Legal pressures and incentives for personalized medicine

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Legal liability has the potential to be a powerful driver pushing implementation of personalized medicine. Individuals injured by adverse drug effects are increasingly likely to bring lawsuits alleging that they have a polymorphism or biomarker conferring susceptibility to the drug that should have been identified and used to alter their drug treatment. Likely targets of such lawsuits include drug manufacturers, third party payors, physicians and pharmacists, of which physicians are most at risk of substantial liability.

Implementation of personalized medicine will be affected by numerous factors, including scientific developments, biomarker validation, economics, reimbursement, regulatory approval, intellectual property, data access and professional training. Another important driver of personalized medicine, more contingent than those above, but potentially as or more powerful than any other, is the potential for legal liability. While the extent and risk of future liability is uncertain and cannot be predicted with precision, it is clear that pharmaceutical manufacturers, healthcare providers and others may be subjected to significant liability for failure to adequately implement pharmacogenomic technologies [1]. That potential liability may accelerate the incorporation of personalized medicine into the healthcare system [2].

The dynamics of litigation are highly non-linear, making predictions of future liability difficult. Most lawsuits brought to recover compensation for personal injury from medical malpractice or product liability are on behalf of injured individuals (‘plaintiffs’) who usually cannot afford to fund the litigation themselves. Such litigation typically involves the use of expert witnesses, requires extensive discovery and can involve numerous judicial proceedings spread over a period of years, all of which can result in costs in the hundreds of thousands, if not millions, of dollars. As individual plaintiffs usually cannot afford to finance the litigation, their attorneys must fund the case using their own resources on a contingency fee basis. One implication of this financial relationship is that plaintiffs’ attorneys are generally reluctant to litigate and fund novel claims based on new scientific evidence. However, once a new claim has proven to be successful by one or more favorable verdicts and ‘blood is in the water’, there will be a swarm of lawyers willing to file and finance similar ‘copycat’ suits. For a new field such as pharmacogenomics, this litigation dynamic means that there will likely be an initial calm until there has been a breakthrough case, and then there will be a sudden storm of litigation that will have immediate and enormous implications for defendants, including manufacturers, providers and payors.

Who then might be at risk from future liability in the area of personalized medicine, what types of claims might be brought, and what is their chance of success? This perspective article identifies four entities at potential risk of liability in the personal medicine realm:

- Pharmaceutical manufacturers;
- Insurers and other third party payors;
- Physicians;
- Pharmacists.

Some of the potential claims that might be brought against each of these actors are identified and evaluated below.

Pharmaceutical manufacturers
Pharmaceutical manufacturers, with their ‘deep pockets’, are a likely target of plaintiffs and their lawyers. A manufacturer who produces a pharmaceutical that is more likely to harm individuals with a particular genotype or biomarker could be sued and held liable under a variety of legal theories. As discussed below, manufacturers have powerful, though not bullet-proof, defenses against such claims.

The most likely cause-of-action against a pharmaceutical manufacturer is for ‘failure to warn’ about a genetic susceptibility to a drug product. Product manufacturers, including pharmaceutical companies, have a legal duty to provide reasonable warnings where it is foreseeable that people might be harmed by their products. The
warning requirements for a drug may be based on side effects observed during initial clinical testing, in which case the warning will likely be part of the label when the drug is approved, or the warning can be based on post-approval clinical experience indicating significant new risk information, which would require an amended label. In the absence of a suitable warning, an individual who carries a genetic polymorphism that increases the risk of an adverse drug reaction (ADR) from a particular drug could bring a lawsuit against the drug manufacturer, arguing that the manufacturer should have provided a warning about this susceptibility.

The manufacturer would have several potential defenses to such a failure-to-warn claim. First, the manufacturer could argue that a warning would have been pointless. Using this defense, the manufacturer would seek to establish that even if it disclosed the fact that particular genotypes put patients at increased risk for an adverse reaction to its product, the plaintiff would not have known he or she carried that genotype (especially given the relative unavailability of genetic testing) and thus would not have had any way to 'heed' the warning and avoid the product. While occasionally successful, this 'heeding' defense is unlikely to shield a manufacturer from disclosing significant risk information, even if few consumers would be likely to use that information [3].

