY 443, 452 (Paul A. Schulte & Frederica P. Perera eds., 2005).

[133] Perera, *supra* note 108, at 604 (noting that proof that molecules of a substance can bond with DNA tends to support the hypothesis that the substance can alter DNA structure or function, and therefore provides a biologically plausible explanation for how the substance causes illness); *id.* at 603 ("many carcinogens, including the PAHs, exert their effects by binding to DNA and forming adducts that may lead to mutation, and ultimately, to cancer"). "Biological plausibility" is one of the criteria epidemiologists apply to help infer that an observed association between an agent and a disease is causal rather than coincidental. Green et al., *supra* note 12, at 376–79.

[134] Perera, *supra* note 108, at 605; *see id.* at 603 ("using adducts as biomarkers has the theoretical advantage that they reflect chemical-specific genetic damage").

[135] *See id.* at 604.

[136] *See id.* at 605; *see also* Milward v. Acuity Specialty Prods. Group, Inc., 664 F. Supp. 2d 137, 146 (D. Mass. 2009) (describing several chromosome defects that are induced by benzene metabolites and cause certain forms of acute myeloid leukemia).

had earlier linked benzene exposure with significantly increased risk of acute myeloid leukemia.[137]

More than a decade ago, an epidemiologist foresaw "a time when" genotype information "will routinely be sought in almost every epidemiologic study."[138] This would add a genetic dimension to "the classic epidemiologic paradigm" of comparing the presence or absence of disease with the presence or absence of a suspected risk factor.[139] From the perspective of genetics, an epidemiologic dimension would be added to the genomic risk matrix described above.[140] Either way, the vision is of a three-dimensional grid with genetic polymorphisms arrayed on one axis, suspected toxic agents on the second, and diseases on the third, with each space in the grid bearing a quantitative risk estimate.[141]

C. Tort Scholars Confront the Genome

The potential implications of genomics, toxicogenomics, and molecular epidemiology for proof of toxic tort causation are immediately obvious. These sciences tantalize with the possibility that "particularistic" information about an individual plaintiff's genetic makeup and how it interacts with the toxic chemical at issue can supplant (or at least supplement) the population-based evidence from traditional epidemiology. In the ideal plaintiff's case, a person with an allele that made him or her specifically susceptible to the action of some toxin would be exposed to that toxin, which would cause a unique and detectable biochemical change, which in turn would be shown to cause an extremely high likelihood of contracting the plaintiff's disease. The ideal defendant's case might occur in several ways: similar biomarker evidence would point a finger at a purely genetic cause or at some other (perhaps voluntary or non-anthropogenic) exposure; or, a person exposed to a toxin known to cause the person's disease in susceptible people might have a gene that completely neutralized the toxic effect and also might lack a biomarker that is uniformly found in people whose disease was caused by exposure.[142] But it isn't necessary to hypothesize ideal cases to see that this

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[137] *See, e.g.*, Henricksen v. ConocoPhillips Co., 605 F. Supp. 2d 1142, 1150 (E.D. Wash. 2009).

[138] Khoury, *supra* note 86, at 176.

[139] *Id.*; *see also* Klein, *supra* note 28, at 32–33 ("a stated goal of those who have worked to map the human genome is to connect the activation or deactivation of particular genes by specific chemicals").

[140] *See supra* Part III.A.

[141] Some leaders of the Human Genome Project described this as "a joint estimation procedure combining variation information of all types, frequencies, and phenotypes to discover and characterize genotype-phenotype correlations. New statistical methods will be required to combine evidence from rare and common *alleles* at a locus and across multiple loci, *phenotypes*, and *nongenetic exposures*." Altshuler et al., *supra* note 82, at 887 (emphasis added).

[142] *See, e.g.*, Gary E. Marchant, *Genetic Data in Toxic Tort Litigation*, 14 J.L. & POL'Y 7, 9–14 (2006).

"fine-grained" information[143] could help either a plaintiff or a defendant overcome adverse epidemiologic data of a more general nature.

Legal scholars have begun to contemplate how well this potential will be realized, though very few reported cases to date have even referred to the results of toxicogenomic or molecular epidemiologic studies in connection with causation. So far, the scholarship has been split between a prophetic and a skeptical view of the new science's likely impact.

The prophetic view asserts that genetic techniques and biomarkers will improve resolution of "vexing causation issues in toxic injury cases."[144] It envisions that plaintiffs' individual genetic susceptibilities to toxins will routinely be plumbed in litigation.[145] Gary Marchant suggested that gene expression data will eventually demonstrate that various toxic substances produce unique profiles, like fingerprints, the presence of which would simultaneously demonstrate the plaintiff's exposure to the substance in question and the causal link between that substance and the disease.[146]

Similarly, the late Jamie Grodsky, focusing in 2005 on government regulation of toxic substances, argued that toxicogenomics offers the opportunity for "redefining public health," by making possible finely-focused consideration of the effects of toxic chemicals on groups with varying degrees of susceptibility.[147] "It is too soon to predict," she wrote then, "how the tort system would respond if these enormously complex scientific questions migrate to the private law."[148] Two years later, she argued that the tort system *should* respond by recognizing sub-clinical molecular changes, induced by toxic exposures, as injury sufficient to confer a cause of action, with medical monitoring as a "narrow, injunctive remedy" for such claims.[149]

Others have debated whether the presumably impending burst of toxicogenomic causation information will enhance or diminish the case for replacing tort liability with a comprehensive administrative compensation system for victims of environmental toxic injury. Albert Lin argued that toxicogenomics and other scientific advances will provide sufficient information to support ex ante determinations of risk that could be compensated

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[143] Grodsky, *Public Health*, *supra* note 122, at 243.

[144] Gary E. Marchant, *Genetic Susceptibility and Biomarkers in Toxic Injury Litigation*, 41 JURIMETRICS 67, 109 (2000).

[145] Marchant, *supra* note 142, at 13–14.

[146] *See id.* at 19–27; *see also* Christiana P. Callahan, Note, *Molecular Epidemiology: Future Proof of Toxic Tort Causation*, 8 ENVTL. LAW. 147 (2001). Much more recently, Professor Marchant and co-authors noted (as biomedical researchers have) that "full understanding of human genetic processes has turned out to be far more complex than initially expected." Rothstein et al., *supra* note 110, at 3. That article explores several possible legal ramifications of developments in the study of epigenetics, but not their significance for toxic tort causation.

[147] Grodsky, *Public Health*, *supra* note 122, at 237–38; *see also* Perera, *supra* note 108, at 608–09 (risk assessment of environmental chemicals must include specific consideration of subpopulations with greater genetic susceptibility to effects of such chemicals).

[148] Grodsky, *Public Health*, *supra* note 122, at 268. I don't think such predictions are all that difficult. *See infra* Part IV.C.

[149] Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1723. *See generally id.* at 1694–1711.

through an administrative system.[150] Andrew Klein countered that the same information would support improved functioning of the tort system through accurate determinations of causation in individual cases, reducing the appeal of administrative replacements.[151] He concluded that administrative systems would be appropriate only to address a small subset of persistent toxic tort problems.[152]

The view that "[g]enomic data have the potential to transform toxic tort doctrine and practice" to be "more informed, consistent and fair"[153] underlies all these arguments — even the one that prefers administrative compensation to tort.[154] They share a belief that it is ultimately possible to "fully characteriz[e] mutations in these genes conferring susceptibility or resilience to toxic substances in individuals carrying the genes"[155] — a faith that it is both theoretically possible and practically achievable to create the three-dimensional array of genes *x* exposures *x* diseases, or at least create enough of it to make a significant difference.

The skeptics reject that vision as pie in the sky. The world, they say, is just too complex. Susan Poulter contended that in general, "genetic testing for predisposition to disease is not mature enough to support a causal analysis of toxic injury claims."[156] Professor Poulter considered principally situations in which an exposed person's genetic predisposition to disease is posited as an alternative cause (as opposed to the toxic exposure). She argued that if both toxic exposure and genetics are risk factors for disease, to properly analyze their causal effects would require knowing, both qualitatively and quantitatively, how they affect risk jointly as compared to separately: are their effects additive, synergistic, or antagonistic?[157] Are they modified by other biological processes such as DNA repair?[158] Poulter con-

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[150] Lin, *supra* note 3, at 1474–75 (arguing that his proposed administrative compensation system would be more effective than tort system in meeting compensation, efficient deterrence, and corrective justice goals).

[151] Klein, *supra* note 28, at 23–25, 35.

[152] *Id.* at 36–38.

[153] Marchant, *supra* note 142, at 36.

[154] Although Professor Lin and Professor Klein disagree about the relative merits of an administrative compensation system, their arguments both depend on at least a qualified embrace of the prophetic vision of toxicogenomics. *See* Lin, *supra* note 3, at 1473–74 (arguing that "[t]oxicogenomics will further the understanding of general causation in at least three ways" but "our knowledge is currently incomplete"); Klein, *supra* note 28, at 34–35 (arguing that "one must temper this discussion with caution" but should assume "that an increasing number of people will have the tools necessary to prove sine qua non causation in toxic tort litigation").

[155] Marchant, *supra* note 142, at 9.

[156] Susan R. Poulter, *Genetic Testing in Toxic Injury Litigation: the Path to Scientific Certainty or Blind Alley?*, 41 JURIMETRICS J. 211, 213 (2001).

[157] *Id.* at 224–30. Scientists puzzle over the same question. *See* Christopher P. Wild, *Environmental Exposure Measurement in Cancer Epidemiology*, 24 MUTAGENESIS 117, 117 (2009) ("precise contribution of specific risk factors and their interaction, both with each other and with genotype, continues to be difficult to elucidate"); Yang & Khoury, *supra* note 120, at 33 (differentiating statistical from biological concepts of interaction; noting that several different models exist for assessing causal interaction).

[158] Poulter, *supra* note 156, at 230.

cluded that because this knowledge would rarely be available, population-wide epidemiologic evidence is superior to consideration of "individualized genetic risk factors," and evidence of plaintiff's genetic makeup should be excluded from the courtroom.[159]

David Adelman made a similar but much broader attack in his article, "The False Promise of the Genomics Revolution for Environmental Law" — an almost simultaneous counterpoint to Grodsky's vision of "Redefining Public Health."[160] His critique, which at its core seemed to reflect a strong aversion to what might be called reductionist genetic determinism,[161] emphasized instead that the interactions of genes and toxins depend on very complex biological responses.[162]

Biological complexity undoubtedly presents huge obstacles to the Environmental Human Genome Project's lofty ambitions for fine-tuned toxic substance regulation. There are so many chemicals that affect or are affected by so many genes. The genes come in so many variations and are affected by so many epigenetic factors. Adelman argued that this complexity creates not just a practical problem of having too many tests to run with a reasonable amount of time and money, but rather a conceptual problem, because the variables that affect gene expression are inherently too complex to characterize fully.[163] He concluded that all this complexity makes it unlikely that toxicogenomics will ever be able to "ascrib[e] fixed toxic susceptibilities to genes."[164]

Professor Adelman's critique is most directly relevant to his central question — whether genomics will provide a basis for a new and comprehensive way of regulating toxic substances. But his argument, if correct, could likewise have dramatic implications for how such evidence may be and should be used in resolving private claims of toxic injury.

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[159] *See id.* at 237.

[160] David E. Adelman, *The False Promise of the Genomics Revolution for Environmental Law*, 29 HARV. ENVTL. L. REV. 117 (2005).

[161] *Id.* at 161 ("Critics of toxicogenomics . . . reject the core genomic dogma that toxic susceptibilities derive directly from genetic mutations . . . .").

