

Physician Liability: The Next Big Thing for Personalized Medicine?



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Abstract and Introduction

Abstract

Liability is likely to be a major driver for the future direction and implementation of personalized medicine, spurring the adoption of genetic tests and other pharmacogenomic technologies, in some cases appropriately, and in other cases prematurely or as inefficient defensive medicine. While all entities in the personalized medicine chain will face liability risks, physicians will be at the greatest risk owing to their lack of defenses, limited experience in dealing with genetics and the growing disparities within the profession in implementing new medical technologies. The history of liability for genetic testing, primarily in the prenatal testing context, suggests that liability will often be both unpredictable and influential in changing medical practice. It is critical to anticipate and attempt to prevent such liability risks in a proactive manner so to minimize the disruptive impact that liability can cause.

Introduction

The era of personalized medicine is approaching – more slowly than many originally predicted, but nevertheless advancing in fits and starts.^[1] The central concept of personalized medicine is sound – healthcare can potentially be more effective and efficient if it is personalized by targeting the genetic or molecular profile of individual patients rather than applying the traditional 'one-size-fits-all' approach to diagnosis and management. As Francis Collins, the Director of the US NIH, recently noted, "the power of the molecular approach to health and disease has steadily gained momentum over the past several decades and is now poised to catalyze a revolution in medicine".^[2]

Yet, despite the promise and potential, a variety of impediments and barriers have slowed down the implementation and uptake of personalized medicine.^[3] Notwithstanding a few noteworthy exceptions, there has been relatively little application of molecular profiling in the routine practice of medicine to date.^[1,4,5] A number of specific challenges have been identified to the wider integration of personalized medicine into routine medical care, including: clinical usefulness and improved outcomes will need to be demonstrated; tests will need to be validated and their costs will need to come down; payers will need to reimburse fairly for genetic tests; and physicians will need to increase their knowledge about genetics in general.^[6,101]

Liability serves as a wild card in the rollout of personalized medicine, though it is a factor that has received relatively scant attention to date.^[7-10] As has been seen for many other scientific advances, liability can be a powerful driver for widespread behavioral change and the adoption of emerging technologies, an effect that may be beneficial or detrimental to the overall societal welfare depending on the circumstances. In the context of genetics, liability could drive the adoption of beneficial personalized medicine technologies that promote patient safety and allow patients to avoid unnecessary costs and side-effects. Alternatively, liability could force actors to prematurely deploy technologies that are unproven, wasteful and detrimental to healthcare. More likely, liability will have both effects in different scenarios and contexts.

To date, there have been but a smattering of lawsuits asserting liability claims based on personalized medicine. But the nature and dynamics of these types of personal injury and medical malpractice lawsuits is that the activity smolders at a low level for years until suddenly catching fire and engulfing entire companies, industries or practice areas in an inferno of expensive litigation. As new genetic technologies and procedures slowly infuse the practice of

medicine, the potential impacts of liability relating to personalized medicine must be considered.

This article addresses the potential role of liability in personalized medicine, focusing primarily on physicians. The next section describes the dynamic nature of liability for medical technologies generally, noting the potential of innovative technologies and procedures to trigger new liability pressures that can quickly catch fire if they gain momentum with some initial plaintiff victories. The next section then discusses the potential doctrinal dimensions of potential liability related to personalized medicine, concluding that physicians are likely to be at the greatest liability risk. After that, we summarize the existing case law on liability relating to personalized medicine, beginning with the handful of cases reported to date directly about personalized medicine, and then drawing lessons from the more mature litigation record for physician liability relating to prenatal genetic testing. Integrating the doctrinal and empirical findings from the previous sections, we next assess the potential physician liability in four specific scenarios involving currently available or proposed applications of personalized medicine. Finally, this article concludes by summarizing the liability dynamics and risks associated with personalized medicine and introduces some policy options that may help address the uncertainty currently giving rise to many of the liability risks.