Another possible defense would be for the manufacturer to argue that evidence of an association between a particular genotype and an increased risk of an adverse reaction to the drug was not sufficiently validated to impose a duty to warn. A manufacturer need only warn about known risks, not speculative risks [101]. Thus, the manufacturer could argue that the information on genetic susceptibility to ADRs from its product had not yet reached a level of sufficient certainty to trigger a duty to warn. The manufacturer's prospects for success with this defense would likely depend on the strength of the specific data available about the drug at issue. This defense will be most helpful to manufacturers in situations where the data on genetic susceptibilities to the manufacturer's drug are less robust than the data for other drugs for which susceptibility warnings are currently provided. Over 70 drug package inserts from the Physicians Desk Reference already contain pharmacogenomic data [4].

The most established defense that a manufacturer could assert in response to a failure-to-warn claim is the 'learned intermediary doctrine', which 'provides that the manufacturer or supplier of a prescription drug has no legal duty to warn a consumer of the dangerous propensities of its drug, as long as adequate warnings are provided to the prescribing physician' [5]. The theory behind this defense is that the physician, rather than the drug manufacturer, is best-positioned to make a full assessment of the individual patient's situation and decide which drug is best for that patient. Although direct-to-consumer marketing [6] and US FDA labeling [7] requirements have the potential to weaken the protection afforded by the doctrine, the majority of courts recognize the learned intermediary defense, and it continues to apply to a broad range of cases. Of course, for the defense to apply, the manufacturer must have communicated appropriate warning information to the injured patient's healthcare provider. In the absence of such a warning, the defense is inapplicable. The defense also does not apply to products such as over-the-counter drugs and vaccines, for which physicians do not make an individualized assessment of the patient.

A final potential defense against a failure-to-warn claim has been created by the US FDA's recent regulatory decision to preempt state warning requirements that exceed the requirements of an US FDA-approved label for a pharmaceutical [8]. Such preemption would apply not only to state legislative and regulatory requirements, but also state courts that attempt to impose liability for inadequate warnings. If the US FDA's authority to preempt state law is upheld by the courts, a manufacturer that complies with the US FDA labeling and warning requirements will be exempt from liability for failure to warn. However, the impact of this US FDA decision remains uncertain, as some courts have declined to follow the US FDA decision [9].

A second type of potential liability for a pharmaceutical manufacturer is design-defect liability. In a design-defect case, the plaintiff contends that the product that caused injury was 'defective' and unreasonably dangerous, such that the manufacturer may be held liable for any ensuing harm. For many years, pharmaceuticals have been held to a less stringent standard of design defect liability. This more forgiving standard is based on the recognition that pharmaceuticals necessarily interact with the body in order to have their beneficial effects, and that they therefore will sometimes produce adverse results, i.e., they are 'unavoidably dangerous' even when they are designed appropriately. Under the
Restatement (Second) of Torts, a statement of the law that guides courts in most states, a manufacturer is not exposed to design defect liability if the drug's benefits exceed its risks.

A recently revised version of the Restatement of Torts provides even more protection for pharmaceutical manufacturers. Under Section 6(c) of the Restatement (Third) of Torts, a pharmaceutical manufacturer is not liable under a design defect theory “if the foreseeable risks of harm posed by the drug or medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable healthcare providers, knowing of such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients” [11].

In the event of an ADR in a patient whose ability to metabolize a drug is adversely affected by a polymorphism, the manufacturer would argue that since the drug was safe for some patients (those who did not have the polymorphism), the drug did not have a design defect. This new expanded protection for pharmaceutical manufacturers from design defect claims has proven to be controversial [11], with some jurisdictions rejecting the new Restatement provision [12].