[162] *Id.* at 122, 141. Much of the scientific support cited in Adelman's article was from evolutionary biologist Richard Lewontin, who has spent many years opposing the misappropriation of genetics for racist, sexist, or other social agendas. *See, e.g.*, Richard C. Lewontin, *The Analysis of Variance and the Analysis of Causes*, 35 INT'L J. EPIDEMIOLOGY 520 (2006) (arguing that genetics is misapplied when a trait's heritability is taken to mean that the trait cannot be environmentally altered). It is not at all surprising that Lewontin emphasized the role of environmental and individual variability, rejecting the view that disease is purely genetically determined. *See* Richard C. Lewontin, *Computing the Organism*, NATURAL HISTORY, Apr. 2000, at 94 ("[A]n organism does not compute itself from its genes. . . ."). This is an appealing heuristic: it is hard to swallow that our fate is purely determined by little self-replicating packets of nucleic acid. *Compare* RICHARD DAWKINS, THE SELFISH GENE (1976) (arguing that gene is unit of natural selection) *with* Elliott Sober & Richard C. Lewontin, *Artifact, Cause and Genic Selection*, 49 PHIL. OF SCI. 157 (1982) (arguing that genic selection model misrepresents causes of evolution).

[163] Adelman, *supra* note 160, at 136–37 ("[T]oxicogenomics may be as important for what it tells us we cannot know as it is for the knowledge that it ultimately generates.").

[164] *Id.* at 162.

IV. The Less Intelligent We Are? Tempting Judicial Mistakes and How to Avoid Them

So who is right, the prophets or the skeptics? The answer, perhaps inevitably, is both, or rather that both are partly right.

On the one hand, there can be no doubt that toxicogenomics and molecular epidemiology will, over time, produce powerful new insights into the cellular mechanics by which numerous toxic substances produce disease, and demonstrate causal links that up to now could only be inferred or speculated. Some of that proof is already in the pudding.

At the same time, it is surely true that sheer numbers present daunting practical limits to how fully we will be able to characterize toxic causation: numbers of exposures to different chemicals, radiation, viruses, and particles; numbers of genes involved in the pathway to disease; numbers of polymorphisms at each gene; numbers of epigenetic factors; numbers of different manifestations of disease. All of these factors could combine in a staggeringly large number of possible ways. Layer on top of those numbers the complexity of the potentially different types of interactions for each combination, and it is easy to believe that a simple matrix of toxic cause-and-effect is a pipe dream.[165]

Moreover, biology has a way of proving to be even more complicated than we think. The discovery that much of the genome does not code for proteins upended the model of DNA as a chain of genes;[166] the astonishing similarity between the genomes of very different organisms made clear that epigenetic factors are even more critical to gene expression than was previously supposed;[167] late last century, biologists identified a hitherto unknown type of RNA that critically mediates gene expression;[168] even more recently, biologists learned that "silent" mutations within genes nevertheless can influence health;[169] and current research aims to understand the mechanisms that control the physical arrangement of chromosomes within a cell nucleus, which can affect disease risk as well.[170] Already, despite the increasing power and speed of analytical techniques,[171] the "genetic analysis of common disease is turning out to be a lot more complex than expected,"[172] even without consideration of possible toxic exposures.[173] As biologists generate

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[165] The "multiple testing . . . problem rapidly becomes intractable when we allow for gene-gene or gene-environment interactions." Carlson et al., *supra* note 112, at 450.

[166] Lander & Weinberg, *supra* note 83, at 1778–80.

[167] Matt Ridley, *Modern Darwins*, Nat'l Geographic, Feb. 2009, 56, 70–71; Kauwell, *supra* note 74, at 1056–57; Wild, *supra* note 157, at 117, 121.

[168] Lau & Bartel, *supra* note 77, at 35; Wild, *supra* note 157, at 118.

[169] Chamary & Hurst, *supra* note 73, at 48–49.

[170] Melinda Wenner, *Nuclear Architecture*, Sci. Am., Oct., 2009, at 20, 22.

[171] *See* Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1689–90.

[172] Nicholas Wade, *Study of Genes and Diseases at an Impasse*, N.Y. Times, Apr. 16, 2009, at A1.

[173] Spitz & Bondy, *supra* note 106, at 131 (describing "unanticipated challenges" in attributing cancer risk to polymorphisms).

exponentially increasing amounts of genomic information, it is reasonable to expect that more surprises wait around the bend.[174]

The skeptical view says that toxicogenomics can never definitively ascribe susceptibilities to individual genes in relation to individual toxins, because actual susceptibility will depend on the genetic and epigenetic environment. To a dyed-in-the-wool reductionist, this just means that science needs to drill down more deeply, ascribing toxicological characteristics to increasingly constrained combinations of factors. Doubters would reply that it is not even theoretically possible ever to drill down deeply enough.

Where will that leave courts?

A. The Train Is Coming, and Courts Can't Get Off the Tracks

Law cannot and does not have to choose between those perspectives. It is enough to accept that at any given moment in the foreseeable future, the drilling project will be only partly complete. Thus, even if the science could eventually support an administrative compensation system, exotic causes of action or other major structural reforms, the "onrushing freight train"[175] of genomics will reach the courts before then.[176] In the meantime, the legal significance of advancing scientific knowledge will continue to be tested in personal injury actions brought by people who allege that their exposure to drugs, workplace chemicals, pollutants, or other agents caused their disease.

It is therefore vital to consider how causation doctrine should best address this new science within the framework of existing tort law. The outcome will be enormously important for injured persons, for the enterprises whose products are accused of causing harm, and for society as a whole.

B. An Exemplar: Trichloroethylene and Kidney Cancer

The officially unsettled link between trichloroethylene ("TCE") and a form of kidney cancer[177] serves as a model to illustrate the issues.[178] TCE is

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[174] "Our understanding of complex disease will be in constant flux over the coming years." Altshuler et al., *supra* note 82, at 888; *see also* Rothstein et al., *supra* note 110, at 22 (noting that current knowledge of epigenetic regulation of genome "may only be the tip of the iceberg").

[175] Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1686.

[176] *See* Lin, *supra* note 3, at 1518–20 (discussing how "current knowledge and technology are insufficient to permit immediate implementation" of a proposed administrative compensation system, but "serious discussion of the proposal now may help to lay the political foundation for implementation"). The same is likely true for proposed major changes in the regulatory regime. *See* Grodsky, *Public Health*, *supra* note 122, at 227–39. It is also far from certain that such regulatory changes would displace the role of tort law for exposed people who claim that injury resulted from exposure. *See also infra* Part IV.C.5 (discussing possible new causes of action).

[177] For accounts of EPA's long-running, controversial, and still-unfinished attempt to complete a risk assessment for trichloroethylene, see GOV'T ACCOUNTABILITY OFFICE, CHEMICAL ASSESSMENTS: LOW PRODUCTIVITY AND NEW INTERAGENCY REVIEW PROCESS LIMIT THE USEFULNESS AND CREDIBILITY OF EPA'S INTEGRATED RISK INFORMATION SYSTEM (GAO-08-440)

a widely used solvent and degreaser. Historically, workers in certain industries were occupationally exposed to high concentrations of TCE for long periods of time. A legacy of haphazard disposal of this ubiquitous chemical, however, has also exposed members of the general public to much lower concentrations of TCE found in the environment. In particular, TCE frequently contaminates groundwater and has been unwittingly consumed by people who drank from contaminated municipal or private wells.[179]

TCE has long been known to be toxic in acute, high-dose exposures. More recently, evidence has developed suggesting that chronic exposure to TCE can cause DNA damage that leads to serious illness.

Renal cell carcinoma ("RCC"), a form of cancer of the kidney, runs in families but also occurs in "sporadic" cases that do not appear to be hereditary.[180] Researchers, aware of the kidney's role in excreting metabolic waste, suspect that environmental carcinogens are a major cause of sporadic cases.[181]

Animal studies in the 1980s and 1990s suggested that TCE could cause this cancer.[182] Exposed animals developed renal cancer more often than unexposed animals.[183] Experiments elucidated a possible biochemical mechanism of TCE's carcinogenic action: TCE reacts with glutathione, a chemical normally present in the body, to begin a series of steps that eventually form several chemicals that have been shown (in bacteria or *in vitro*) to alter DNA.[184] DNA alteration is considered a critical first step in carcinogenesis.[185] Other biochemical reactions may provide additional metabolic pathways for TCE's suspected carcinogenicity, including, inter alia, conversion

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39–41 (March 2008); Ralph Vartabedian, *How Environmentalists Lost the Battle Over TCE*, L.A. Times, March 29, 2006, at A1. EPA recently revived the moribund effort by publishing and soliciting public comment on a "pre-dissemination" external review draft "Toxicological Review of Trichloroethylene." 74 Fed. Reg. 56,834 (Nov. 3, 2009). More scientific peer review and public comment will follow. *Id.* EPA has not announced a planned completion date.

[178] This discussion is not intended to argue that TCE does (or does not) cause kidney cancer. A full review of the scientific, judicial, and regulatory treatment of TCE is beyond the scope of this article.

[179] Agency for Toxic Substances & Disease Registry, Public Health Statement for Trichloroethylene § 1.3 (Aug. 2008), http://www.atsdr.cdc.gov/toxprofiles/phs19.html (giving average concentrations); Philip H. Abelson, *Volatile Contaminants of Drinking Water*, 247 Science 141, 141 (1990) (noting that TCE is the most frequently detected chemical at Superfund sites).

[180] Hiltrud Brauch et al., *Trichloroethylene Exposure and Specific Somatic Mutations in Patients with Renal Cell Carcinoma*, 91 J. Nat'l Cancer Inst. 854, 854 (1999).

[181] *Id.*

[182] *Id.* at 859–60 nn.28–33.

[183] Comm. on Human Health Risks of Trichloroethylene, Nat'l Research Council, Assessing the Human Health Risks of Trichloroethylene: Key Scientific Issues 126 (2006).

[184] Brauch et al., *supra* note 180, at 859.

[185] *See* Kathryn Z. Guyton et al., *Improving Prediction of Chemical Carcinogenicity by Considering Multiple Mechanisms and Applying Toxicogenomic Approaches*, 681 Mutation Research 230, 231 (2009); Perera, *supra* note 108, at 603.

of some TCE to closely related compounds that may themselves be carcinogens.[186]

Epidemiologic studies in humans detected higher relative risk of RCC associated with TCE exposures. These studies typically compared occupationally exposed workers to the general population. The reported relative risk values varied. Generally they were greater than one but less than two.[187]

Other toxic substances, including tobacco smoke, are also suspected of causing RCC. Epidemiologic studies revealed higher (but not doubled) relative risk for RCC among smokers than among non-smokers.[188]

This particular type of kidney cancer "is one of the few human tumors known to evolve from mutations of a specific gene,"[189] the von Hippel-Lindau tumor suppressor ("VHL") gene. Mutations in this gene can prevent the associated protein from performing its tumor suppression function.[190]

A person who inherited an altered form of the VHL gene carries that germ-line mutation in all of his or her body cells. By contrast, a person who acquired a VHL gene mutation during life — perhaps by exposure to a toxic substance — will carry that somatic mutation only in tissue descended from the mutated cell(s). A mutation that arose in a kidney cell that gave rise to a malignancy, for example, will be found in the cells of the tumor but not elsewhere in the person's body.[191]

Genomic techniques further revealed that the pattern of VHL mutations, as well as their location, can distinguish "hereditary" cases of RCC from sporadic cases.[192] A molecular epidemiology study compared the DNA of sporadic RCC patients with that of healthy controls. The patients' tumors had many different mutations in the VHL gene. One particular mutation, however, was found in a number of patients who had been occupationally exposed to TCE, but in none of the unexposed patients. The authors concluded that they had found "the first molecular evidence for a relationship between exposure to a defined carcinogen, gene damage, and kidney cancer" — a "unique mutation pattern" in a gene associated with RCC in patients with high, cumulative exposure to TCE.[193]

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[186] Weihsueh A. Chiu et al., *Key Scientific Issues in the Health Risk Assessment of Trichloroethylene*, 114 ENVTL. HEALTH PERSP. 1445, 1446 (2006).

