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Liability Issues in Pharmacogenomics

*Mark A. Rothstein**

Liability concerns involving pharmacogenomics inevitably raise broad issues of ethics and policy. The first of these issues, often called “genetic exceptionalism,” deals with whether genetic information is so unique that it should be considered separately from other medical information. In other words, is there something different about pharmacogenomics as opposed to any other pharmaceutical research discipline? Is there something unique about drug development strategies and drug regulation involving pharmacogenomics compared with traditional drug development strategies and regulations? Is there something different about liability issues for manufacturers and health care providers involved with this technology? These questions will inform our analysis of pharmacogenomics.

Another important, overarching issue is the effect on liability of increasingly sophisticated medical technologies. In medicine, the more that health care providers attempt or promise they can do, the greater the likelihood that patients and their family members will be disappointed after an adverse outcome. Disappointment, personal loss, and high health care expenses sometimes translate into lawsuits. But, I am getting ahead of myself, and first I want to trace the ethical, policy, and potential liability issues all the way back to the research stage.

Let us assume that I am the CEO of a large biotech or pharmaceutical company engaged in research on a certain disease. Scientists working for my company discover that there are ten common polymorphisms of a particularly promising drug target. We can design drugs to attack one, two, or maybe three of these polymorphisms, but it would be prohibitively expensive to design a drug strategy and do research on all ten gene variations. How do I decide which polymorphism to pursue? If I am a savvy CEO, the first thing I am going to ask is, “Tell me what the market is for each of these ten potential drug targets.” I want to know more than simply the overall population frequency; I want to know who these people are. Are they likely to be well-insured, or otherwise have money? Where do they live? If they live in developing countries, I doubt I would be interested in spending one hundred million

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J.D., Herbert F. Boehl Chair of Law & Med. & Dir., Inst. for Bioethics, Health Policy & Law, University of Louisville School of Medicine. This work is based upon a live presentation made on February 5, 2004, and does not necessarily reflect events and changes thereafter.

dollars on research and development (“R&D”) to make a product that few potential customers could afford to buy.

From the standpoint of distributional ethics, how do we decide what drug targets are appropriate? The answer involves more than simply rich and poor. It may be a matter of numbers. As a drug company CEO, I’m also not interested in spending money to find drugs for rare genotypes—what may be called “orphan genotypes.” Should public policy be formulated to try to promote the research and development of drugs aimed at rare genetic variations? One possibility is to enact legislation along the lines of the Orphan Drug Act¹ to help subsidize such drug development.

As for liability, the two main legal theories likely to be raised by individuals who allege that they were injured by taking a pharmacogenomic-based medication are products liability and negligence. Products liability would be used in actions against manufacturers and retailers of pharmaceutical products.² For those of you not familiar with the concept of products liability, it is liability without fault. That means there is no requirement that the injured party prove the manufacturer failed to exercise reasonable care in designing or manufacturing the drug.³ The main theory behind strict liability for dangerously defective products is that the costs of injuries are allocated to the manufacturers of the products, who are more able to bear the costs and pass them on to the ultimate consumers of the products. In this way, the costs of injuries are distributed among all users rather than the unfortunate ones with adverse outcomes.⁴ Negligence is the most likely legal theory on which to base a lawsuit against a health care professional who erroneously prescribed a particular pharmaceutical product. In such a case, the allegations would be similar to those in medical malpractice cases—that the health care provider failed to meet a reasonable standard of care.⁵

Another legal theory that could be used in lawsuits against pharmaceutical companies is failure to warn.⁶ Manufacturers have a legal duty to warn consumers of dangers flowing from both the intended uses of their product and the foreseeable misuses of their product.⁷ Did you ever wonder why ladder manufacturers put a

1. 21 U.S.C. §§ 360aa-360ee (2004).

2. Larry I. Palmer, *Medical Liability for Pharmacogenomics, Pharmacogenomics: Social, Ethical, and Clinical Dimensions* (Mark A. Rothstein ed., 2003).

3. David G. Owen, *Products Liability Law* 249 (2005).

4. 2 Dan B. Dobbs, *The Law of Torts*, 976-77 (2000).

5. 1 Dan B. Dobbs, *The Law of Torts*, 632-33 (2000).

6. Owen, *supra* note 3, at 564.

7. *Id.* at 853.

warning on the little ledge that holds the paint can that says, "This is not a step?" The answer is that, even though it is a foolish thing to do, it is foreseeable that someone will try to use the ledge as a step, fall off, and suffer serious injuries. The law has developed to hold that if a product's misuse is foreseeable, then the manufacturer may be liable if it failed to take steps to protect the consumer, including warnings about the dangers of misusing the product. In the pharmaceutical setting, manufacturers satisfy the duty to warn through warning labels, package inserts, and product descriptions in the Physician's Desk Reference.