Dynamics of Litigation

Litigation is often a crapshoot. Clear-cut disputes rarely get decided in courtrooms. If the outcome of a dispute is predictable, the parties will usually come to some agreement rather than incurring the substantial transaction costs of litigating a case through discovery, pretrial motions and preparation, trial and appeal. In the US, plaintiffs' attorneys are generally the key decision-makers on whether or not a particular type of case is litigated because the contingency fee payment system allows them to collect payment only if their client's argument is successful. In personal injury cases, successful plaintiffs' lawyers can collect a windfall, often earning 30% or more of the plaintiff's judgment plus expenses under a typical contingency fee arrangement. If the plaintiff loses, however, the lawyer not only doesn't earn any revenue, but also loses the thousands or sometimes millions of US dollars he or she invested to bring the case to court, consisting of not only their own time, but the salaries paid to their junior attorneys and support staff fees to experts, discovery costs, court filing fees, and other expenses associated with litigation.

The consequence of this payment system is that plaintiffs' attorneys are often quite risk averse in bringing new types of cases when the evidence is relatively undeveloped and there is no track record to help them predict how such cases will fare in front of judges and juries. However, once a few cases have been successful on a particular issue, lawyers will respond to that favorable precedent, benefit from the evidentiary development in the previously litigated cases, and feel increasingly confident in their ability to secure their own favorable judgment. The more successes, the more plaintiffs and their attorneys will exhibit a herd response and converge on the new opportunity, creating a 'gold rush' mentality that can overwhelm and empty even the deepest-pockets of defendants. Examples abound, including the litigation surrounding Bendectin silicone breast implants, Vioxx®, fen-phen and the Dalkon Shield. Whether or not these products presented real risks, they were eventually removed from the market by a tidal wave of litigation, at the cost of millions or even billions of dollars.

Medical procedures and practices have also been the subject of asymmetrical litigation dynamics. Previous litigation experiences involving past innovations in medical technologies help predict how genetic technologies may be handled by the courts. Even when new technologies improve overall healthcare, they tend to increase liability as patients' expectations are raised and the gap in outcomes widens between early and slow adopters.^[11,12] Thus, based on this historical pattern, the advent of a new set of medical technologies and procedures associated with personalized medicine would be likely to increase liability risks for physicians, both because of the increased patient expectations associated with the new innovations, and the inevitable gap in utilization between early and late adopters of these new technologies and procedures.

Historical analysis of medical malpractice litigation also reveals that increased litigation against physicians relating to a particular health outcome or procedure can significantly change physician practice. For example, after lawsuits started being filed against physicians who delivered children with cerebral palsy, the frequency of caesarean sections

increased significantly.^[13] Similarly, after a wave of lawsuits against physicians alleging missed nascent tumors on mammograms, the rate of breast biopsies following mammograms shot upward.^[14] More generally, the fear of liability drives physicians to order more diagnostic tests and perform more procedures than medically indicated in order to protect against potential lawsuits, a practice known as defensive medicine.^[15]

Liability Landscape for Personalized Medicine

Today, there is substantial uncertainty and disagreement about the appropriate use of genetics and other personalized medicine data in clinical care, giving rise to the types of disagreements and disputes that can spawn litigation.^[16] On one hand, some experts claim certain personalized medicine techniques are ready for clinical application today, and several leading medical institutions have begun to deploy such techniques.^[4,17,18,102] Experts with this perspective have expressed frustration that physicians and other stakeholders in the healthcare system have been too slow to uptake personalized medicine methods and tools.^[9,18] Other experts, however, are more skeptical about the near-term deployment of personalized medicine, contending that such methods are not likely to benefit patient care and are not yet ready for widespread adoption.^[19,103] We are thus currently at a critical and unsettled juncture in the implementation of personalized medicine, where much uncertainty and disagreement exists about which technologies and approaches are ready for use, what outcomes they will provide and who will pay for them. In such a period of uncertainty, the potential for liability is at its greatest.^[20]

These uncertainties can create liability risks for every entity across the personalized medicine lifecycle, including physicians, pharmacists, insurance companies, hospitals, laboratories and drug manufacturers. Of these potential targets, physicians are likely at the greatest risk for a variety of reasons.^[8] For example, there is a well-established plaintiffs' bar experienced at suing physicians for medical malpractice. Physicians lack the types of defenses that at least partially protect other parties such as **the learned intermediary doctrine, which allows drug manufacturers to shield themselves from failure to warn liability by simply listing risk information on their drug labels. The US FDA is increasingly requiring manufacturers to put pharmacogenomic data and warnings on patient package inserts for drugs, setting up physicians for potential liability if they fail to heed those data and warnings and an adverse event occurs.**^[21] In addition, only a handful of medical schools and training programs include formal genetics education, creating major disparities in the genetics proficiencies of practicing physicians that can be exploited by deft plaintiffs' lawyers. For these reasons, physicians are likely to have the greatest liability exposure with respect to the implementation of personalized medicine, and accordingly are the focus of this article.

