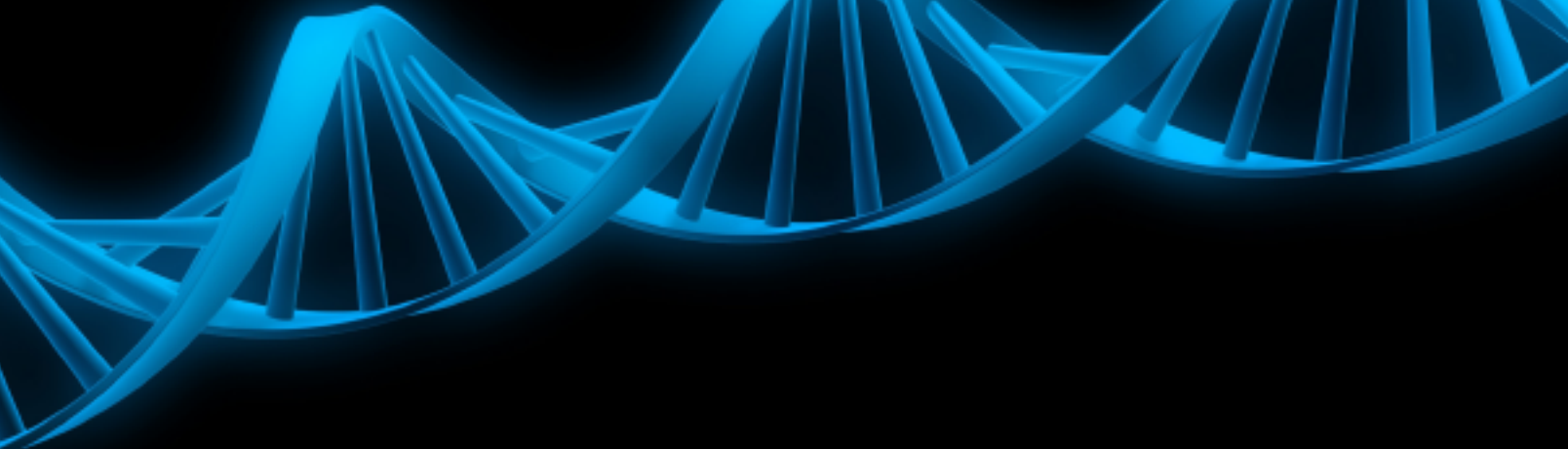Gary E. Marchant, Ph.D. J.D., is the Lincoln Professor of Emerging Technologies, Law & Ethics and Executive Director, Center for the Study of Law, Science & Technology, Sandra Day O'Connor College of Law, Arizona State University.

PERSONALIZED MED

BY GARY E. MARCHANT

ICINE AND THE LAW

It may be an understatement to suggest that health care in the United States is in a state of flux. Whether one looks at the science, the policy, the ethics or the business of medicine, Americans are witnessing changes like they never have in the past. Though many of these trends are affected by the vast numbers of people needing ever-increasing modes of treatment, one trend heads in the other direction: toward a focus on the needs of the individual.

We are on the verge of a fundamental transformation from the "one size fits all" approach of the past to what may be called "personalized medicine." In this approach, pharmaceuticals and other treatments are tailored to an individual's genetic profile. This rapid change under way in the practice of medicine will have profound significance and implications for the practice of law.

In a few important ways, Arizona is poised to be at the forefront of this paradigm shift to personalized medicine (PM) in both its medical and legal contexts.

• The Translational Genomics Research Institute (TGen), which opened in Phoenix in 2002, is one of the nation's leading research institutes in the field of PM.

• Tucson's Critical Path Institute (C-PATH) is at the forefront of improving pharmaceutical development, regulatory approval and post-marketing surveillance using new PM tools.

• The Biodesign Institute at ASU is led by Dr. George Poste, one of the world's foremost experts on PM.

• In January 2006, the Piper Foundation announced a $50 million program to attract to Maricopa County 10 of the world's leading experts in the field of PM.

Arizona is also at the forefront in training the professionals who will be needed to implement the new paradigm of PM. The new downtown Phoenix medical school will include an innovative teaching module in PM. The University of Arizona College of Pharmacy is pioneering a clinical pharmacogenomics program (the basic science underlying PM) for pharmacists-in-training. And ASU's Sandra Day O'Connor College of Law recently launched the world's first LLM degree program for lawyers that specifically focuses on legal aspects of genomics and biotechnology, of which PM is a major emphasis.