[187] Cheryl Siegel Scott & Weihsueh A. Chiu, *Trichloroethylene Cancer Epidemiology: A Consideration of Select Issues*, 114 ENVTL. HEALTH PERSP. 1471, 1477 fig.3 (2006).

[188] Ryan P. Theis et al., *Smoking, Environmental Tobacco Smoke, and Risk of Renal Cell Cancer: a Population-based Case-control Study*, 8 BMC CANCER 387, *2 (2008).

[189] Brauch et al., *supra* note 180, at 854.

[190] Yih-Horng Shiao, *Genetic Signature for Human Risk Assessment: Lessons from Trichloroethylene*, 50 ENVTL. & MOLECULAR MUTAGENESIS 68, 70 (2009).

[191] *See* Brauch et al., *supra* note 180, at 854, 859 (explaining that by comparing DNA in tumor cells with DNA in blood cells and in normal kidney tissue near the tumor site, researchers could distinguish inherited mutations found in both tumor and non-tumor cells from somatic mutations found only in tumor cells).

[192] *Id.* at 854.

[193] *Id.* at 854, 859.

Another study reported that polymorphisms in an entirely different gene, which code for an enzyme involved in glutathione metabolism,[194] also appear to affect RCC risk associated with TCE exposure.[195] The full extent of differential susceptibility to TCE toxicity has not been fully characterized or quantified.[196]

C. How Will Courts Respond? How Should They?

Imagine a plaintiff with RCC who has been exposed to TCE and alleges that the exposure caused the cancer. This hypothetical case illustrates some of the benefits that genomic understanding may provide to litigants and fact finders. It also highlights a number of the challenges that toxicogenomics and molecular epidemiology will present.

For a court confronting such a case, the allure of toxicogenomics is plain enough, for classical epidemiology has a weakness: "the failure to consider the genetic component of any disease-risk factor association . . . dilute[s] the impact of the risk factor in the population, thereby reducing the ability to detect effects of genotypes and exposures."[197] But similarly, in a genetic epidemiology study the failure or inability to consider other environmental factors, epigenetic factors, multi-gene interactions, and the like will dilute the impact of both the genotype and the toxin being studied.[198]

Thus, even where toxicogenomic information is available, it will not represent a "fixed" toxic susceptibility value for a particular gene, but rather the average of a range of susceptibility values associated with that gene across the range of modifying factors.[199] That average, estimated by a sampling process, will be characterized by a degree of uncertainty. This uncertainty, spawned by random chance and the undetected influence of other factors, helps to explain why toxic susceptibility genes do not *determine* disease causation — "[t]hey modify risk."[200] In the final analysis, the output of toxicogenomics and molecular epidemiology, even where we have it, usually will still be probabilistic.

So, despite the change in the nature of causal proof that these sciences truly represent, in a way nothing much will change at all. This understanding should suffuse judicial treatment of toxicogenomics and molecular epidemiology as they seep into courtrooms. The doctrinal problems presented

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[194] *See supra* text accompanying note 184.

[195] *See* Thomas Brüning et al., *Influence of Polymorphisms of GSTM1 and GSTT1 for Risk of Renal Cell Cancer in Workers with Long-Term High Occupational Exposure to Trichloroethene*, 71 ARCHIVES TOXICOLOGY 596, 597 (1997).

[196] *See* Chiu et al., *supra* note 186, at 1447.

[197] Khoury, *supra* note 86, at 176–77.

[198] *See* Imyanitov et al., *supra* note 88, at 8–9 (noting that borderline risk estimates for a polymorphism may result from "failure to find circumstances in which [it] plays a strong predisposing role").

[199] *See infra* text accompanying notes 240–55.

[200] Kenneth Olden & Janet Guthrie, *Genomics: Implications for Toxicology*, 473 MUTATION RES. 3, 5 (2001).

by toxicogenomics and molecular epidemiology will be eerily reminiscent of those that have been associated with toxicology and classical epidemiology, which have remained unresolved for decades. Nevertheless, courts should seize the opportunities that the new science affords to improve old doctrine. This section considers those problems and opportunities in light of existing jurisprudence and developing science, discussing the TCE/RCC exemplar where it is salient.

1. *The Search for the Particularistic?*

Joseph Sanders has said that "[s]pecific causation evidence seems to be the holy grail of toxic torts."[201] History shows that he chose an apt metaphor. Both law and science long perceived the link between toxic exposure and eventual disease as a black box, into which similarly situated people might enter, only to emerge with highly disparate outcomes determined by an invisible, mysterious, and stochastic mechanism within the box. The touted promise of toxicogenomics for providing particularistic evidence — at long last opening the black box[202] — may lead courts to conclude that the grail is found.

In some cases it probably will be. Even classical epidemiology turned up signature diseases. The chances of getting mesothelioma in the absence of asbestos exposure are so vanishingly small that medicine and law conclude that causation is shown if both the exposure and the disease are proven: the disease itself speaks its cause.[203] With molecular techniques the disease need not be uniquely associated with the exposure, so long as the biomarker is. It seems safe to predict that toxicogenomics and molecular epidemiology will produce at least some consistent, strongly correlated, and highly specific biomarkers of exposure and/or effect.[204] These would link toxic exposures to illness and distinguish "true" causation cases from "background" cases and from cases caused by some other detectable environmental insult. Even if molecular "signatures" are rare, toxicogenomics and molecular epidemiology very likely will uncover other links that, if not quite so individualized, will nevertheless define more narrowly the subpopulation to which a plaintiff belongs for risk purposes.

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[201] Joseph Sanders, *Apportionment and Proof in Toxic Injury Cases*, 10 KAN. J.L. & PUB. POL'Y 200, 202 (2000).

[202] Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1687–88.

[203] *See* Boston, *supra* note 4, at 293 (observing that by the mid-1970s, courts held as matter of law that asbestos causes mesothelioma); Irving J. Selikoff, Jacob Churg & E. Cuyler Hammond, *Relation Between Exposure to Asbestos and Mesothelioma*, 272 NEW ENG. J. MED. 560 (1965) (finding an extremely strong link); *see also* Norfolk & W. Ry. Co. v. Ayers, 538 U.S. 135, 142 n.4 (2003) ("Asbestos is the only cause of mesothelioma established thus far, although some instances of the disease are not traceable to asbestos.").

[204] A specific and consistent association with the causative exposure is a component of a biomarker's overall scientific validity. *See generally* Paul A. Schulte & Frederica P. Perera, *Validation*, *in* MOLECULAR EPIDEMIOLOGY, *supra* note 84, at 79.

As the amount of available particularistic or quasi-particularistic evidence of causation increases, courts inevitably will reconsider their view of what makes the "best" evidence. Many courts already charge epidemiology with delivering an "answer," and display great unwillingness to engage in (or to allow juries to engage in) a process of inference from indirect evidence, of weighing the logical coherence of competing conclusions derived from facts of disputed significance.[205] It is predictable that some court somewhere will conclude that genetic evidence, probably a biomarker of exposure or effect, is *required* as proof of causation. In an analogue to the "get it or forget it" rule some courts have applied to classical epidemiology, some courts may doubt the acceptability of mere epidemiology (which cannot *really* address an individual plaintiff) as scientifically reliable and relevant, when "better" genomic evidence is available. For a court so inclined, the general causation—specific causation dichotomy would provide a convenient doctrinal handle.

Arguments and rulings approaching this conclusion already exist. In *Henricksen v. ConocoPhillips Co.*, a gasoline tanker truck driver alleged that his exposure to benzene in gasoline fumes caused his acute myelogenous leukemia ("AML").[206] Defense experts testified that although ten to twenty percent of AML cases are caused by known carcinogens, the rest have no known cause.[207] They further testified that certain characteristics of a person's disease could help distinguish between these categories:

> Either cytogenetic or a distinct pattern of chromosomal aberrations have been considered characteristic findings in nearly ninety percent of all secondary [carcinogen-induced] AML, which includes AML caused by exposure to benzene as opposed to gasoline containing benzene. In *de novo* AML cytogenetic abnormalities are observed only in approximately fifty percent of the time. There was no evidence of chromosomal abnormality in Mr. Henricksen's case.[208]

The plaintiff proffered a doctor's opinion on both general and specific causation. The court excluded the testimony as unreliable under *Daubert*. The court, which appeared to equate idiopathic cases ("with no readily identifiable cause") with "endogenous" cases ("onset without external or environmental stimulus"),[209] effectively held that admissible testimony of specific causation of AML requires particularistic biomarker information:

> [T]he only reason cited for distinguishing Henricksen's disease from one of "no known cause" was the existence of a known risk

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[205] *See, e.g.*, Downs v. Perstorp Components, Inc., 126 F. Supp. 2d 1090, 1125–28 (E.D. Tenn. 1999) (giving examples of such inference that the court considered fundamentally unscientific and improper).

[206] Henricksen v. ConocoPhillips Co., 605 F. Supp. 2d 1142, 1148 (E.D. Wash. 2009).

[207] *Id.* at 1149.

[208] *Id.* at 1149–50 (citations omitted).

[209] *Id.* at 1149.

> factor, namely exposure to benzene. Standing alone, the presence of a known risk factor is not a sufficient basis for ruling out idiopathic origin in a particular case . . . . [Plaintiff's expert] could have compared the presentation of Henricksen's symptoms with those in chemically induced AML cases. . . . None of the features characteristic or commonly seen in secondary AML have been associated with Henricksen's case.[210]

The court apparently agreed with defendant's experts that without particularistic evidence "there is no scientific way to separate the AML affecting Henricksen from the *de novo* AML occurring in people with no particular exposure to chemicals."[211] As a result, the court excluded all of plaintiff's causation experts and granted summary judgment to defendants.[212]

Similarly, in *Cord v. City of Los Angeles*,[213] plaintiffs contended that the decedent's lymphatic cancer was caused by exposure to benzene and other chemicals emitted from the municipal landfill near his workplace. A defense expert testified that the plaintiffs could have tested for biomarkers to determine the extent of the exposures, but because they did not, "it is impossible to determine to a medical certainty" whether the decedent had been exposed to a potentially carcinogenic dose.[214] In *Tompkin v. Philip Morris USA, Inc.*,[215] a cigarette manufacturer apparently persuaded a jury that smoking did not cause the lung cancer of a smoker who had also worked with asbestos. An expert testified that cigarette smoke is known to cause certain mutations in the *p53* and *k-ras* cancer suppressor genes and the decedent's tissue lacked those mutations.[216] The trial judge called the expert's testimony "devastating."[217]

Milward v. Acuity Specialty Products Group, Inc.[218] presented a different twist. In *Milward*, the issue was not the absence of a biomarker but the lack of a clearly-proven connection between the exposure and the observed cellular damage. The plaintiff, who alleged exposure to benzene, suffered from a form of AML.[219] The parties agreed that benzene could cause chro-

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[210] *Id.* at 1162–63.

[211] *Id.* at 1150. The court also concluded that evidence of benzene toxicity could not support a causation finding in a case involving exposure only to the benzene present in gasoline. *Id.* at 1176.

[212] *Id.* at 1178–79.

[213] No. B167756, 2004 Cal. App. Unpub. LEXIS 8967 (2d Dist. Sept. 30, 2004).

[214] *Id.* at *5. This expert opinion did not determine the outcome. The court struck the plaintiff's one causation witness, because the only epidemiologic study on which he relied "ultimately concluded only 'possible' links between benzene exposure and non-Hodgkin's lymphoma," despite finding a "relative risk" of 4.2. *Id.* at *18.

[215] 362 F.3d 882 (6th Cir. 2004).

[216] *Id.* at 890 n.5.

[217] *Id.* at 894. The expert also testified that microscopic examination of the decedent's tissues revealed no cellular markers of tobacco smoke damage. *Id.* The opinion does not make clear whether the expert testified that *all* tobacco-caused lung cancer displays these cellular or genetic markers.

[218] 664 F. Supp. 2d 137 (D. Mass. 2009).