To bring a successful medical malpractice case against a physician, a plaintiff must show that: the physician had a duty of care to the plaintiff; the physician breached that duty; the plaintiff incurred an injury; and the physician's breach caused the plaintiff's injury. Traditionally, the plaintiff was required to demonstrate the breach of a duty of care with expert testimony showing that the physician's actions were not in accord with the customary practice of physicians in the same specialty in that same local region. This traditional basis for establishing the standard of care is undergoing transition in many jurisdictions. First, the locality rule is being replaced in a number of jurisdictions with a national standard of care, in which a physician is not judged solely against similar practitioners in the same geographic region, but rather against doctors across the nation.^[22] Second, the standard of care based on custom (i.e., what other doctors are doing) is giving way in many jurisdictions to a more objective 'reasonableness' standard in which the jury gets to determine whether a physician's actions were reasonable, regardless of the practice patterns of other physicians.^[23] Under this new standard, a jury might find in some circumstances that the current practice of all or most physicians in a certain context was below the standard of care that could and should be achieved.^[24]

Finally, some jurisdictions are recognizing new causes of action that circumvent many of the defenses used by physicians under the traditional negligence-based medical malpractice cause of action. For example, an injured plaintiff may allege that the physician violated informed consent requirements by failing to ascertain or disclose relevant genetic information that could have influenced the patient's treatment options and choice. Each of these doctrinal developments are likely to increase physicians' liability risks relating to personalized medicine because they heighten or broaden the standard of care expected from a physician.

Other trends in addition to legal doctrine are increasing the liability exposure of physicians with respect to implementation of personalized medicine. The number of commercially available genetic tests continues to grow steadily, and now exceeds 2000.^[104] Physicians could potentially be hauled into court and found liable for failure to apply almost any one of the genetic tests in appropriate circumstances, yet most physicians have not received significant training in genetics.^[105] Another problem for physicians is that some genetic tests can cost upwards of US\$3000, and in many cases are not reimbursed by the patients' health insurance policy.^[106] The fact that a patient may not have the economic means to obtain a genetic test does not protect the physician from liability for failing to inform the patient of the test.

Existing Case Law

Unless providers reach a consensus about how and when to adopt personalized medicine technologies, court decisions involving those technologies are likely to play a lead role in setting the standard of care for their use within the medical field. While the medical community has been slow to adopt new genetic technologies, public expectations for personalized care have been fueled by fantastical accounts of futuristic medicine in best-selling novels, popular television shows, magazine covers and some news accounts of direct-to-consumer genetic testing services. Because juries in many jurisdictions now decide malpractice cases by considering how reasonable physicians should act rather than how most physicians act, public expectations play a major role in setting the standard of care and may influence jurors to hold physicians liable for failing to understand and use these highly publicized genetic technologies.

The handful of cases already decided by the courts involving clinical genetics, often involving prenatal testing, illustrate the liability threat that physicians face when dealing with this field. In addition to the traditional claims for negligence, genetic testing has also given life to ideas such as wrongful conception, wrongful birth and wrongful life, while creating new applications for claims such as loss of chance and duty to third parties. Although drug manufacturers, hospitals and pharmacists have all been the subject of these lawsuits, physicians may be the most vulnerable to claims by aggrieved patients and their families.^[8] As the following litigated cases illustrate, physicians are vulnerable to a quickly-expanding array of lawsuits related to the screening, diagnosis, treatment and prevention of genetic conditions.

Failure to Recognize Genetic Risk

Despite the current lack of formal genetics training in medical education, courts have held physicians responsible for being able to recognize patients at high risk for a variety of genetic conditions. In 1981, a federal court found a doctor negligent for failing to screen a woman's fetus for Down syndrome based on the fact that her sister had the condition. Though only 2% of Down syndrome is inherited and the screening technology for Down syndrome was still being developed at the time, the court in this case found that the woman's family history should have prompted the physician to perform more rigorous screening, and thus awarded the mother \$1.5 million.^[25,26] More recently, a court found a physician negligent after his patient's child was born with the same rare genetic condition he had failed to diagnose in the child's sibling. Although the physician had only seen the condition a few times in his career and it had not yet fully manifested in the sibling, the court awarded the family \$23.5 million for the physician's failure to recognize the disease.^[27] Similarly, a New Jersey (NJ, USA) court awarded \$14 million to a family after the physician failed to recognize that the mother's ethnicity put their child at high genetic risk for a rare blood disorder.^[28]