So what is personalized medicine, and what are its legal implications?

The Coming Era of Personalized Medicine

Personalized medicine can be described as the right treatment at the right dose at the right time for the right patient with the right disease. In other words, treatments are tailored to the genetic and molecular profile of a specific patient and their disease. As the Director of the National Institutes of Health explained to Congress in his budget request last year, "Our hope is to usher in an era where medicine will be predictive, personalized and pre-emptive."

One major application of PM is pharmacogenetics, which involves customizing drug treatments to the genotype an individual is born with. The genes involved in metabolizing pharmaceuticals (as well as other agents, such as foods and chemicals) turn out to be highly variable or polymorphic, such that we all differ in how we metabolize drugs. In many cases, these genetic variations result in the drug being ineffective in some individuals.

For example, approximately 7 percent to 10 percent of women have a genetic profile that does not allow them to properly metabolize and benefit from the breast cancer drug tamoxifen. Genetic testing can now be used to avoid giving this drug to such women, avoiding the waste of time and money from treating those patients with drugs that will not work for them. This allows them to refocus their treatment on other therapies that may be more effective for their genotype.

Genetic variations not only make any drug ineffective for some patients, but they also make drugs toxic for those patients whose genetic profile causes them to under-metabolize or over-metabolize the drug. One recent study published in the *Journal of the American Medical Association* estimated that more than 100,000 Americans are killed by drug side effects each year, and more than 2 million Americans are hospitalized. Many of these adverse side effects are likely attributable to inherited genetic differences between individuals. For example, almost 10 percent of the population has a gene mutation that affects metabolism of the common anti-clotting drug warfarin and can cause strokes and serious bleeding in those patients. A recent study by FDA staff estimated that genetic testing of all patients prescribed warfarin could avoid 85,000 serious bleeding events and 17,00 strokes annually, and save an estimated $1.1 billion in health care costs.

A second major application of PM is to subcategorize diseases—rather than people—based on genetics. This approach is most developed for cancers, where tumors in each of several types of cancer categorized by tissue of origin (e.g., lymphomas, breast cancers, brain tumors, prostrate cancers) were considered indistinguishable by traditional approaches. New technologies such as DNA microarrays or "gene chips" can measure quickly and relatively inexpensively the changes in genetic content or gene expression in the cancerous cells. These genetic changes show that previously indistinguishable tumors in a particular tissue (e.g., breast cancers) tend to fall into discrete subcategories with very different prognoses, and thus different treatment recommendations.

Two genetic tests are already on the market: Agilent's MammaPrint and Genomic Health Inc.'s Oncotype DX, which predict the risk of tumor recurrence and spread in women treated for breast cancer. These test results are being used to determine whether to follow-up surgery to remove the tumor with chemotherapy to suppress growth of any remaining cancer cells. Chemotherapy is an unpleasant treatment many breast cancer patients do not need, but who could not be identified until now. More than 14,000 of the Oncotype DX tests were purchased last year, and much higher sales are expected this year as insurers expand coverage for such tests and doctors become more knowledgeable about them.

As these examples demonstrate, PM is not just something for the future; it is beginning to affect clinical health care today, especially at the nation's leading health care institutions, including some in Arizona.

The first example of PM in practice is the breast cancer dug herceptin, which is prescribed only for patients with tumors that over-express a specific gene (HER2) involved in cell growth. Drug treatments for some patients with HIV, childhood leukemia, and non-small cell lung cancer are other examples in which the leading health care providers are using genetic testing to personalize drug treatments to avoid potentially life-threatening adverse effects. Commercial tests have been approved by the FDA for testing for variations in drugs that affect drug metabolism, such as Roche's Amplichip© diagnostic test that screens for variations in the gene coding for the drug-metabolizing enzymes CYP2D6 and CYP2C19, which are responsible for metabolizing more than 25 percent of all prescription drugs.

Although PM has demonstrated enormous promise and progress, there remain important impediments and challenges that must be overcome before it can achieve widespread adoption and achieve its full promise. The scientific underpinnings of PM are much more complex than often appreciated, with many gene–gene and gene–environment interactions that complicate the targeting of therapies at specific genetic markers.

Economics is also a major issue, as it is very expensive to identify and validate genetic associations in large, genetically heterogeneous populations. Reimbursement by insurers for genetic tests that may need to accompany drug prescriptions is also uncertain.