For both failure to warn and design defect claims, a particular concern for manufacturers would be the imposition of liability based on a retrospective analysis of its products. Many manufacturers collect pharmacogenomic data or samples during clinical testing of a new drug. At the time of data collection, the significance of the collected data may be unknown. However, years later, the significance of the data may have become clear, and a patient injured by the drug will argue that the drug manufacturer should have known that the data it collected indicated the existence of a risk that warranted a warning or other action. A manufacturer would attempt to defend against this argument using the ‘state of art’ defense, recognized by most states, which requires the reasonableness of the manufacturer's actions to be judged by the knowledge existing at the time of its decision, rather than by what is known at the time of trial [13]. However, given the benefit of hindsight, juries may be likely to view the evidence less favorably toward the manufacturer when:

- An injury has occurred;
- The injured plaintiff is sitting before them in the courtroom;
- The evidence accumulated as of the time of trial strongly suggests that the manufacturer’s product was responsible for that injury [14].

A third and related potential source of liability for a pharmaceutical manufacturer would be failure to adequately test its product. In the personalized medicine context, this claim would be based on an allegation that a manufacturer failed to conduct a thorough scientific investigation of potential biomarkers of risk to a drug product; that a thorough investigation by the manufacturer would have uncovered the risk and would have provided an appropriate warning; and that the warning would have protected the plaintiff from harm [15].

Unlike the well-established failure to warn and design defect claims above, this claim is rather novel and not accepted by all courts [16,17]. Consequently, in addition to arguing that it did in fact undertake due diligence, a manufacturer could defend against such a claim by contending that this claim is not a recognized legal cause of action. In jurisdictions that have recognized the claim the claim is more likely to succeed if there is evidence that the manufacturer has deliberately refrained from investigating potential suspected differences in susceptibility. Thus, statements of drug company executives to the effect that “[o]ur general philosophy is not to initiate a drug-development program that would limit the group of patients a drug could treat,” [19] could be very damaging to a manufacturer’s defense.

The first true pharmacogenomic lawsuit was filed in 1999 against SmithKline Beecham (Brentford, London, UK) for its Lyme vaccine, LYMErix® [20]. The lawsuit alleged that the vaccine caused a chronic autoimmune arthritic reaction in people carrying a particular genetic variant that is found in approximately 30% of the general population. The complaint alleged that the company was liable for failing to genotypically screen participants for the variant in the safety studies for the vaccine, for failing to warn of the increased risk of treatment-resistant Lyme arthritis to consumers who have the variant, and for failing to recommend preliminary screening of potential LYMErix users with the variant. SmithKline Beecham, supported by an analysis from the federal government, contended that extensive clinical data and postmarketing surveillance indicated no association with arthritis or any other adverse effect [21,22]. Nonetheless, the company settled the cases with the plaintiffs shortly after it withdrew the vaccine from the market in 2002. As the LYMErix litigation involved a vaccine, the learned intermediary defense did not apply. Nevertheless, similar lawsuits against pharmaceutical manufacturers are almost certain to be filed in the future.
Insurers/third party payors
Healthcare payors include both public entitlement programs, such as Medicare and Medicaid, and private payors, including independently purchased plans and Employer Sponsored Health Plans (ESHPs). To date, public payors have not been liable for coverage decisions, but certain types of private payors could face liability for failing to authorize and pay for pharmacogenomic testing.

ESHPs have broad and durable protections against liability granted to them by the Employee Retirement Income Security Act (ERISA) [23]. ERISA provides this protection by preempting all state law claims against ESHPs that "relate to" employee benefit plans [24]. The most effective protection provided by ERISA is a limitation of remedies. Where ERISA applies, a claimant who can show that the payor improperly refused to provide a benefit can only recover the cost of the benefit that was denied. Furthermore, the Supreme Court has interpreted ERISA preemption broadly to protect payors from any liability for negative coverage determinations resulting in claims against the plan [25]. Thus, with few exceptions, ERISA preemption leaves ESHPs free from any serious liability risk.

For individually purchased insurance plans not covered by ERISA, the managed care organization's (MCO's) utilization review process for treatment coverage decisions has become a prominent focus of liability. That liability might arise from the setting outlined below, which may become common as pharmacogenomics gains traction in clinical practice.