Of course, most such cases settle, for which information is generally not available, and other cases are decided in favor of the physician, and tend not to be appealed, making a published decision (which are often at the appellate level) less likely. Notwithstanding these uncertainties, the willingness of at least some courts to hold providers responsible for staying informed about newly emerging technologies, rare disorders and a broad set of risk genetic factors suggests few limits on the scope of liability for physicians in this field.

A Texas (TX, USA) court recently outlined what seems to be a growing consensus about what is expected from doctors in handling patients with genetic conditions. The expert testifying to the standard of care in this case

recognized both the duty to identify patients' genetic concerns and to refer them to appropriate resources when appropriate: "An obstetrician confronted with this information has the option of either knowing the information and doing the counseling themselves, or referring the patient to a subspecialist in medical genetics or maternal fetal medicine".^[29] Similar expectations have been imposed by courts related to a wide variety of genetic diseases, including relatively common conditions, such as sickle cell anemia and Fragile X syndrome, but also much rarer disorders to which most physicians have little, if any, exposure (e.g., Smith-Lemli-Opitz syndrome and anhidrotic ectodermal dysplasia).^[27,30–32]

Loss of Chance

The loss of chance doctrine poses one of the greatest threats to physicians, whose limited knowledge of genetics may reduce the chances of favorable outcomes for their patients in a variety of ways. Traditionally, this claim required significant reductions in the patients' probability for a positive outcome, so its application has been fairly limited. However, many courts are now allowing claims to go forward even when the physicians' negligence increases the risk of harm only slightly. Related to genetics, physicians who fail to identify or explain genetic risk factors may be liable to patients who lose the chance to prevent or mitigate an injury because of the physician's negligence.

Delays in the identification and treatment of genetic diseases both fit within the loss of chance framework. A New York (NY, USA) court recently found a physician negligent for taking 3 weeks to diagnose a child with propionic acidemia, an enzyme deficiency affecting just 1 in 150,000 births.^[33] By the time the child was diagnosed, he had suffered irreversible brain damage that could have been prevented with a more prompt diagnosis, and the court awarded the family \$3.5 million in damages.^[34] Although this case did not formally invoke the loss of chance doctrine, it may serve as a harbinger of claims to come. Its result implies an expectation that physicians should be well versed in quickly recognizing a growing number of genetic disorders, or at least recognizing the possibility of a genetic disease and making the appropriate referral.

Informed Consent

Physicians have also been held liable in their handling of genetics by failing to fully obtain informed consent related to diagnostic and treatment procedures. Informed consent claims are increasingly powerful tools for patients, especially as courts transition towards a patient-centered approach to this doctrine, which requires physicians to disclose all information that reasonable patients would consider material to their decision-making (rather than the information that reasonable physicians would consider material, as the traditional doctrine required). This cause of action is similar to loss of chance in that plaintiffs must claim that they would have made different decisions and potentially averted their injuries if they were provided the right information. In 2008, for example, a federal court held a physician liable when his patient gave birth to a child with Down syndrome. The woman had turned down the chance to test for the condition at 15 weeks gestation, but claimed she would have undergone a different form of testing offered at 11 weeks if the doctor had told her about that type of testing. The court awarded her \$2.5 million based on her claim that if she would have been told about the earlier screening option, she would have aborted the fetus.^[35] In general, this doctrine allows any patients who suffers injuries that could have been avoided by making different decisions about their own care based on genetic information or tests not disclosed by their physician to hold that physicians liable for any resulting injuries, placing great weight on physicians' knowledge of available genetic tests.

Failure to Warn

Traditionally, physicians have no responsibility to anybody except patients with whom they've entered into a professional doctor–patient relationship. However, exceptions have been carved out of this rule in extreme circumstances. The Tarasoff court made headlines in the 1970s for holding a psychiatrist liable for failing to warn a woman with whom he had no prior contact that his patient may pose a threat to her.^[36] This case represented a major expansion of a psychiatrist's duties at the time, and has been applied only sparingly since then. Recently, however, some courts have drawn an analogy between the psychiatrist's duty to warn about his murderous patient to contemporary physicians' duty to warn family members of their patient about the patients' potentially risky genes, significantly expanding physicians' responsibilities in the process.