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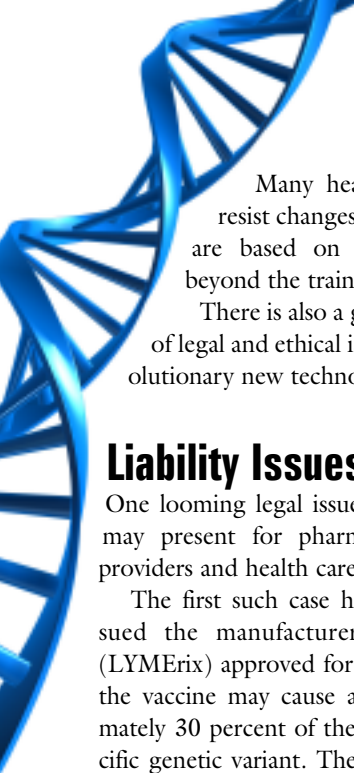
Many health care professionals and institutions resist changes to clinical practice, especially when they are based on molecular genetic knowledge that is beyond the training of many physicians and pharmacists.

There is also a growing realization that PM raises a host of legal and ethical issues that must be navigated for this revolutionary new technology to succeed.

Liability Issues

One looming legal issue is the potential liability risks that PM may present for pharmaceutical manufacturers, genetic test providers and health care professionals.

The first such case has already occurred, in which plaintiffs sued the manufacturer of the only lyme disease vaccine (LYMErix) approved for sale in the United States, claiming that the vaccine may cause a serious adverse effect in the approximately 30 percent of the population who were born with a specific genetic variant. The vaccine manufacturer and federal government disputed the factual predicate of these assertions, but the cases eventually settled, and the vaccine was taken off the market.

All drug manufacturers now routinely collect genetic information of patients enrolled in pharmaceutical clinical studies. A manufacturer may face liability if these data show that certain genotypes are more susceptible to adverse side effects to a drug that is subsequently marketed without adequate genetic warnings. Drug manufacturers are legitimately concerned that genetic data of unknown or ambiguous significance at the time it is collected will be seen in hindsight by a jury in a product liability case many years later, relying on new evidence available at the time of trial, as evidence of a genetic susceptibility for which a warning should have been provided. Drug manufacturers are also concerned that pharmacogenomics will limit the sales of their new blockbuster drugs to specific genotypes within the population, and may be vulnerable to "failure to test" claims if they do not diligently investigate potential genetic susceptibilities to their drugs that may reduce their market by 50 percent or more.

Drug manufacturers do, however, have a number of defenses available to protect them against lawsuits relating to genetic susceptibilities to their products. These include the learned intermediary doctrine, under which the manufacturer is protected from liability if it adequately warns the prescribing physician about potential side effects. Already, manufacturers include genetic information on the warning labels of more than 120 prescription drugs.

Health care professionals are likely the most vulnerable to liability risks associated with PM. State-of-the-art diagnosis, prognosis and treatment of disease will increasingly rely on genetic characterization of the patient and his or her disease. Yet many doctors lack any training in genetics. And even those who have understanding lack the infrastructure and guidance needed to effectively use the pharmacogenomic information that is increasingly appearing on drug labels.

For example, most doctors don't have a genetic counselor available to them, and many genetic tests are not as easily available as other diagnostic tests that doctors routinely order. As the nation's leading medical institutions implement new PM tests and knowledge as they emerge, the standard of care will shift rapidly, leaving many physicians behind. These doctors may increasingly face the risk of lawsuits if they fail to consider genetics adequately when prescribing a drug with known severe side effects or recommend the wrong course of treatment for a tumor with a genetic profile suggesting a different approach.

Regulatory Issues

Personalized medicine is already creating a maze of novel issues in the regulatory approval of pharmaceuticals and genetic tests.

Manufacturers and the FDA are facing challenges in deciding what to do when clinical testing indicates that a drug is only effective, or causes adverse effects, in individuals with a certain genotype:

• Should the drug be approved regardless, but limited to the compatible genotype?
• How will this be achieved, and how can we ensure that people with the wrong genotype don't take the drug if it is allowed on the market?
• How will patients know which genotype they have?
• Will they be required to take a genetic test before being prescribed the drug?
• Should the drug only be approved if the companion genetic test has also been approved?

The FDA's recent approval of the heart drug BiDil only for self-identified African Americans foreshadows some of the controversies and difficulties of a new generation of drugs that may only be safe and effective for some groups in the population.