Although research in pharmacogenomics has a long way to go, there is already litigation in this area. Pharmacogenomic-based products are not a prerequisite for pharmacogenomic-inspired litigation. As soon as it is possible to detect varied response to a pharmaceutical product, manufacturers may have a duty to inform potential users of that variation and suggest that they undergo genetic testing, even though there is no special product, special dosage, or other attempt to target the product to a particular genotype.⁸ Here, the duty to warn involves warnings about potential adverse events identifiable by genetic testing.

An important concept in failure to warn cases is the "learned intermediary doctrine."⁹ This doctrine is premised on the fact that, with a prescription drug, there are at least two levels of professionals between the patient and the product—the prescribing physician and the distributing pharmacist. Pharmaceutical companies have a reasonable expectation that the patient will be told by a prescribing physician how to take the prescription and that there will be directions given to the patient by the pharmacist—how many pills to take, what time of day, with or without food, etc. The defendant-manufacturer may rely on these other professionals to provide instructions as long as the learned intermediaries themselves have been given sufficient information about what to tell the patient.

Another important issue in pharmaceutical litigation involves off-label uses. The Food and Drug Administration (FDA) does not regulate the practice of medicine; it regulates drugs and devices. The FDA is not in the business of telling physicians for what conditions they can prescribe medications. The main exceptions involve information the FDA compels manufacturers to put on the

8. Mark A. Rothstein, Epilogue: Policy Prescriptions, *Pharmacogenomics: Social, Ethical, and Clinical Dimensions* 327 (Mark A. Rothstein ed., 2003).

9. James O. Castagnera et al., *The Gradual Enfeeblement of the Learned Intermediary Rule and the Argument in Favor of Abandoning It Entirely*, 36 *Tort & Ins. L.J.* 119 (2000–2001).

label or package insert, and "Dear Doctor" letters advising physicians of newly discovered problems involving certain medications. Therefore, if a physician thinks that a medication for asthma will work wonders for patients with diabetes, the FDA is not going to limit the ability of the physician to prescribe this so-called off-label use. Nevertheless, if a manufacturer promotes a harmful off-label use, then the manufacturer may be found liable.¹⁰ There have been instances where a manufacturer has "winked" at an off-label use because the use greatly increased the market for the product. In the future, it is at least theoretically possible that a pharmaceutical company, that has invested millions of dollars for a genetically-limited drug, would have an incentive to encourage wider off-label use.

Direct-to-consumer (DTC) advertising¹¹ poses yet another liability issue. It is difficult to imagine that it is only in the last ten years that there has been such a seemingly endless barrage of commercials during the evening news for new pharmaceutical products. Manufacturers have realized that DTC advertising is a very effective way to stimulate demand for their products. Now, I have to admit that some of these commercials absolutely baffle me. They must work or the drug companies would not spend such great sums of money making and airing them, but sometimes I don't see the point of advertising directly to consumers. One product that comes to mind is Procrit. The voiceover says something like: "Are you undergoing chemotherapy? Are you weak? Do you have anemia? Do you have a hard time walking? Ask your doctor about Procrit." I can't help but think, if I am on chemotherapy and having those problems, my doctor had better not wait for me to tell him or her about medications to alleviate such debilitating symptoms. At any rate, absent a regulatory change, DTC advertising is not going away, and it is likely to be increasingly important for a wide range of pharmaceutical products.

The intersection of DTC advertising and pharmacogenomics raises some important ethical issues involving race and ethnicity. Scientists may well discover certain individuals in certain culturally defined groups who have a much higher incidence of X, Y, or Z condition. They may also discover that some treatments work better for people with certain genotypes linked in one way or another to a certain ethnic group. And I can imagine the

10. Margaret Gilhooley, *When Drugs Are Safer for Some But Not Others: The FDA Experience and Alternatives for Products Liability*, 36 *Hou. L. Rev.* 927, 939 (1999).

11. Food and Drug Administration, *Final Guidance on Direct-to-Consumer Advertising*, 64 *Fed. Reg.* 43, 197 (1999).

announcers on the commercials asking: "Are you African-American? Do you have hypertension? My company has just developed a new drug for you." Or: "Are you of Hispanic origin? Do you have diabetes? We've got a drug for you." And I think this would be just awful in terms of fostering the public's misunderstanding of the relationship between genotype, "race and ethnicity," and adverse drug reactions in certain groups. Unfortunately, I can see it happening unless we are careful.