At least two courts have held physicians responsible for failing to tell patients' relatives that they may share a risk-conferring mutation with the patient, even in situations in which neither the physician nor the patient has a relationship with those relatives.^[31,37] One court held that a physician could be negligent for failing to tell his patient's daughter about her father's diagnosis of hereditary colon cancer, though she was only 10 years old at the time of his death, and the father intentionally hid the diagnosis from his family. That court found the duty to protect at-risk individuals outweighed the duty to maintain patient–doctor confidentiality: "We see no impediment, legal or otherwise, to recognizing a physician's duty to warn those known to be at risk of avoidable harm from a genetically transmissible condition. In terms of foreseeability especially, there is no essential difference between the type of genetic threat at issue here and the menace of infection, contagion or a threat of physical harm".^[38] Opinions like this are complicated by the conflicting yet traditional notion that a doctor's duty stops with warning the patient to tell family members. Medical privacy laws at the federal (e.g., Health Insurance Portability and Accountability Act) and state levels further complicate the physician's obligations in such situations. These confusing and inconsistent instructions thus create a situation in which there is no safe decision for a physician to make when disclosing sensitive genetic information.

Four Examples

This section provides four hypothetical examples where a physician may be held liable for medical malpractice relating to personalized medicine. In setting forth these scenarios, we do not intend to suggest that physicians should or necessarily would be held liable for their actions, only that they might be held liable. Given the volatile mix of disagreement within the published literature and among credentialed experts, the idiosyncrasies of individual juries, juries, experts and attorneys, and the importance of intangible influences on litigation outcome such as the group dynamics of a particular jury or how well a particular lawyer performed on a specific day, the four scenarios described below, which involve different types and uses of genetics tests, could lead a jury to find a physician liable for medical malpractice in at least some instances.

Example 1: *BRCA* Testing

This first example involves a physician's duty to warn patients about inherited disease predisposition genes. Among the strongest and best validated of these disease predisposition genes are the *BRCA1/2* genes for breast cancer, as women carrying a mutation in either of these genes have a 50–85% risk of breast or ovarian cancer.^[39] Interventions such as prophylactic bilateral radical mastectomies and oophorectomies have been shown to substantially reduce the risk of cancer in asymptomatic women carrying a *BRCA1/2* mutation.^[39] Various expert evidentiary reviews have recommended genetic testing of women who have certain risk factors for carrying one of these mutations, such as having two first-degree female relatives who have developed breast cancer. These expert guidelines are not binding on courts, and so it is possible that a judge or jury could hold a doctor responsible for failing to recommend genetic testing for a woman who does not meet the screening recommendations in the guidelines. For example, many of the guidelines may not be relevant for a woman with few if any available first degree female relatives, such as an adopted woman with unknown birth parents, or a single child family in which the mother is no longer available. In such cases, the lawyer for a woman who develops breast cancer may argue that the physician should have recommended *BRCA1/2* testing even if the evidence of risk is less than called for in the guidelines to recommend testing.

A physician could potentially be sued if he or she sees an asymptomatic patient with a strong family history of breast cancer, but does not recommend the patient undergo genetic counseling or testing. If that patient subsequently develops breast cancer, she or her surviving family members could bring a lawsuit alleging that the physician breached a duty to warn her of her potential genetic risk, and the failure to recommend genetic testing resulted in the patient's 'loss of chance' to have prevented or successfully treated the disease. The plaintiff would argue that if her doctor had warned her about her genetic risk, she would have undertaken testing for *BRCA1/2*, and if she had tested positive, would have either undergone prophylactic surgery to prevent the disease or performed more frequent surveillance to detect the disease in an earlier, more treatable stage. At least one doctor has already been sued by a patient for failing to recommend counseling or testing for the *BRCA1/2* mutation, leading the patient to undergo an unnecessary mastectomy.^[40] The jury in this case found that the treating physician had adequately recommended

genetic counseling, but that the patient declined to seek such counseling because she could not afford the *BRCA1/2* genetic test.