[219] *Id.* at 143.

mosomal aberrations that lead to certain forms of AML,[220] but the court found that benzene had not been linked to the "characteristic genetic alteration" almost always found in plaintiff's type of AML.[221] The court therefore excluded plaintiff's proffered expert (who would have testified that the link could be inferred), holding that the expert proposed to testify to a hypothesis rather than a scientifically reliable opinion.[222] *Milward*, although different from *Cord* and *Tompkin* (in which defendants argued that the absence of biomarker evidence tended to disprove a causal connection that might have been believed based on classical epidemiology alone), further demonstrates that the understanding of disease at the molecular level has already reached the courtroom.

The coming demand for genetic evidence in addition to or instead of epidemiologic evidence, which is incipient in *Henricksen*, *Cord*, and *Tompkin*, was foreshadowed by a passage with which the *Havner* court closed its discussion of scientific evidence in toxic tort causation: "courts should not foreclose the possibility that advances in science may require reevaluation of what is 'good science' in future cases."[223] That is equal parts thrilling and chilling.

It is thrilling because the court recognized the dynamic nature of scientific inquiry, which accepts, modifies, or discards hypotheses and explanatory paradigms depending on their consistency with the empirically observable world. Yet it is chilling, because the court failed to appreciate that scientific dynamism is not simply an upward arc of progress but also an instantaneous state of flux. Although there is such a thing as "bad science," or more properly, "non-science," even among scientists "good science" is not some unanimously-endorsed Platonic ideal at any given time. As sometimes happens in law, in science today's lonely dissenter may represent tomorrow's consensus.[224]

Havner implied, to the contrary, a view that at any given time there is a single standard for proving causation scientifically, and further, that law should reject any inference of causation from evidence not matching whatever that single standard is. Courts would make a serious mistake were they to adopt this stance with respect to molecular epidemiology — replacing the ill-conceived requirement of specific classical epidemiologic evidence with a similarly rigid requirement of specific toxicogenomic evidence.

First, relevant, individual toxicogenomic evidence is likely to be only sporadically available, just as relevant, tight-fitting epidemiologic evidence

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[220] *Id.* at 146.
[221] *Id.* at 143.
[222] *Id.* at 149.
[223] Merrell Dow Pharm., Inc. v. Havner, 953 S.W.2d 706, 720–21 (Tex. 1997).
[224] This recognition seemed to animate *Daubert*'s abandonment of "general acceptance" as the touchstone of admissibility. Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579, 588 (1993); *see* Eggen, *supra* note 9, at 214; *see generally* David L. Faigman et al., *How Good Is Good Enough?: Expert Evidence Under Daubert and Kumho*, 50 CASE W. RES. L. REV. 645 (2000) (arguing that courts should not require "best evidence" but should impose a flexible requirement for "better evidence" in appropriate circumstances).

is only sporadically available. The evidence might not have been found yet, or a particular causation pathway might not leave observable biomarkers, or the biomarkers might be transient or obscured by subsequent molecular events and thus not observable after the fact.[225] Yet even if such proof is lacking, other evidence could support an inference of causation. It is just as wrong to mesh the substantive element with a formal evidentiary requirement of toxicogenomic information as it is to do so with respect to epidemiologic evidence.

Second, if a relevant biomarker of exposure or effect is known, to require its presence to support a causation inference is to assume that the absence of the biomarker precludes causation.[226] The assumption can be true only if no causal pathway exists between a chemical and a disease *other* than the pathway that produces the biomarker. That negative hypothesis is probably incorrect in many cases.[227] Even if it were true, proving it may well be beyond the ability of science. The only way to disprove it conclusively would be to elucidate an alternative molecular pathway, which is considerably more than courts normally ask plaintiffs to do.

The TCE/RCC case illustrates the problem. As noted above, researchers identified, in their sample of TCE-exposed kidney cancer patients, a "unique" VHL gene mutation that was absent from their sample of unexposed patients. Professor Grodsky cited this as an example of a signature biomarker,[228] as suggested by the study's authors.[229] Yet even though none of the subjects without known TCE exposure had this particular mutation, the mutation appeared in only 39% of the *exposed* subjects.[230] Four-fifths of the subjects with medium or high exposure had *some* mutation in the VHL gene, but so too did most of the subjects with no known exposure.[231]

It is easy to envision a court, adopting the view that the "best" scientific evidence is required,[232] concluding that absent proof that the plaintiff's tumor displayed the "signature" mutation, there is no "scientific" way to

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[225] *See* Wild, *supra* note 157, at 117 ("Progress has been made with biomarkers . . . . Nevertheless, much remains to be accomplished in order to establish aetiology . . . .").

[226] Even the defense testimony in *Henricksen* acknowledged that this assumption is incorrect in more than one-tenth of carcinogen-induced AML. Henricksen v. ConocoPhillips Co., 605 F. Supp. 2d 1142, 1149 (E.D. Wash. 2009).

[227] *See* Guyton et al., *supra* note 185, at 231–32 (describing necessity of evaluating multiple modes of action of carcinogens); Shiao, *supra* note 190, at 69 ("Some agents can produce more than one type of DNA damage.").

[228] Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1708.

[229] Brauch et al., *supra* note 180, at 859.

[230] *Id.* at 855–56. The study grouped exposure levels into high, medium, low, and none (controls). The mutation was more common in those with high exposure than in those with medium exposure, and was absent in the three subjects in the low exposure group. *Id.* at 859.

[231] *Id.* at 859. The frequency of VHL mutations overall was 15/17 for the high exposure group, 18/24 for the medium exposure group, 0/3 for the low exposure group, and 42/73 for the unexposed group. *Id.*

[232] *E.g.*, *Agent Orange Opt Out*, 611 F. Supp. 1223, 1230–31 (E.D.N.Y. 1985), *aff'd*, 818 F.2d 187 (2d Cir. 1987); Merrell-Dow Pharmaceuticals v. Havner, 953 S.W.2d 706, 720 (Tex. 1997); *see* Boston, *supra* note 4, at 363–83 (arguing that courts hearing "mass exposure cases" should apply stringent requirements to scientific proof of causation).

separate a plaintiff's case from an idiopathic case.[233] Indeed, a federal district court's cursory opinion in a workers' compensation case, without mentioning genetics or biomarkers, employed similar reasoning to the link between occupational exposure to TCE and non-Hodgkins lymphoma ("NHL"), a different type of cancer.[234] Yet the study that identified the putative signature mutation pattern by no means established that cases without that pattern were background cases not caused by TCE exposure.[235] A later study of a different population failed to show any association between TCE and that mutation pattern — although it could not totally rule out the "signature" hypothesis, either.[236] Scientific evidence suggests that TCE actually may cause cancer through multiple metabolic pathways.[237]

As molecular epidemiology has provided a glimpse inside the black box, epidemiologists have begun to appreciate that the better image may be "a nest of boxes, each with a succession of smaller ones," with relations within and between them.[238] The presence or absence of a validated biomarker of exposure or effect — one datum from inside the black box — could of course be relevant to an alleged causal relationship. Relatively rarely, however, is it likely to be absolutely conclusive. The proper approach to evidence regarding such biomarkers is to throw it in the hopper with other relevant evidence that the parties may present. The fact finder would have the task of weighing that evidence to determine whether causation has been proven by a preponderance of the evidence. Doing so would inevitably entail reaching a conclusion about the relative significance of the biomarker evidence as compared to other evidence on the causation question.[239]

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[233] *Cf.* Henricksen v. ConocoPhillips Co., 605 F. Supp. 2d 1142, 1150 (E.D. Wash. 2009) (describing statements of defense experts that "there is no scientific way to separate" plaintiff's illness from cases of illness occurring without known exposure).

[234] Hoffman v. Monsanto Co., No. 2:05-CV-00418, 2007 U.S. Dist. LEXIS 77975 at *3 (S.D. W. Va. Oct. 11, 2007). The plaintiff's expert admitted that no "specific characteristics" of plaintiff's NHL identified it as "occupational as opposed to idiopathic," *id.* at *25, or in other words, that there were no identifiable biomarkers of effect. Asked if there was "nothing about" plaintiff's disease that would "confirm or deny with any certainty that it is due to exposure to TCE," the witness responded: "*I don't think you can be certain*, but I think you can say more likely than not there was a causal relationship." *Id.* The court held that this testimony did not satisfy the "direct and proximate result" standard of the state workers' compensation statute. *Id.* at *26.

[235] To be clear, Professor Grodsky did not argue for such an inference. Rather, she contended that even without clinically manifest cancer, the presence of the unique mutation in a TCE-exposed plaintiff could be sufficient "injury" to support a tailored recovery. Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1708–11; *see infra* Part IV.C.5.

[236] Barbara Charbotel et al., *Trichloroethylene Exposure and Somatic Mutations of the VHL Gene in Patients with Renal Cell Carcinoma*, 2 J. Occupational Med. & Toxicology 13, *6 (2007).

[237] Jane C. Caldwell et al., *Difficulty of Mode of Action Determination for Trichloroethylene: An Example of Complex Interactions of Metabolites and Other Chemical Exposures*, 49 Envtl. Molecular Mutagenesis 142, 152 (2008) ("multiple internal and external exposures to TCE . . . may act via differing" modes of action).

[238] Spitz & Bondy, *supra* note 106, at 132.

[239] Professor Grodsky also emphasized the importance of other evidence, particularly if " 'signature' [bio]markers are lacking." Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1708.

2. *It May Be Molecular, But It's Still Epidemiology: Relative Risk Shall Rise Again*

Even if biomarker evidence does not become a sine qua non, where it is available litigants will use it. Plaintiffs will try to show that they belong to genetic subgroups that face heightened risk from exposure — especially if more general studies show relative risk less than two. Defendants will try to show that plaintiffs belong to genetic subgroups that face reduced risk from exposure — especially if more general studies link the defendants' substance to a relative risk greater than two.

Easter v. Aventis Pasteur, Inc.[240] does not quite fit this mold but again presages things to come. *Easter* involved an autistic and otherwise impaired child who had received a vaccine that included the mercury-containing preservative thimerosal. The court assumed, for purposes of decision, that "sufficiently reliable epidemiological and other" evidence existed to support general causation of autism by thimerosal "in a predisposed subpopulation of children in the United States."[241] The plaintiffs conceded that their child did not have the genetic predisposition, but argued that the mercury had caused his other conditions.[242] The court noted that the other conditions frequently accompanied autism, with or without thimerosal exposure. Therefore, absent proof that thimerosal had caused the autism itself, the court refused to allow the plaintiffs' expert to testify about specific causation of the other conditions.[243]

The court's analysis assumed that a genetically-based susceptibility to toxic exposure would have constituted specific — that is, individualized or "particularistic" — causation evidence. That assumption is wrong. The genetic subpopulations studied by molecular epidemiology are still populations, not individual cases of disease. A study that controls for known genetic polymorphisms allows a narrower focus on people who share important observable traits with a plaintiff. This may make a fact finder more confident in reasoning from a population study to an individual. But what one learns from the study is still a probabilistic relative risk that exposure poses to a person of a given genotype as compared to the risk faced by a person of the same genotype in the absence of exposure. Molecular epidemiology studies "fit into the same framework" as classical epidemiology, except that in molecular studies "risk factors, outcomes, confounders or effect modifiers are measured with biomarkers."[244]

"When considered as part of a larger body of evidence," she argued, "the criticism that many molecular events are insufficiently distinctive to be correlated with particular chemicals loses some of its bite." *Id.* at 1709. Some, but not nearly all. *See infra* Part IV.C.5.

[240] 358 F. Supp. 2d 574 (E.D. Tex. 2005).

[241] *Id.* at 576.

[242] *See id.* at 575–76.

[243] *See id.* at 577–78.

[244] Paolo Boffetta, *Biomarkers in Cancer Epidemiology: An Integrative Approach*, 31 CARCINOGENESIS 121, 125 (2010).