A physician wants to prescribe a drug for a patient, but there are data suggesting that the drug causes ADRs in a percentage of patients who have a particular polymorphism. The physician orders a test to determine whether the patient has that polymorphism. The patient's MCO determines that the data supporting the association between the polymorphism and ADRs are too attenuated, and refuses to authorize the test, based on a benefit plan provision that excludes coverage for 'experimental' tests and treatments. As a result of that refusal, the physician prescribes the drug without the test, and the patient suffers a serious or fatal ADR. If it can be shown that the patient had the polymorphism that was thought to be associated with an increased risk, the patient or his estate might pursue a claim against the MCO. Possible theories of liability under this scenario include breach of contract, breach of the implied duty of good faith and fair dealing, and bad faith [26].

Physicians
There are a number of ways in which pharmacogenomic testing can expose physicians to liability. However, it seems likely that in the not-too-distant future, a failure to employ pharmacogenomic testing will pose the greatest liability threat to physicians [27]. At present, there are no published decisions that address the existence or contours of a physician's duty to recommend genetic testing prior to prescribing or dispensing a medication. However, analogous cases provide some suggestions as to how the law will develop.

For example, there are a number of cases that hold that under certain circumstances a physician can be liable for failing to recommend and/or perform genetic testing [28-31]. There also are cases that hold that, having ordered genetic testing, a physician can be liable for negligence (i.e., failure to exercise reasonable care) in connection with the performance of the test, or in the interpretation and communication of the results [32-34].

The jury instructions applicable to conventional malpractice cases would likely apply neatly to claims based on a failure to recommend pharmacogenomic testing: the plaintiff would have the obligation to prove the existence of a duty of due care, a breach of that duty, and damages resulting from the breach [35]. The establishment of a duty would be determined by the applicable 'standard of care'. To some extent, the current absence of pharmacogenomic testing in clinical practice would make it more difficult for plaintiffs to establish this element of their claim.

However, there are a few potential weaknesses in this argument. First, a plaintiff who is obligated to introduce evidence establishing the standard of care does not need to show that testing is commonplace. In Arizona, for example, a malpractice plaintiff must establish that the defendant physician "failed to exercise that degree of care, skill and learning expected of a reasonable prudent physician acting in the same or similar circumstances" [36]. Normally, that failure must be established by expert testimony [37]. However, there are no reported medical malpractice decisions in Arizona that require the expert to testify that the defendant's conduct was at odds with what most physicians do.
Another possible weakness in the “no one is doing it” defense is that some jurisdictions relax the expert testimony requirement in informed consent cases, and many jurisdictions do not require expert testimony to establish a breach of duty where the court is persuaded that the jurors do not need expert assistance to evaluate the reasonableness of the defendant’s conduct. In some cases arising out of a failure to recommend testing, the claimants or the court have characterized the claim as a type of informed consent case [38,39]. Using this theory, the plaintiff would attempt to prove that he or she would have made a different decision regarding treatment if the physician had provided all of the information necessary to permit an informed consent to treatment.

In some jurisdictions, the decision to pursue an informed consent claim would not affect the need for expert testimony: these jurisdictions require a plaintiff in an informed consent case to show, by expert testimony, that the defendant’s disclosure of risks and alternatives did not conform to standards set by the medical community [40,41]. However, in other jurisdictions the relevant inquiry is not what a reasonable doctor would say, but what a reasonable patient would want to know [42]. As one court explained, “a patient’s right to know all material facts pertaining to proposed treatment cannot be dependent upon the self-imposed standards of the medical profession” [43]. The standard is “not what a reasonable medical practitioner would have done in the situation but whether the physician disclosed those risks which a reasonable man would have considered material to his decision whether or not to undergo treatment” [43]. In jurisdictions adopting this approach, expert testimony might be needed to establish the nature and extent of the risks and benefits from alternative treatments, but the question of what most doctors are telling their patients would not be determinative, and might not even be relevant.

In jurisdictions where this rule prevails, a plaintiff who was injured as a result of an adverse reaction to a drug prescribed by a physician might well conclude that a reasonable person would not have taken the drug without first getting the genetic test, even if there was undisputed testimony that other doctors do not recommend the test. Relevant factors in this case-by-case factual assessment that would weigh in favor of recovery include:

- The test has acceptable sensitivity and specificity;
- The cost of the test was reasonable in light of the risk of an ADR;
- There were other drugs that could have been used to treat the patient’s condition without the increased risk of an ADR.