Example 2: Gene-expression Profiling

A second type of genetic test that could potentially lead to liability is gene-expression profiling. This test measures changes in gene expression, rather than inherited genetic changes, to classify a diseased tissue (such as a tumor) with respect to its prognosis and best treatment options. Many types of tumors can now be classified based on different patterns of gene expression into subcategories that previously were indistinguishable using traditional clinical parameters. These different subcategories of tumors often have a very different prognosis, including risk of recurrence, which may affect treatment or management regimens. The first commercial tests are now available to identify such patterns. For example, the *Oncotype DX*® assay is marketed by Genomic Health, Inc. (CA, USA), and screens the expression of 21 genes to predict the risk of cancer recurrence for certain subtypes of breast cancer. Expert opinion is currently divided on whether physicians should recommend gene-expression profiling of tumors in some or all patients, and this difference of opinion and uncertainty is likely to increase as more tests become available.^[41–43] The Evaluation of Genomic Applications in Practice and Prevention Working Group, an expert panel established by the Centers for Disease Control and Prevention (CDC) to make recommendations on the clinical use of genetic tests, concluded in 2008 based on a comprehensive evidence report it commissioned that there was "insufficient evidence to make a recommendation for or against the use of tumor gene-expression profiles to improve outcomes in defined populations of women with breast cancer".^[44] Accordingly, "until more data are available, clinicians must decide on a case-by-case basis if the use of a gene-expression profile test adds value beyond the use of the current prognostic markers".^[44] This uncertainty opens the door to disparate physician practice and potential liability.

The uncertainty surrounding gene-expression profiling leads physicians to face a 'damned if they do, damned if they don't' dilemma. If the physician recommends a gene-expression assay, and the test results suggest that the patient has a low risk of recurrence and they decide not to undergo chemotherapy as a result, the physician might face liability risks if a tumor recurs. The plaintiff's lawyer could likely find an expert who would testify that the gene-expression assay was not sufficiently validated for such decisions, and thus the physician acted negligently by recommending the test or for not trying to dissuade the patient from foregoing chemotherapy based on the (allegedly) unreliable test results. Conversely, in an appropriate case, the same physician could be sued for being too conservative and not recommending the gene-expression test to another patient. In this hypothetical situation, the patient may be classified as having a low risk of recurrence using traditional clinical parameters, and therefore elects not to undertake chemotherapy, and is then disappointed to find the cancer reoccurs nonetheless. In this case, the patient's lawyer may find an expert to testify that the gene-expression assay is the most reliable predictor of recurrence, and if the doctor had recommended such a test, it would have given a more accurate risk of recurrence than the traditional clinical parameters. To buttress this claim, the plaintiff would likely need to undertake the test after the fact to show that it does indeed indicate a higher risk than suggested by the traditional clinical parameters.

Example 3: Drug–gene Interaction (Pharmacogenetics)

The third class of genetic tests that may create a liability scenario involves the growing number of genetic variants that affect patients' responses to drugs – in some cases resulting in the drug being ineffective, and in others causing a potentially adverse side effect. Given that drug side effects kill over 100,000 Americans each year, and genetic variants likely contribute to a considerable proportion of those fatalities, there is a potentially large pool of prospective plaintiffs who could bring lawsuits alleging that a physician's failure to recommend genetic testing for relevant variants before prescribing a drug contributed to a patient's death or adverse effect.^[45] As in the previous example, the applicable standard of care – in this case whether and which gene variants should be tested for prior to prescribing a drug – is likely to be highly indeterminate and contested. Consider clopidogrel (Plavix®), the second most prescribed drug in the world, which is taken by more than 2 million patients every year to prevent the formation of a stent-induced blood clot, a frequent and often fatal occurrence among patients following heart surgery.^[46] It has been well established that individuals vary significantly in their response to clopidogrel, and variations in two genes (*CYP2C19*

and *PON1*) contribute significantly to the wide variation in drug response, although the studies reported to date are not entirely consistent in the role they attribute to this genetic variation.^[47–50] When clopidogrel is prescribed, an estimated 1–2% of patients still suffer serious adverse events, presumably because, in most cases, the clopidogrel failed to prevent clot formation as expected.^[51] **The widespread use of this drug, combined with the relatively high rate of side effects and the well-characterized genetic influence on efficacy, generates thousands of potential plaintiffs each year.**