Just as the regulatory approval of pharmaceuticals raises new issues in the era of PM, the regulation of genetic tests is also controversial.

Despite the recommendations of several government committees that genetic tests need regulatory oversight, most genetic tests currently require no regulatory approval in the United States. Except for the few genetic tests sold as commercial "kits," any laboratory can offer genetic tests that have received no federal government approval. Some companies are already selling pharmacogenomic tests directly to consumers over the Internet without any oversight by regulators or health care professionals.

In September 2006, the FDA proposed to expand its regulatory approval requirements for genetic tests to include PM tests that use proprietary algorithms to produce a diagnosis or prognosis. In response to many criticisms of the initial proposal, the FDA issued a revised draft in July 2007, but the proposal remains controversial, and its final adoption is uncertain.

Intellectual Property

Intellectual property is also a hot issue in PM, with several recent patent disputes ending up in the courts.

Not only are there frequent disputes between companies over who has the patent rights to a particular gene or molecular diagnostic test, but there is also a fundamental tension within the PM industry over the appropriateness and breadth of patents on
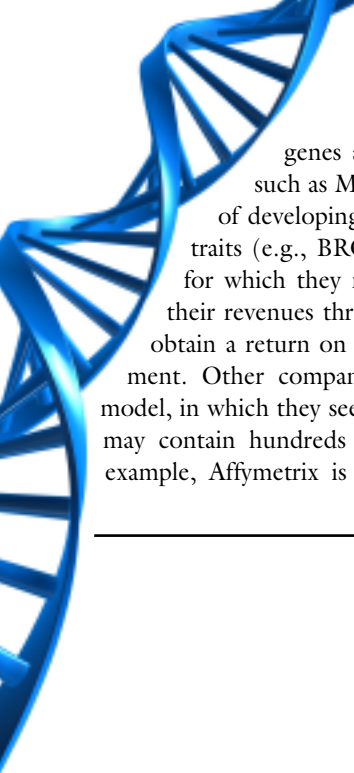
genes and diagnostic tests. Some companies, such as Myriad Genetics, follow a business model of developing genetic tests for one or a few genetic traits (e.g., BRCA1 breast cancer susceptibility gene), for which they rely on patent protection to maximize their revenues through market exclusivity or licensing to obtain a return on their research and development investment. Other companies are pursuing a different business model, in which they seek to offer genetic testing products that may contain hundreds or thousands of different genes. For example, Affymetrix is the industry leader in microarrays or "gene chips," which contain every known gene in the human genome. Obtaining licenses from every individual gene patent holder would be very burdensome for such companies, so these purveyors of multiple gene tests generally oppose the availability of broad patenting rights for individual genes.

Another major subject of discussion and debate is to the extent to which patenting of genes and gene tests promotes or deters PM innovation and implementation.

The traditional view is that patent protection encourages innovation by rewarding inventors with exclusive rights for a limited time to profit from their discovery. Some scholars have sug-

gested that excessive patenting in the genomics field, especially of "upstream" discoveries and research tools, is impeding innovation by creating a "tragedy of the anti-commons" in which a thicket of overlapping patent rights precludes anyone from fully developing the patented technologies.

There have been reports that some university researchers and nonprofit testing facilities have been blocked from pursuing PM by excessive patent licensing fees. Such reports have led to a variety of proposals, including a broadened research exception from patent infringement, restrictions on exclusive licensing, and open source models in the life sciences.

Privacy and Discrimination Concerns

One of the greatest potential impediments to the implementation of PM is the real and perceived risk of genetic discrimination and privacy violations. Many people are reluctant to take advantage of existing genetic tests, such as those for cancer susceptibility genes, out of fear that employers, insurers or other third parties will use that information against the individual.

Although there have been anecdotal reports of genetic discrimination, empirical studies have yet to detect any widespread detrimental use of genetic information, although that could change if genetic testing becomes more widespread. In
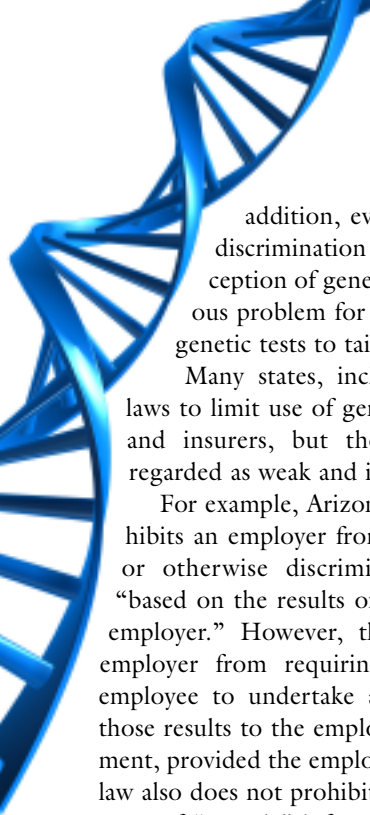
addition, even if the actual risk of genetic discrimination is relatively low, the public perception of genetic discrimination risks is a serious problem for PM, which relies on individual genetic tests to tailor therapies.