This simple truth is easily overlooked when considering technological achievements that allow scientists "to scan the entire human genome to search for genetic responses to specific chemicals."[245] But it is central to consideration of how courts likely will respond, as well as how they should respond, to the output of this technology. Courts' simultaneous over-enthusiasm for and chariness of epidemiologic data will doubtless carry through to molecular epidemiology. The tightness of fit that many courts have demanded between a plaintiff's situation and a proffered study will likely get tighter. Where there is information about the epidemiology of genetic subpopulations, particularly if some subpopulations show relative risks greater than two and others do not, courts may conclude that to satisfy the causation burden a plaintiff must prove membership in a subpopulation with a genotype that confers a threshold-exceeding level of susceptibility to the exposure in question.

It is entirely predictable that some courts will decide that to establish causation all toxic tort plaintiffs must prove a genotype-specific doubling of relative risk, just as in the pre-genomic era some courts required plaintiffs to demonstrate that exposure more than doubled risk in genetically heterogeneous populations. The medical community's vision that genomics will "individualize" toxicology and other medical sciences,[246] as it infiltrates the popular culture and the judicial mind, cannot but hasten this eventuality. How, a court might reason, can one conclude that *your* disease was "more likely than not" caused by a toxic exposure, if exposure causes a doubling of risk only in *some* people — those with a particular genotype? *Easter* represents a relatively crude example of this type of reasoning.[247]

Population heterogeneity with respect to toxic susceptibility appears to be the norm.[248] Courts will therefore be tempted to require a plaintiff to make a showing of genetic susceptibility to the accused toxin. But this would impose an additional substantive requirement. A plaintiff might be unable to satisfy the requirement simply because molecular studies had not been conducted, even if classical epidemiology showed relative risk greater

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[245] Grodsky, *Public Health*, *supra* note 122, at 191.

[246] *See, e.g.*, William E. Evans & Mary V. Relling, *Moving Towards Individualized Medicine with Pharmacogenomics*, 429 NATURE 464, 464 (2004) (describing vision of how to overcome challenges and "understand fully the contribution of genetic polymorphisms to inter-individual differences in drug effects and to translate this new knowledge into clinical practice"); George Orphanides & Ian Kimber, *Toxicogenetics: Applications and Opportunities*, 75 TOXICOLOGICAL SCI. 1, 5 (2003) (predicting understanding of "idiosyncratic" toxic responses); Trujillo et al., *supra* note 105, at 405 (noting that understanding polymorphisms will make it "easier to predict those who might benefit most from dietary intervention").

[247] Easter v. Aventis Pasteur, Inc., 358 F. Supp. 2d 574, 575 (E.D. Tex. 2005) (noting that autistic child did "not meet the genetic profile" that plaintiffs claimed would increase risk of developing autism after exposure to thimerosal).

[248] *See* Perera, *supra* note 108, at 608 ("Scientists and policy makers now widely agree that the new molecular epidemiologic and other data invalidate the assumption of population homogeneity . . . ."); Ofer Shpilberg et al., *The Next Stage: Molecular Epidemiology*, 50 J. CLINICAL EPIDEMIOLOGY 633, 637 (1997) (predicting that very high relative risks for specific genotypes "may be the order of the day, rather than significant relative risks of 1.4, 1.5, etc., common in many epidemiological studies").

than two in the population as a whole. But even if there were molecular epidemiologic data, and it failed to show a relative risk greater than two for the plaintiff's genotype, courts should not treat that as ironclad disproof of causation or refuse to consider any other evidence of causation. To do so with respect to molecular epidemiology of genetic subpopulations would be wrong for the same reasons that doing so with respect to classical epidemiology is wrong.

Many commentators have noted that a risk-doubling threshold implies that *any* amount of increased incidence of disease caused by a substance that is less than a doubling results in no compensation for anybody, and thus in inadequate deterrence[249] — no matter how conclusive the proof of increased risk. Equating the causation element with relative risk greater than two conflates the evidentiary standard of persuasion with the substantive burden of proof and eviscerates the function of the preponderance rule as a standard of persuasion.[250] To illustrate the problem, one district court opined that a plaintiff could prove that asbestos caused his bladder cancer in only one of two ways: by "epidemiological evidence falling short of 2.0 in combination with" other evidence "specifically" applicable to his case, or by studies "*conclusively* establishing" relative risk greater than two.[251] Whatever "conclusively" means, it does not seem to mean the same thing as "by a preponderance of the evidence."

Given the inherent limitations of (classical) observational epidemiology, obtaining clear results showing a relative risk greater than two has been difficult, even when a real biological connection exists between exposure and disease.[252] Scientific reviews concluded that epidemiology had found only "[a]bout a dozen specific occupation [*sic*] exposures and several complex mixtures" that "caused high risks of certain cancers . . . in heavily

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[249] Conversely, to allow compensation in every case with relative risk greater than two results in overdeterrence, unless the causal connection is so strong that virtually no one contracts the disease in the absence of exposure. Overdeterrence is likely to be only theoretical, however, because not all injured persons sue and most suits are settled for compromise amounts.

[250] If a plaintiff presents a study showing more than doubled risk, to what degree must a fact finder believe it, in order to find for the plaintiff? There is no answer. The study exists, or it does not; the degree of belief a fact finder holds in a particular state of the world is eliminated from the standard. *See* Gold, *supra* note 2; *see also* Chris Miller, *Liability for Negligently Increased Risk: The Repercussions of* Barker v. Corus UK (plc), 8 L. PROBABILITY & RISK 39, 51–52 (2009) (discussing how "we can have a subjective or epistemic degree of belief in an objective probability").

[251] *In re* Joint S. & E. Dist. Asbestos Litig., 52 F.3d 1124, 1128 (2d Cir. 1995) (emphasis added), *rev'g in pertinent part* 827 F. Supp. 1029 (S.D.N.Y. 1993).

[252] *See, e.g.*, Carruth & Goldstein, *supra* note 31, at 205–09; Green, *supra* note 3, at 371–84. Because controlled epidemiologic experimentation on human subjects is both impossible and unethical, *see* Boston, *supra* note 4, at 232 (society "will not tolerate . . . experimentally subjecting humans to putative carcinogens"), it is difficult to ensure that the groups sampled in an epidemiologic study are really comparable in every way except for the factor being studied. For example, epidemiologists typically cannot precisely quantify the exposure received by each individual in the exposed group, but heterogeneous degrees of exposure can lead to false negative results and obscure dose-response relationships. Furthermore, achieving sufficient statistical power may be difficult, *see supra* note 14.

exposed workers,"[253] which explain only a relatively small proportion of cancers,[254] despite a widely prevalent view that chemical or other environmental insult to cells is a key step in carcinogenesis.[255]

Researchers hope that molecular and genomic techniques, by allowing them to study genetically distinctive subpopulations, will expose strong associations that have remained obscure in classical epidemiologic studies. How successful they will be remains to be seen. The tandem of toxicogenomics and molecular epidemiology, it appears, may also face limited resolving power.

For example, much variation in susceptibility to toxin-produced disease may be multigenic, but gene-gene interactions are difficult to assess.[256] Epigenetic differences, perhaps only from an earlier stage of a patient's life, may affect susceptibility.[257] A welter of personal factors — nutrition and diet, for example — may promote differential susceptibility to toxic exposures,[258] even in genetically similar people.[259] Some of the apparent heterogeneity in susceptibility to toxic substance exposure may itself result from toxic substance exposure![260] And even if a genetic variation affects susceptibility to a substance's disease-producing effects, the heightened susceptibility may be

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[253] Julian Peto, *Cancer Epidemiology in the Last Century and the Next Decade*, 411 NATURE 390, 392 (2001).

[254] Boffetta, *supra* note 244, at 121 (based on a study of cancer in France). "Only a few environmental pollutants have been *definitely* associated with human cancer," illustrating "the limitations of current epidemiological understanding of cancer." *Id.* (emphasis added).

[255] *See, e.g.*, Perera, *supra* note 108, at 602 (stating that the "great majority" of many "cancers are, in principle, preventable because the factors that determine their incidence are largely exogenous or environmental . . . . There is . . . increasing recognition that controlling external factors presents the greatest opportunity for primary cancer prevention . . . ."); REUBEN, *supra* note 114, at 2 (noting that estimates of cancer attributable to environmental exposures "are now believed to underestimate significantly the true toll").

[256] Carlson et al., *supra* note 112, at 450; *see* Boffetta, *supra* note 244, at 124 (noting that variations at several genes are involved in smokers' risk of lung cancer); Spitz & Bondy, *supra* note 106, at 130 (same; stating that multigenic risk models "have shown only modest improvements in discrimination").

[257] Guyton et al., *supra* note 185, at 235 (noting that epigenetic effects are important "especially during critical developmental windows"); Rothstein et al., *supra* note 110, at 7 (stating that epigenetic effects are sensitive to developmental stage).

[258] *See* Olden & Guthrie, *supra* note 200, at 6 (listing factors affecting susceptibility).

[259] *E.g.*, Ferguson, *supra* note 79, at 456 (noting that green tea consumption reduced breast cancer risk in women with high-risk ACE genotype but not in women with low-risk allele); Perera, *supra* note 108, at 606 (stating that antioxidant-poor diets increased lung cancer risk in subpopulation of smokers with similar genotype); *see* Altshuler et al., *supra* note 82, at 887 ("Genetic effects will likely vary across [ancestry] groups because of modification by environment and behavior, *which may vary more across groups than does genotype*.") (emphasis added); Kauwell, *supra* note 74, at 1056 (stating that diet-induced epigenetic modification of genome has potential to influence risk of cancer and other diseases).

[260] Guyton et al., *supra* note 185, at 235 (stating that epigenetic changes are important in cancer; "[e]nvironmental contaminants can affect multiple types of epigenetic changes"). To further complicate matters, in some cases the same gene may affect both the likelihood of exposure and the effect of exposure. Boffetta, *supra* note 244, at 125. For example, "the same genetic variants may contribute to nicotine dependence and directly to lung carcinogenesis." Spitz & Bondy, *supra* note 106, at 131.

elusive if it manifests only when exposure exceeds a threshold dose.[261] These difficulties suggest that although molecular epidemiology will sharpen the picture, it may not provide quite as high definition as hoped.

Nevertheless, genetic variability in susceptibility, even before it has been thoroughly plumbed, is not entirely irrelevant. It has a very important corollary lesson to teach courts about classical epidemiology. Because undetected genetic variability "will dilute the impact of the [suspected toxic] risk factor" under study,[262] *negative* results from classical epidemiology — whether "negative results" is defined as a reported relative risk value lower than two, a 95% confidence interval that includes one, or a lack of any observed increase in risk at all — may be fallacious.[263] Courts should therefore be substantially less deferential to negative epidemiologic results. Epidemiologic studies that don't support the hypothesis of causation may be relevant, of course, but if there is other evidence (genomic or otherwise) tending to prove causation, it is a mistake to assign dispositive weight to epidemiologic studies that do not consider genetic variability.

The evidentiary and substantive rules that courts have evolved for the treatment of classical epidemiology and toxicology, and that they may extend and apply to the treatment of toxicogenomics and molecular epidemiology, allocate the cost of scientific uncertainty.[264] If courts limit legally admissible and/or sufficient proof to a specific category and strength of scientific proof, they choose to make plaintiffs bear the cost of toxic injury during the time when science is developing evidence but has not yet produced the judicially-mandated "best science" du jour. Because scientific "truth" is not absolute or absolutely knowable, that choice reflects more than just a manifestation of the legal allocation of burdens of proof. Rather, the rules appear to demonstrate a predominant preference for false negatives (denying compensation in cases where scientific proof may later become stronger) over false positives (awarding compensation in cases later disproven by science).[265]

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[261] Imyanitov et al., *supra* note 88, at 9 (giving example of certain polymorphisms that affected lung cancer risk only in heavy smokers).

[262] Khoury, *supra* note 86, at 176–77.