These factors will often be contested and will require the jury to weigh the evidence and opposing expert opinions to reach a judgment that may differ from case-to-case and jurisdiction-to-jurisdiction.

Even in states where the general rule requires expert testimony to establish a breach of the standard of care, an apparently egregious fact pattern and a seemingly insensitive professional community might persuade a court to relax the requirement for expert testimony [44]. In states where the Restatement has persuasive authority, a plaintiff seeking to show that the failure to order pharmacogenomic testing was negligent might rely on Section 295A of the Restatement (2d) of Torts, which provides as follows:

“In determining whether conduct is negligent, the customs of the community, or of others under such as circumstances, are factors to be taken into account, but are not controlling where a reasonable man would not follow them.”

A plaintiff injured as a result of an ADR might also try to circumvent the requirement for expert testimony by arguing that the negligence of a physician who failed to disclose the risk of a genetically related ADR, and the availability of a diagnostic test, was “so grossly apparent that a layman would have no difficulty in recognizing it.” [45]. Admittedly, however, it would be a challenge to argue successfully that the entire medical profession is engaged in such a practice.

Pharmacists

In the majority of courts, pharmacists who fill prescriptions as written by the prescribing physician do not have a duty to warn the patient of the risks or dangers associated with the use of the prescribed medication. This rule is another application of the learned intermediary doctrine
described above. Pharmacists may nevertheless find themselves at risk for liability as a result of provisions contained in the Omnibus Budget Reconciliation Act (OBRA) of 1990 [46]. OBRA has arguably codified pharmacists’ common law duties and created duties to:

- Screen for potential drug therapy problems;
- Make reasonable efforts to maintain relevant customer history;
- Offer to discuss significant matters with customers [46].

Under these provisions, a pharmacist who learns of a contraindication to a prescription due to the information provided by a pharmacogenomic test, and fails to counsel the patient about the risk, may be found liable for breaching these duties and causing personal injury. In practice, most courts have, to date, been reluctant to impose legal liability on pharmacists based on duties under OBRA [47], but several commentators have suggested that the advent of pharmacogenomics may impose new legal duties and associated liability risks on pharmacists [48-50].

Conclusion
There are a number of hurdles to the incorporation of pharmacogenomics into clinical practice. These include scientific uncertainty as to the validity of the data supporting its use, social concerns about the potential uses of genetic information; and economic concerns about the costs and benefits of pharmacogenomics. These hurdles are likely to slow the pace at which pharmacogenomics becomes an everyday part of medicine. While the benefits of pharmacogenomics will work against these challenges, the risk of potential liability for failing to employ pharmacogenomic testing may accelerate the pace of its adoption. Manufacturers and healthcare providers, and the attorneys representing them, should start preparing now for preventing and defending a new class of personalized medicine lawsuits.

Highlights
- Legal liability is one of many potential drivers of personalized medicine, along with scientific developments, biomarker validation, economics, reimbursement, regulatory approval, intellectual property, data access and professional training.
- The impact of liability on the implementation of personalized medicine is more contingent than other drivers, in that there is substantial uncertainty on whether and to what degree liability will actually occur.
- If significant liability does occur, its effect will be dramatic, as potentially liable parties will need to undertake immediate and significant changes to protect against large legal liabilities.
- The potential targets of liability include pharmaceutical manufacturers, third party payors, physicians and pharmacists.
- Of the potentially liable parties, physicians are most at risk because they lack the legal defenses available to the other parties. Manufacturers, and to a lesser extent third party payors and pharmacists, also face liability risks.
- The first personalized medicine lawsuits have already been brought alleging that special protections are needed for individuals who have a genetic susceptibility to a pharmaceutical product.
- Manufacturers, insurers, physicians, pharmacists and healthcare institutions, and the attorneys who represent them, must start preparing for and trying to prevent a potential onslaught of new lawsuits based on personalized medicine.

Bibliography
20. Cassidy v. SmithKline Beecham, Amended Complaint, Class Action, 10, No. 99-10423, Court of Common Please, Chester County, PA, USA.
35. Revised Arizona Jury Instructions (Civil) 3d Medical Malpractice 1.
36. A.R.S. Section 12–563.

Website