Many states, including Arizona, have adopted laws to limit use of genetic information by employers and insurers, but these protections are generally regarded as weak and inconsistent.

For example, Arizona law (A.R.S. § 41-1463) prohibits an employer from refusing to hire, discharging or otherwise discriminating against an individual "based on the results of a genetic test received by the employer." However, this law does not prohibit an employer from requiring an existing or prospective employee to undertake a genetic test and to disclose those results to the employer as a condition for employment, provided the employee "consents" to the test. The law also does not prohibit an employer from using other types of "genetic" information other than a genetic test, such as family history, in making hiring decisions. Arizona law also prohibits insurers from discriminating against pre-symptomatic individuals based on genetic information (A.R.S. § 20-448), but it provides no protection to an individual who has been diagnosed with a genetic condition that is associated with a higher rate of claims.

Congress has been considering federal legislation to prohibit genetic discrimination for almost a decade, but it appears that Congress may be poisied to finally enact the Genetic Information Nondiscrimination Act (GINA); the House passed its version of the bill in April 2007 by a vote of 220 to only 3 against. Of course, legislation banning discrimination will not end all abuse, as we have seen with attempts to ban racial, sexual and age discrimination. Moreover, as we have seen with frequent privacy breaches involving financial information databases, there will continue to be the potential for accidental or malicious releases of private genetic information collected in large PM genetic databases. Nevertheless, the enactment of federal legislation will likely go a long way in assuring the public against the real and perceived risks of genetic discrimination.

Genetic Samples

The medical research underlying PM generally consists of looking for associations between genetic markers and health outcomes in large populations of people. These studies therefore require the availability of large numbers of genetic samples donated by research volunteers and patients.

Many legal and ethical issues are raised by how these samples are obtained and used. Tissue donors are required to give their informed consent for any research use of their genetic information. And that can provide a cause for contention. For example, the Havasupai tribe in Arizona and some individual tribal members sued Arizona State University because researchers allegedly used genetic samples from tribal members

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for research studies outside the scope of their informed consent. In April, the superior court dismissed the remaining claims of the tribe's suit on a technicality, which the tribe is appealing; the separate lawsuit by individual tribal members is awaiting trial.

There are unresolved issues about whether researchers can ask tissue donors to consent to any future use of their tissue, when many of those uses cannot be anticipated in advance. Also unresolved is whether and when researchers have a legal or ethical duty to report back genetic risks and medical advice to tissue donors, and have a duty to re-contact the donors if new information becomes available in the future.

Other controversies (and lawsuits) have recently arisen when researchers have obtained patents from gene discoveries using tissue samples from donors who were not informed that their genetic information would be used by the researchers to obtain patents. Other disputes (and again lawsuits) have involved who owns genetic samples donated to research: the donors, the researchers or the research institutes that employ the researchers. To date, the research institutes have prevailed, but more litigation is expected on this question, as is the case for most of the topics in this brief review.

Conclusion

Personalized medicine will present many legal issues. In some cases, those issues will serve as an impediment to the implementation of PM, such as regulatory hurdles or patent thickets. In other cases, legal issues, and in particular the potential for liability for both manufacturers and physicians, may serve as a powerful driver speeding the adoption of PM.

Most lawyers practicing today received no training in law school on the legal aspects of genetics, just as many doctors who graduated from medical school until very recently received little or no training in genetics. To meet the growing need for genetically sophisticated lawyers, the Sandra Day O'Connor College of Law recently launched the nation's first LLM degree program in legal aspects of genomics and biotechnology. Just as the practice of medicine will change dramatically over the next decade as PM becomes the new dominant model for health care delivery, so too will the practice of law need to change dramatically to address the challenge and reality of PM. Skilled, trained practitioners will be needed in both fields to realize the enormous potential of personalized medicine. AZ AT