Given this unsettled situation, some experts recommend that genetic testing should now be a part of routine clinical practice when prescribing clopidogrel, while others disagree.^[52] **The FDA further complicates the appropriate standard of care by requiring a black box warning about the genetic risks associated with clopidogrel while paradoxically not requiring physicians to conduct genetic tests before prescribing the drug.** Another complication for both the prescribing physician and the legal fact-finder determining causation and liability is that interindividual differences in susceptibility to adverse side effects from drugs is affected by many other factors in addition to genetics, including age, gender, hepatic and renal status, nutrition, smoking and alcohol intake, and drug–drug interactions. Thus, while a patient with a relevant genetic variant (which would probably need to be demonstrated by after-the-fact genetic testing) who is not referred for a genetic test and reacts adversely to clopidogrel may have a viable lawsuit against the prescribing physician, the outcome will be dependent largely on the specific facts of that case and the skills and performance of the particular attorneys, experts and jury members involved in that case.

Example 4: Whole-genome Sequencing

The final example involves a very recent type of genetic testing that is only in early research stages at this time but could become part of clinical care relatively quickly in at least some practices. The potential for rapid adoption of whole-genome sequencing may fuel a discrepancy in care that could leave slower adopter physicians and provider institutions at risk of liability. This technique is already being used, for example, to sequence the entire genome of a cancer patient's tumor and compare it to that same patient's inherited genome.^[53,54] Genetic changes revealed in tumors using this comparative approach could be used to identify otherwise unexpected treatment regimens that target the particular molecular identity of the tumor. Although this method has only been used in research studies on a relatively small number of patients to date, the results today are promising and have generated significant interest in the method. While the technique is too expensive and experimental to be used in routine cancer care now, leading institutions and physicians may adopt the technology on selected patients in the relatively near future. As will be the case for any new, expensive and highly technical new medical procedure, a gap is likely to quickly grow between those providers at the leading edge of technology and care, and those that lack the resources, expertise and wherewithal to keep up with the leaders in the field or those physicians who are more cautious about adopting new technologies until they have a proven track record. Especially as more and more jurisdictions migrate to a national rather than local standard of care, this growing discrepancy between the leaders and the slow adopters creates an opening for litigation and liability.^[22]

Slow adopters of whole-genome sequencing and related genetic technologies may face liability risk in a number of different scenarios. For example, tissue from the tumor of a patient who succumbed to cancer at a local hospital may be sent to a leading laboratory conducting a cancer genetics research project, where it might be discovered that the tumor had a specific mutation that had been successfully targeted by therapies given to cancer patients at a different hospital, where their tumors had been analyzed using whole-genome sequencing. In this situation, the family of the deceased patient may be able to bring a lawsuit alleging that the treating physician and hospital had failed to apply the appropriate standard of care in not conducting whole-genome sequencing of their family member. Once again, the outcome of such a case would likely depend on very context-specific facts of the particular case and the participants in the trial, which would be hard to predict at the outset.

Conclusion

Based on the historical patterns of increased liability risks following medical technology innovation, as well as the stringent and unpredictable expectations that judges and juries have placed on physicians in genetics-related

litigation to date, physicians are increasingly vulnerable to liability as the approaching wave of personalized medicine begins to envelop clinical practice. The wide discrepancies between physicians in their willingness to adopt personalized medicine technologies, the rapid pace at which new data and technologies are becoming available, the large number of patients dying every year from drug side-effects that likely have some genetic attribution, and the doctrinal shifts in medical malpractice liability including the demise of the locality rule and the increased prominence of the reasonableness standard, all contribute to the potential for impending liability risk for physicians. The absence of many lawsuits today should not provide much comfort, given that the typical dynamics of litigation are that it starts slow, but then picks up momentum in a cascade that is very hard to stop once it starts.

What can be done to head off this potential liability explosion? It is in the interest of both physicians and patients to ensure that personalized medicine approaches are applied in a careful and appropriate manner to prevent adverse effects and to improve clinical outcomes when the new technologies offer such benefits. At the same time, premature or unsupported use of such technologies, perhaps driven by defensive medicine in response to liability pressures, can jeopardize the most effective care for patients and unnecessarily increase medical costs.