[263] *See supra* note 125 and accompanying text (providing an example of smoking and breast cancer). Genetic variability may also obscure beneficial effects. *See, e.g.*, Trujillo et al., *supra* note 105, at 406 (discussing genetically variable response to anti-cancer effect of selenium supplements).

[264] *See* Milward v. Acuity Specialty Prods. Group, Inc., 664 F. Supp. 2d 137, 146 (D. Mass. 2009) (holding that expert testimony must be excluded where evidence indicates expert's conclusion is subject to scientific debate and consensus is "we don't know").

[265] *Cf.* Klein, supra note 28, at 6 ("law . . . seek[s] assurance that one 'is responsible for all he does, but for *only* what he does' "; emphasis on "only" suggests higher value on avoiding incorrect attribution of causation (quoting Robert A. Baruch Bush, *Between Two Worlds: The Shift from Individual to Group Responsibility in the Law of Causation of Injury*, 33 UCLA L. Rev. 1473, 1474 (1986) but omitting original's emphasis on "all")). Professor Klein suggested one concern that may animate the emphasis on avoiding false positives: "confidence in the legal system deteriorates when hindsight shows that liability was imposed on an entity that did not 'cause' another's harm using any meaning of the word." *Id.* at 30. Justice Breyer's concurring opinion in *Joiner* provided a glimpse of another concern. Although he acknowl-

Again, the TCE/RCC case study is instructive. Overall, the epidemiology has been "inconsistent."[266] It suggests an enhanced, but less than doubled, relative risk from long-term high exposure. For many courts following current doctrine, these results would completely bar recovery, despite the substantial body of animal and molecular evidence pointing to a link between TCE and renal cell carcinoma. There is evidence that these overall relative risks may be masking differential susceptibilities, but genetic variation in susceptibility is not yet well defined.[267] A requirement that a plaintiff, at this point, demonstrate an individually susceptible genotype would be based on a still-unproven assumption of variable susceptibility and would require evidence that is not yet attainable. In such circumstances, bright line rules, although they simplify a court's task, do not particularly ensure that the court performs its task correctly.

3. *Genes as Alternate Causes*

Courts will also have to figure out how causation doctrine should address assertions that "the genes did it" (in the nursery, with a DNA molecule) rather than the toxic substance (at work, with a benzene ring). This argument will take several forms.

A relatively weak form of the argument will rely on the genetic variability in susceptibility to toxins that was discussed in the preceding subsection. That discussion assumed (as most commentators have) that proof of increased susceptibility to a particular toxin would bolster a plaintiff's case,[268] and considered whether courts would or should require plaintiffs to produce such proof. Nevertheless, it is not hard to imagine a defendant arguing that a plaintiff's particularly heightened genetic susceptibility should be considered a superseding cause: "but for" the plaintiff's rare genetic defect, my product (harmless to 99.9% of the population) would not have

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edged that "scientific evidence implicates some chemicals as potential causes of some cancers," Justice Breyer worried that "modern life, including good health as well as economic well-being, depends upon the use of artificial or manufactured substances." General Elec. Co. v. Joiner, 522 U.S. 136, 148 (1997). Therefore, he reasoned, judicial evidentiary gatekeeping was needed to "help assure that the powerful engine of tort liability, which can generate strong financial incentives to reduce, or to eliminate, production, points towards the right substances *and does not destroy the wrong ones*." *Id.* at 148–49 (emphasis added). Of course, confidence in the legal system might deteriorate when injury that is caused by an entity goes unredressed, and good health and economic well-being may warrant less (or no) production of substances that cause disease while serving purposes that are of limited benefit or could easily and cheaply be otherwise achieved. The two types of errors are not equally visible, however. Incorrect imposition of liability is easily observed if the allegedly causative substance later is absolved. Harm actually caused but not remedied is easily missed: it lies partly in cases that were lost, but even more in cases that were never brought. A full exploration of the rationale for and merits of the apparent preference for false negatives is beyond the scope of this article.

[266] Shiao, *supra* note 190, at 72–73.

[267] To further complicate the issue, genetic polymorphism is not the only possible cause for differential susceptibility to TCE, *id.* at 73 (noting confounding effects including exposure to other chemicals), or to toxic substances in general, Perera, *supra* note 108, at 608.

[268] *See, e.g.*, Marchant, *supra* note 142, at 10–13.

caused the disease.[269] If the defendant could link the gene's presence to some other condition or behavior, like inbreeding in the royal families of Europe, so much the better for the argument.

A plaintiff would respond that genetic susceptibility to toxins is akin to an "eggshell skull," so the defendant should be liable notwithstanding the unexpectedly severe result of defendant's toxic tort.[270] Yet even if genetic susceptibility to toxins did not vitiate the causation element of a plaintiff's prima facie case, it could affect other elements. For example, if a defendant's product were shown to cause disease only in people with a genetic susceptibility, that could affect a court's view of whether the product is unreasonably dangerous or required a warning, especially if the susceptible genotype occurs infrequently in the population.[271] Alternatively, if a defendant could persuade a court that the plaintiff's genotype conferred so much susceptibility to toxins that another environmental exposure would eventually have caused disease even without the exposure caused by defendant, this argument could limit damages.[272]

More commonly, a defendant could be expected to claim that genetics made a plaintiff more susceptible to a disease itself, rather than to the disease-producing effects of a toxic exposure. The argument will be that a given plaintiff's genome includes one or more genes that create an innate predisposition to a disease, and the disease developed because of the genetic "weakness," not because of exposure to the toxic chemical. This argument has already succeeded even in the absence of specific knowledge of the genotype involved, at least when pitted against relatively poor evidence of toxic causation.[273] Where the causal link between toxic exposure and disease is stronger, pinning the blame on the genes would likely require stronger evidence of the link between genotype and disease as well.

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[269] *See* Gary E. Marchant, *Genetics in the Courtroom: Genetics and Toxic Torts*, 31 SETON HALL L. REV. 949, 960–61 (2001) (suggesting that an "idiosyncratic response" defense in drug reaction cases could apply to toxic tort plaintiffs with high genetic susceptibility).

[270] *See* Carl F. Cranor, *Eggshell Skulls and Loss of Hair from Fright: Some Moral and Legal Principles that Protect Susceptible Subpopulations*, 4 ENVTL. TOXICOLOGY & PHARMACOLOGY 239, 242–43 (1997) (asserting that the "eggshell skull" rule reflects the principle that even the most vulnerable should be protected from harm caused by invasion of legally protected rights).

[271] *Cf.* Green, *supra* note 3, at 387–88 (describing cases in which alleged tort was failure to warn of a product's dangers, but manufacturer would have no duty to warn of an effect that the product does not cause).

[272] Michael D. Green, *The Intersection of Factual Causation and Damages*, 55 DEPAUL L. REV. 671, 679 (2006) (noting that damages are reduced where tort accelerated harm that "eggshell skull" plaintiff likely would have suffered eventually even if tort had not occurred).

[273] *See, e.g.*, Blackwell v. Wyeth, 971 A.2d 235, 260 (Md. 2009) (affirming exclusion, under general acceptance test, of testimony that thimerosal in vaccine caused autism, where trial judge found that prevailing view holds autism caused by "a gene or series of interacting genes that have not yet been identified"); Stapleford v. Sec'y of Dep't of Health and Human Servs., 89 Fed. Cl. 456, 458 (2009) (affirming a finding that cause of child's seizure disorder "was likely a genetic defect" rather than immunization against chicken pox, based on similar condition in plaintiff's brother).

Test cases may arise from litigation over hormone replacement therapies that have been linked to increased risk of breast cancer. In one recent case, a trial judge allowed an expert to testify that such medications were the only possible source of hormones that were essential to growth of the plaintiff's tumor.[274] The defendant appealed the admission of the testimony, arguing that the expert failed to consider the possibility of causation by plaintiff's family history of breast cancer and other risk factors.[275] The court of appeals affirmed, in part because the plaintiff had "submitted to every available genetic test . . . all of which," despite the plaintiff's family history, "came back negative for the most common breast cancer genes."[276] The defendant's expert "testified that he continues to believe that genetics" caused the illness, "but the jury concluded otherwise," and the court did not disturb that finding.[277]

An opposite situation occurred in *Bowen v. E.I. Du Pont de Nemours & Co., Inc.*,[278] in which plaintiff's parents alleged that their daughter's serious birth defects resulted from the mother's exposure during pregnancy to the fungicide Benlate. The defendant contended that the child's condition constituted a syndrome of genetically-determined developmental abnormalities; the plaintiffs contested that diagnosis. While the litigation was pending, a newly available test showed that the child had a mutation in a newly discovered gene believed to be "the cause of" the syndrome.[279] The genetic test result led one of plaintiff's experts to concede that the child had the syndrome, and another of plaintiff's experts conceded that Benlate did not cause the mutation itself.[280] Based on this evidence, the trial court excluded the plaintiff's proposed causation testimony.[281]

The results of each plaintiff's genetic tests made these two cases relatively easy, but in each case the presentation of genetics and exposure as competing causal alternatives finessed an important potential difficulty. Any argument that a genetic risk factor was the "real" cause of illness, despite exposure to a toxic risk factor, would depend on an assumption (which evidence may support or contradict) that the toxic and genetic risk factors are additive, i.e., when both are present each acts independently to increase risk.[282] If instead the risk factors interact synergistically, then a plaintiff's genetic predisposition may not be an "alternate" cause at all.[283] Yet deter-

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[274] In re Prempro Products Liab. Litig., 586 F.3d 547, 566 (8th Cir. 2009).
[275] *Id.*
[276] *Id.*
[277] *Id.*
[278] Bowen v. E.I. du Pont de Nemours & Co., Inc., No. 97C-06-194, 2005 WL 1952859 (Del. Super. Ct. Aug. 5, 2005), *aff'd*, 906 A.2d 787 (Del. 2006).
[279] *Id.* at *5.
[280] *Id.* at *6.
[281] *Id.* at *7.
[282] *See* Poulter, *supra* note 156, at 234.
[283] After the genetic test in *Bowen*, plaintiff attempted to salvage the case by offering testimony that the mutation and the Benlate exposure had interacted to cause the child's condition. *Bowen*, 2005 WL 1952859, at *6. The trial court held the expert unqualified to give that opinion. *Id.* at *7. The Delaware Supreme Court did not opine on the interaction issue be-

mining and quantifying such interaction is difficult and controversial even as a scientific matter, much less a matter of law.[284]

There is an even more fundamental problem with treating genetic predisposition as an alternate cause. The very derivation of the relative risk of a particular genetic variant is unlikely to be independent of toxic exposure, because toxic exposure almost certainly will not be a controlled variable in the study.[285] In the same way that classical epidemiologic studies have implicitly assumed the genetic homogeneity of the exposed and unexposed populations, studies that look for and find susceptibility alleles implicitly assume that the populations with and without the gene are homogeneous with respect to toxic exposures.[286]

Not everybody who has the *BRCA1* susceptibility allele develops breast cancer. Studies estimating the degree to which the gene increases risk have produced varying results. What if some or all of the variance is explained by toxic exposures, or by the interaction of toxic exposures with epigenetic factors?

Some evidence already suggests this may be the case for the relatively large risks imparted by certain *BRCA* alleles that appear to increase breast cancer risk in general but also may act like toxic susceptibility genes with respect to cigarette smoke.[287] For smokers with either the *BRCA1* or *BRCA2* high-risk mutation, a study found relative risks of 2.3 and 2.6, respectively, compared to non-smokers with the same gene.[288]

The question seems even more pressing for relatively common polymorphisms that appear to confer relatively small increments of risk.[289] Because these alleles are more common in the population, routine genotyping of plaintiffs would detect them more often. Disentangling their effects from the effects of toxic exposure is difficult even if the toxic effect is strong, as with cigarette smoking and lung cancer.[290] If numerous susceptibility alleles at multiple loci are identified, the game of pin-the-blame-on-the-genes could become commonplace, as various hereditary risk factors are added together in an effort to discount the risk contribution of a toxic exposure. That attribution may be misleading if the small population-wide increases in risk mask an unequal distribution of risk associated with environmental exposures.

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cause it upheld the trial court's exclusion of the plaintiff's only witness on exposure, without whose predicate testimony none of the other causation opinions could stand. 906 A.2d at 798.

[284] *See* Altshuler et al., *supra* note 82, at 885. *See generally* Yang & Khoury, *supra* note 120.

[285] *See* REUBEN, *supra* note 114, at 98 (noting lack of accurate methodologies to assess gene-environment interactions); Altshuler et al., *supra* note 82, at 886–87 (noting the importance of gene-environment interactions and difficulty of measuring environmental exposures).

[286] Toxic exposures may not be randomly distributed in the population. *See generally* ROBERT D. BULLARD ET AL., TOXIC WASTES AND RACE AT TWENTY: 1987–2007 (areas near toxic waste facilities disproportionately populated by people of color).

[287] Phillips & Garte, *supra* note 125, at 2.

[288] *Id.* Each estimate had a 95% confidence interval that straddled the relative risk of two.

[289] *See* Pharoah et al., *supra* note 90, at 2797, 2801.

[290] Chung et al., *supra* note 71, at 115; Imyanitov et al., *supra* note 88, at 9.

The TCE/RCC link models several of these issues. Because renal cell carcinoma runs in families, a plaintiff's heredity would be on trial even if genomic analysis were not available.[291] Gene sequencing should make it possible to determine definitively whether a particular plaintiff was born with any mutations in the VHL gene. Whether that would rule out causation in a plaintiff who could *also* prove exposure to significant levels of TCE is much less definitive. If risk is in some way proportional to the amount of DNA alteration,[292] TCE's ability to cause VHL mutations would increase the danger to people already made vulnerable by their own genetics.[293] Moreover, the preliminary evidence that genotype affects individuals' susceptibility to the effects of TCE squarely presents the issue of how to address such variability, particularly before science has fully characterized it.[294]

Despite the difficulties, I do not share Poulter's view that the answer, as a doctrinal matter, is a rule precluding evidence of a plaintiff's genetic predisposition to disease. Evidence of genetic predisposition can have some probative value just as animal studies, *in vitro* toxicology, differential diagnosis, and imperfectly fitting epidemiologic studies can. What the underlying studies of genetic risk assume, and what possibilities they disregard, are more properly the subject of opposing testimony, cross-examination, and inference. Courts should not place impossible information demands on defendants any more than they should on plaintiffs. Avoiding the implicit creation of substantive rules via evidentiary narrowness is a two-way street.

4. *Other Toxics as Alternate Causes*

Toxicogenomics and molecular epidemiology also promise to present courts with progressively more numerous and difficult doctrinal challenges with respect to arguments that some toxic exposure other than the defen-

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[291] Courts understandably demand that a plaintiff's experts at least consider heredity as a cause of conditions that appear to have a genetic component. *See, e.g.*, Chikovsky v. Ortho Pharm. Corp., 832 F. Supp. 341, 346 (S.D. Fla. 1993); Castillo v. E.I. Du Pont de Nemours & Co., 854 So. 2d 1264, 1271 (Fla. 2003); Blackwell v. Wyeth, 971 A.2d 235, 243 (Md. 2009). In a TCE/RCC case, a court would likely require proof that plaintiff had no family history of RCC and that family history was controlled for in any epidemiologic study on which an expert relied.

[292] *See* Guyton et al., *supra* note 185, at 233 ("Cancer involves the accumulation of multiple genetic mutations over time (average 11 for solid tumors) and epigenetic alterations."). Plaintiffs in tobacco cases have contended that cigarette smoke increases risk in this way. *See, e.g.*, Caronia v. Philip Morris USA, Inc., No. 06-CV-224, 2010 U.S. Dist. LEXIS 12168, at *23–*24 (E.D.N.Y. 2010).

[293] *See* Brauch et al., *supra* note 180, at 858–59 (noting that VHL gene in persons exposed to TCE often displayed multiple alterations, some of which were also found in persons with inherited VHL mutations).

[294] A further intriguing question about "hereditary" cases is: what caused the inherited mutation in the first place? Mutations are thought of as "random" mistakes, but what if the initial damage to an ancestor's DNA was itself the result of environmental insult? It would be rather exceptional for such a mutation to be traced and linked to exposure to a particular toxic substance. But in principle, if the facts were found, an ancestor's exposure would be a cause-in-fact of illness in a descendant.

dant's was the actual cause of the plaintiff's injury. Manufacturers of cigarettes and asbestos are already adept at blaming each other for causing lung cancer in people exposed to both products, who suffer a synergistic, multiplicative increase in risk.[295] Toxicogenomics could identify many more instances in which multiple toxic substances are shown to increase risk of developing the same disease. If a sick plaintiff had been exposed to more than one of these toxic substances, defendants would naturally argue that even if the illness was caused by *an* exposure and was not a "background" case, one of the *other* exposures was the *real* cause. Toxicogenomics could make it easier to test the argument by examining the plaintiff for biomarkers of susceptibility or effect with respect to each toxin. But what if all the results were positive?

TCE and cigarette smoke, for example, both appear to be associated with kidney cancer.[296] Certain components of tobacco smoke produce, in animals, VHL gene mutations similar to those observed in TCE-exposed people with RCC.[297] Does the requisite proof of causation change for a plaintiff exposed to both? What proof would a court require to rule out smoking as a cause?

TCE illustrates other potential toxic interactions as well. People exposed to TCE from landfills and groundwater almost always are also exposed to other, similar compounds that may themselves cause cancer.[298] These compounds affect TCE metabolism and may increase TCE's kidney carcinogenicity.[299] The confounding effects of such co-exposures make it hard for epidemiologists to specify a causal link between TCE and cancer.[300] Regarding liver cancer, even a person's drinking habits may affect TCE toxicity and carcinogenicity.[301]

For the causation element of a plaintiff's case, positing a different toxin as an alternate cause presents analytical issues no different from positing genetic predisposition to disease as the alternate cause.[302] The validity of the

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[295] *E.g.*, Tompkin v. Philip Morris USA, Inc, 362 F.3d 882, 889 (6th Cir. 2004) (defense expert testifying that only asbestos, not smoking, caused plaintiff's cancer); Borman v. Raymark Indus., Inc., 960 F.2d 327, 331 (3d Cir. 1992) (defense expert testifying that only smoking, not asbestos, caused plaintiff's cancer).

[296] *See* Shiao, *supra* note 190, at 69 (describing evidence linking TCE to RCC); *id.* at 70 (noting that tobacco smokers are known to be at high risk of kidney cancer).

[297] *See id.* at 70–71.

[298] *See, e.g.*, Caldwell et al., *supra* note 237, at 143; Scott & Chiu, *supra* note 187, at 1476.

[299] *See* Caldwell et al., *supra* note 237, at 151.

[300] Shiao, *supra* note 190, at 73 (noting that link between TCE and cancer is in category of diseases involving multiple exposures that show weak association with epidemiologic criteria for causation).

[301] Caldwell et al., *supra* note 237, at 150.

[302] Exposures to additional toxic hazards could also raise other issues, depending on the circumstances. A person with RCC who alleged the disease was caused by inhaled emissions of chlorinated solvents from a nearby dry cleaner, but who also used TCE as a degreaser in a weekend sculpting hobby, would have difficulty proving causation *and* would face a contributory negligence or comparative responsibility argument. By contrast, the claim that a person's cancer was caused by exposure to radiation from natural sources, rather than from an allegedly

alternate cause argument still depends on whether the causative processes are independent, and if not, on how they interact to increase risk. But the numbers and combinations of possible toxic causes make the problem more difficult, both theoretically and practically.

Current scientific thinking favors complex models of carcinogenesis. Causation of any particular cancer probably requires multiple "hits": genetic and/or epigenetic alterations.[303] Conversely, more than one group of biochemical changes may be sufficient to cause a particular cancer.[304] And any particular cancer is probably characterized by many alterations, not all of which were necessary to causation.[305] If a plaintiff receives multiple exposures that are capable of causing distinct and possibly overlapping sets of "hits," the potential complexity of interactions increases with the permutations.[306]

The great potential of toxicogenomics and molecular epidemiology to demonstrate causal connections may therefore end in irony. If the science succeeds a little bit, linking relatively uncommon diseases to exposures that are relatively confined to fairly discrete segments of the population (such as workers in a particular industry), it will probably help plaintiffs overcome the otherwise huge hurdle that proving causation has been. But if the science succeeds spectacularly — if the three-dimensional grid is filled in with detailed profiles of the incremental risk, for both common and rare diseases, presented by numerous combinations of genetic polymorphisms and toxic substances[307] — the resulting range of causative possibilities will likely aid defendants by swamping the suspect cause in a deluge of alternatives.

We are all, after all, constantly exposed to potentially toxic substances in our workplaces, in products we use in our homes or on our bodies, in our food, and in the environment. When a science writer submitted to tissue testing for 320 toxic or potentially toxic chemicals, 165 were detected, including several at levels thought to be potentially harmful.[308] More system-

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tortious anthropogenic release, would present only a causation issue (absent unusual circumstances suggesting that the plaintiff's behavior negligently increased the exposure to the natural source).

[303] Guyton et al., *supra* note 185, at 238 ("multiple biological alterations . . . are necessary to convert a normal cell to . . . ultimately a tumor . . . . Chemicals . . . impact this . . . process in multiple ways").

[304] *Id.* at 233 ("there are multiple genetic pathways to the development of a specific type of cancer").

[305] *Id.* (noting that it is unlikely that all 1,149 somatic mutations found in a group of breast and colorectal cancers are key events); Shiao, *supra* note 190, at 69 (explaining that, of multiple genetic alterations in tumors, only some are tumorigenic "driver[s]" while others are "passenger[s]").

[306] *See* REUBEN, *supra* note 114, at 2 ("impact of various exposures, whether individual, simultaneous, sequential, or cumulative over a lifetime, may not be simply additive").

[307] *See* Altshuler et al., *supra* note 82, at 885 (acknowledging that gene-environment interactions are not well understood but predicting that once they are, "effects of specific gene and environmental exposures on each phenotype may be larger" than currently appear).

[308] David Ewing Duncan, *The Pollution Within*, NAT'L GEOGRAPHIC, Oct. 2006, 116, 126. Detected chemicals included PCBs, pesticides, dioxins, and metals.

atic studies suggest that he is not atypical.[309] With such diverse exposures, the more we know about the incremental risk each chemical poses, the harder it may be to place causative responsibility on any of them. Tort law will have to develop more sophisticated methods for dealing with causal interaction than existing rules for apportionment of liability allow.[310]

5. *Reductionism to the Rescue?*

Perhaps the way through the thicket does not run through causation doctrine at all, but rather through a redefinition of the concept of "injury" in tort law. Professor Grodsky proposed that a chemical punch to DNA is no less an injury than a fist punch to the body.[311] The difference is that the former has only recently become detectable. Now that it is, early detection also offers at least the potential of early intervention — in essence, a form of mitigation of damages to the benefit of both the injured and the liable. To take advantage of this opportunity, Grodsky proposed that tort law provide a medical monitoring remedy for those with subclinical molecular injury caused by toxic exposure.[312] Will tracing disease back to its smallest observable origin solve the causation problem? Can reductionism rescue the tort system?