One factor that can help reduce liability risks is to improve the knowledge and training of physicians on genetics-based healthcare. Relatively few doctors receive significant training during medical school in genetics and related molecular sciences, and thus lack the background needed to effectively integrate new genetic findings into their practice. The availability of more authoritative evidence-based guidelines on when genetic testing is and is not warranted could provide physicians with a more rational approach to genetics in the short term. Without credible guidelines to guide their decision-making, physicians are currently forced to wade on their own through a stack of conflicting studies, expert advice and recommendations on whether or not genetic testing is indicated and useful in particular circumstances and patients. Guidelines have had a checkered history, with many problems such as conflicts of interest, out-dated recommendations and noncompliance, yet standardized guidelines have often enhanced the quality and efficiency of clinical care.^[55] Unfortunately, one source of credible guidelines, the Evaluation of Genomic Applications in Practice and Prevention Working Group on which one of us served (Doug E Campos-Outcalt), was recently disbanded due to funding shortages, portending an even more pronounced absence of clear, authoritative guidance that physicians can follow in the future. Given this development, there is a need for professional societies, governmental organizations such as the US Preventive Services Task Force and the CDC, or payers and health plans to step up to the plate and provide greater certainty for physicians by providing genetic testing recommendations. Other possibilities that may help physicians include liability reform, strengthening of the Clinical Laboratory Improvement Act of 1998 to improve genetic testing by laboratories, limits on those direct-to-consumer genetic tests that are misleading or deceptive, and the creation of a genetic test registry by the NIH.^[56] In the absence of such actions, physicians are stranded out in the wilderness of genetic indeterminacy, with the wolves howling on the horizon. Now is the time to address this problem before it becomes too late.

Future Perspective

Approximately 100,000 people die every year in the USA from drug side effects.^[45] Medical innovation transforms what has been thought of as 'natural risk' into 'medical risk' that can and should be prevented, and ultimately 'liability risk' for which the patient seeks compensation through the courts.^[57] As a result of this dynamic, it is quite possible that 10 years from now, physicians may be beset by perhaps the biggest surge in liability risk (and associated malpractice premiums) ever. Just as other clinical technologies have sparked increased malpractice liability because of disparities in practice, unfamiliarity with the new technologies, and increased expectations by patients, the fundamental transformation of medicine promised by personalized medicine could carry with it an equally fundamental shift in liability exposure for physicians. One leading medical expert recently opined that "the discrepancy between current medical practice and the capabilities for improvement is greater now than at any time since the early part of the 20th Century".^[58] The current gap between current practice and that which will soon be enabled by new personalized medicine technologies could arguably mean the difference between life and death for thousands of patients per year. Physicians are likely to be hauled into court and called to account for this discrepancy unless steps are taken to provide physicians with better education and guidelines to integrate the new data and

technologies into their clinical practice. The window of opportunity to act is short. Once the litigation snowball starts to roll, it will quickly become unstoppable.

Sidebar

Executive Summary

Background

- The adoption of personalized medicine has been slowed down by a number of factors such as regulatory and approval barriers, low reimbursement for genetic technologies, and low awareness of genetic advances among providers.
- Due to these factors, clinical adoption of personalized medicine technologies has fallen behind public expectations, creating a gap that breeds liability.

Dynamics of litigation

- Litigation on a particular issue often starts slow but can quickly snowball after just a few cases are tried successfully and plaintiffs' lawyers see that success in a particular practice area is possible.

Liability landscape for personalized medicine

- The uncertainty surrounding the appropriate use of personalized medicine technologies creates a huge risk of liability because it is possible to find evidence and experts to contradict almost any decision physicians make related to genetic technologies.
- Among potential targets of lawsuits, physicians may be the most vulnerable to future lawsuits.

Existing case law

- Physicians have already been held liable for their negligence in the use of genetic tests, most notably by extending the traditional doctrines of informed consent, duty to warn and loss of chance.

Examples of potential lawsuits

- Because of differences in physician education and hospital testing capabilities, new technologies are likely to be rapidly adopted by some providers and not adopted by others.
- *BRCA* gene testing, gene-expression profiling of tumors, drug–gene interaction screening and whole-genome sequencing are all technologies that have entered or are likely to enter clinical practice soon, are likely to be adopted disparately by providers, and will therefore generate substantial liability risk for physicians.

Conclusion

- Personalized medicine technologies are likely to give rise to new and substantial liability risks.
- Among the groups involved in the lifecycle of personalized medicine technologies, physicians may be the most vulnerable to liability.
- The medical community needs to make a concerted effort to resolve the uncertainties and disparities surrounding personalized medicine in order to avoid a future in which litigation, rather than sound science and policy, directs the practice of personalized medicine.

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