It may make sense to count as "injury" certain sub-clinical precursors of clinical disease and to provide a medical monitoring remedy for such injury.[313] But who would bring a claim for that remedy? Some groups of people affected by hazardous waste sites have sought medical monitoring based on alleged increased risk resulting from site pollutants.[314] People who

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[309] CTRS. FOR DISEASE CONTROL & PREVENTION, FOURTH NATIONAL REPORT ON HUMAN EXPOSURE TO ENVIRONMENTAL CHEMICALS (2009), *available at* http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf (presenting data on blood and urine levels of 212 chemicals in a sampling of the American population); CTRS. FOR DISEASE CONTROL & PREVENTION, FOURTH NATIONAL REPORT ON HUMAN EXPOSURE TO ENVIRONMENTAL CHEMICALS EXECUTIVE SUMMARY 3 (2009), *available at* http://www.cdc.gov/exposurereport/pdf/FourthReport_ExecutiveSummary.pdf ("Findings in the *Fourth Report* indicate widespread exposure to some commonly used industrial chemicals.").

[310] *See* RESTATEMENT (THIRD) OF TORTS: APPORTIONMENT OF LIAB. § 17 (2000) (identifying different schema for joint and several, several only, and hybrid forms of liability); *id.* § 26 (defining circumstances when damages "can be divided by causation").

[311] Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1704–09, 1711 (distinguishing this "injury" from "risk").

[312] *Id.* at 1711.

[313] Even if it makes sense, courts may not be ready to treat sub-clinical manifestations as injuries. *See* June v. Union Carbide Corp., 577 F.3d 1234, 1249 (10th Cir. 2009) ("In our view, [radiation-induced] 'DNA damage and cell death,' which creates only a possibility of clinical disease does not constitute a 'bodily injury' under the Price-Anderson Act."). *But cf.* Donovan v. Philip Morris USA, Inc., 914 N.E.2d 891, 901 (Mass. 2009) (holding that smokers not diagnosed with lung cancer satisfied injury and damage elements for medical monitoring claim by proving "physiological changes indicating a substantial increase in risk of harm from exposure to a known hazardous substance").

[314] Under current law, most of these claims have failed. *E.g.*, Redland Soccer Club v. Dept. of the Army, 55 F.3d 827 (3d Cir. 1995); Stites v. Sundstrand Heat Transfer, Inc., 660 F. Supp. 1516, 1523–26 (W.D. Mich. 1987).

suffered a massive, acute exposure to a hazardous agent might seek legal remedies even if they were not yet sick.[315] So might people who know they have taken a drug, or been exposed to some other substance, that has a particularly well-publicized connection to latent disease. The much-criticized claims by "persons who have been exposed to asbestos and who usually have some marker of exposure, but who are not impaired by an asbestos-related disease and likely never will be,"[316] constitute by far the most prominent example to date.[317] Such asbestos claims resemble, to some extent, a cause in search of a disease rather than the reverse.[318]

Many people, however, would not make a connection between their exposure and a disease until they get sick.[319] This would almost certainly be the case for chronic, relatively low-level exposure to relatively ubiquitous environmental contaminants, which may collectively be major causes of disease.[320] Even people who may understand that an exposure has increased their risk of disease might not pursue a legal remedy, if one were granted to them. Being a plaintiff is costly in time and stress, and fees and expenses eat away at recoveries.[321] The chance of winning compensation for a manifest serious illness might justify those costs, but for a person who has merely been exposed, the chance of winning a monitoring remedy might not.

Claims for medical monitoring based on molecular or subcellular injury, therefore, probably would never fully supplant traditional claims for compensation for the harm of manifest illness. To the extent that traditional toxic tort claims for clinical disease continue, courts will still be asked to resolve the question of whether the exposure caused the *disease*, not simply whether the exposure caused molecular changes observed in the plaintiff. Allowing the tort system to look for injury earlier and at a smaller scale will not circumvent the toxic causation problem.

Further, whether a biomarker can make the link from exposure to disease will depend on whether the biomarker is persistent enough to be detectable at the time disease manifests, after latency. Even for subclinical harm, a biomarker will need to be consistent and reliable enough as an indicator of exposure or effect, and specific enough to rule out other causes. Professor Grodsky argued that the need for such strong biomarkers is exaggerated,

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[315] *E.g.*, *In re* Three Mile Island Litig., 87 F.R.D. 433, 442 (M.D. Pa. 1980) (certifying class for medical monitoring claim after nuclear accident).

[316] Satterfield v. Breeding Insulation Co., 266 S.W.3d 347, 370 (Tenn. 2008) (stating that such claims divert limited compensation from people with debilitating and fatal asbestos-caused disease).

[317] Claims by smokers not yet diagnosed with lung cancer are another example. *E.g.*, Caronia v. Philip Morris USA, Inc., No. 06-CV-224, 2010 U.S. Dist. LEXIS 12168 (E.D.N.Y. 2010); *Donovan*, 914 N.E.2d 891.

[318] *See* Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1729 n.233 (attributing "surge" of claims by unimpaired plaintiffs to "aggressive claim-solicitation campaigns" by some lawyers and labor unions).

[319] *See Donovan*, 914 N.E.2d at 903 ("notice of harm and cause in many cases may not occur until the plaintiff is so advised by a physician").

[320] *See* Lin, *supra* note 3, at 1441, 1470–72, 1476–80.

[321] *See* Grodsky, *Risk-Injury Divide*, *supra* note 121, at 1729–30.

because "new subcellular data will not be used in isolation but will supplement traditional evidence of exposure, risk and harm."[322] In this more likely scenario, molecular epidemiologic and toxicogenomic data do not provide conclusive answers but are another important piece of the puzzle.

Certainly, biomarkers can be relevant and useful even if they do not provide the whole picture. A biomarker might provide important circumstantial evidence of causation. Its validation might produce quantitative estimates of its predictive value.[323] Inferences could be drawn. But this is all true of more traditional toxic tort causation evidence as well. The problem is the history of judicial reluctance to assemble the puzzle. So even if courts were to change their conception of disease, if they do not respond appropriately to genomic information, causation doctrine will still be in the soup. Science is teaching us, and causation doctrine must learn.

D. Toward a More Realistic Causation Doctrine in Toxic Torts

Though it may never provide a comprehensive table of risk values for every combination of exposure, genetics, and disease, toxicogenomic research surely will produce a vast amount of information that will improve our understanding of toxic causation. The science seems to be pointing at a world of numerous risk factors, some genetic and some environmental, most of which add relatively small amounts of incremental risk.[324] Any of these factors *could* cause disease on its own, or could combine with other factors in predictable or unpredictable ways to create larger risks. The more this understanding of the world prevails, the clearer and clearer it will become that a legal model of cause derived from observable physical impacts does not fit toxicological reality.

In the 1980s, as toxic tort cases began reaching the courts in significant numbers, some courts and many commentators suggested that the inherent scientific indeterminacy of toxic causation justified changes in causation rules for such cases. A few courts relied on the substantial factor formulation of the Second Restatement of Torts as an exception to the traditional but-for test for cause-in-fact.[325] Many commentators, noting the problem of matching all-or-nothing awards to exposures that could be shown to increase risk but could not be shown to produce clearly identifiable individual cases of disease, suggested various types of proportional recovery.[326] But neither

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[322] *Id.* at 1708.

[323] *See id.* at 1709 n.157.

[324] *See, e.g.*, Yang & Khoury, *supra* note 120, at 41.

[325] *E.g.*, Allen v. United States, 588 F. Supp. 247 (D. Utah 1984), *rev'd on other grounds*, 816 F.2d 1417 (10th Cir. 1987); *see also* Rutherford v. Owens-Illinois, Inc., 941 P.2d 1203, 1219–20 (Cal. 1997) (using substantial factor formulation to address "irreducible uncertainty" of determining which defendants' asbestos fibers actually contributed to the cellular development of cancer).

[326] *See, e.g.*, David Rosenberg, *The Causal Connection in Mass Exposure Cases: A "Public Law" Vision of the Tort System*, 97 HARV. L. REV. 849 (1984); *see also* Green, *supra* note 3, at 357–71 (summarizing the scholarship though disagreeing with its conclusion).

of these movements led to any widespread changes in doctrine. The Third Restatement of Torts, like most courts, fully embraced the but-for causation test, and rejected even the phrase "substantial factor."[327] Despite a "strong scholarly consensus, proportional liability has failed to establish a foothold in the courts."[328]

The early, so far unsuccessful, arguments for reform were premised on science's inability to shed sufficient light on the black box of disease causation. One might expect that seemingly "particularistic" information derived from analysis of an individual plaintiff's genome, as anticipated by the prophetic view of toxicogenomics, would only further weaken the argument that toxic tort cases present problems warranting a reformed causation standard.[329] Yet molecular epidemiology and toxicogenomics — for all the mechanistic insights we expect from them — presage increasingly exposed complexity rather than increasingly defined determinism. If toxicogenomics and molecular epidemiology really show that the world is composed of many little risks, this may warrant reconsideration of allowing proportional recovery based on the creation of incremental risk of realized disease. The ability at last to peer into the molecular black box may, ironically, strengthen rather than weaken the case for changes in causation doctrine similar to those changes that were proposed precisely because the black box was impenetrable.

Fully developing that case is beyond the scope of this Article. Any such proposal would need to address broad objections that have been raised in the past.[330] Numerous implementation issues would need to be resolved as well. How should courts allocate burdens of proof relating to proportional shares? Should a threshold increment of risk be required to impose liability? What rules should govern cases of multiple, potentially interacting risk factors, and should those rules vary depending on whether exposure to the factor results from a defendant's tortious behavior, a plaintiff's fault or voluntary act, or an independent and innocent cause? Where should the cost of unattributable causal shares, which inevitably will exist, lie? Exploration

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[327] "Conduct is a factual cause of harm when the harm would not have occurred absent the conduct." RESTATEMENT (THIRD) OF TORTS: LIAB. FOR PHYSICAL & EMOTIONAL HARM § 26 (2010); *id.* § 26 cmt. j (rejecting substantial factor because the term "has proved confusing and been misused"); *see* June v. Union Carbide Corp., 577 F.3d 1234, 1244 (10th Cir. 2009) (expressing approval of the Third Restatement formulation and concluding that the Second Restatement and Third Restatement both required satisfaction of but-for test as sine qua non for proof of factual causation).

[328] Green, *supra* note 3, at 396.

[329] *See* Klein, *supra* note 28, at 35 ("proponents of law reform should operate under the assumption that an increasing number of people will have the tools necessary to prove sine qua non causation in toxic tort litigation"); *id.* at 43 (proposing that courts require "individualized evidence" from biomarker and genetic analysis where such evidence is available).

[330] *See, e.g.*, Klein, *supra* note 28, at 8 (advancing the "normative position that tort law should prefer and encourage proof of traditional *sine qua non* causation in toxic exposure cases"); Green, *supra* note 3, at 385–96 (arguing against proportional liability in part because of doubt that information could be adequate to provide a theoretically optimum deterrence signal).

of these issues in light of the expected scientific contributions of toxicogenomics and molecular epidemiology is a subject for future work, which will become more urgent as the science continues to develop.

V. Conclusion

Courts have struggled with the probabilistic nature of toxic tort causation. As the Massachusetts Supreme Judicial Court said when it recognized a medical monitoring claim for increased risk resulting from toxic exposure, "[o]ur tort law developed in the late Nineteenth and early Twentieth centuries, when the vast majority of tortious injuries were caused by blunt trauma and mechanical forces. We must adapt . . . ."[331] Yet the law still lags.

Toxicogenomics and molecular epidemiology will clarify some causal connections but will not provide a magic bullet for resolving causation problems. The practical limitations of these sciences mean that some causal connections will remain unexplored for a significant time; their conceptual limitations mean that other causal connections will remain uncertain despite investigation.

Nevertheless, the emergence of toxicogenomics and molecular epidemiology undermines the rigid substantive and evidentiary approaches that evolved in response to classical epidemiology. Courts could apply old doctrine to these new sciences. Or courts could recognize and seize the opportunity to improve.

Toxicogenomics and molecular epidemiology will provide a wealth of information while simultaneously demonstrating that complete knowledge is unattainable. That combination may finally force doctrine to catch up to biology.

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[331] Donovan v. Philip Morris USA, Inc., 914 N.E.2d 891, 901 (Mass. 2009).