I also think that post-marketing surveillance may be increasingly important as there are more clinical trials involving genotype-matched subjects. Compliance by pharmaceutical manufacturers with their post-marketing surveillance obligations has been lagging.¹² Many experts believe that clinical trials in smaller and genetically homogeneous cohorts may miss potentially adverse drug events. Therefore, post-marketing surveillance will be increasingly important.

One last type of pharmacogenomics inspired lawsuit might arise out of the use of home testing kits to detect pharmacogenomic variations. It does not take too much imagination to contemplate the sale of such a product, perhaps with instructions to match your dosage to blue, red, purple, or whatever color your sample turns. I think we need to be very careful before we turn every residential bathroom into a clinical pharmacogenomics laboratory. I think it is reasonable to predict that adverse events from such do-it-yourself pharmacy practice will inevitably result in litigation.

The preceding discussion has focused on special litigation issues raised by pharmacogenomics. In addition, "traditional" personal injury lawsuits may implicate pharmacogenomics. For example, managed care organizations (MCOs) often adopt formularies of medications for which they will provide payment under a particular health plan. The decisions whether to include a pharmaceutical product on a formulary are extremely important to the diffusion of any new product. Without reimbursement, the uptake of the technology will be low because people do not like to pay out-of-pocket. MCOs will have to undertake a drug-by-drug cost-benefit analysis to determine whether a pharmacogenomic test to identify differential drug response and prescribing the new drug indicated by the test are cost-effective. For example, a drug may be ten percent more efficacious, but cost twenty times more than standard therapy. The decision whether to cover the new drug will be based on the degree of efficacy of standard therapy, the nature

12. Food and Drug Administration, Report to Congress on Postmarketing Studies (2003), available at www.fda.gov/cber/fdama/pstmrktfdama130.htm.

of the condition, the degree to which timing is essential to treatment, and numerous other factors. Suppose that the formulary does not include a certain drug because the MCO has determined that the benefits are not significant when compared with the cost. Does the physician have an obligation to tell the patient the following: "There is another drug that studies show may be a little bit more effective, but it is much more expensive, and your health plan does not pay for it. So, if you want that drug, I will write you a prescription, but keep in mind that it will cost you around \$400 a month for this drug, and the other would be completely paid for by your insurance." Would there be liability for the physician who fails to provide this information when the patient does not get better using the formulary medication?

If current trends continue, one of the most likely ways we are going to see pharmacogenomic testing introduced commercially is to rule out certain drugs that would cause side-effects to the patient. I suspect that before we actually have replacement drugs, some of these tests will be used as a safety screen. If physicians fail to use them and an adverse event occurs, there could be liability. A fundamental question is whether physicians have the training to incorporate these tests and products into their practices. In the past, medical genetics was largely the domain of obstetricians, pediatricians, and a handful of specialties besides the genetics field itself. In the future, pharmacogenomics will be integrated into all medical specialties and in the practices of generalists as well. For example, in the future internists may be unlikely to prescribe medications for diabetes or hypertension unless the patient first undergoes some pharmacogenomic analysis. Clinical pharmacogenomics may also increase the responsibilities of clinical laboratories. Who is going to teach and attend all of those Continuing Medical Education programs? And how much information will a laboratory have to report to an ordering physician about the outcome of the test?

Another potential source of malpractice liability for physicians, nurses, and pharmacists is the failure to provide genetic counseling.¹³ Keep in mind that counseling for pharmacogenomics would not be the typical genetic counseling—for example, before someone decides to take a cystic fibrosis carrier test. But, even beyond medicinal and psychological implications, the outcomes of these tests could bring about negative economic consequences to the patient by adding information to the individual's health record that he or she is more difficult or expensive to treat.

13. Ellen Wright Clayton, *Ethical, Legal and Social Implications of Genetic Medicine*, 349 *New Eng. J. Med.* 562 (2003).

The economics of genetic testing are also likely to raise more challenges for genetic counseling. For the cost of testing for a single pharmacogenomic variation, why not test for 1,000 or 10,000 polymorphisms and build the record for future medicinal needs? How can a health care provider get informed consent for so many tests being run at the same time? Today, a single informed consent is used for multi-test panels; should a different approach be used with genetic or pharmacogenomic tests? When considering genetic counseling in the primary care setting, an important question that comes to mind is: Who is going to do this? Who has time for it? Who is going to reimburse for the counseling? Because the answer to all of these questions is usually "nobody," it is essential to identify other mechanisms to assist with the counseling function, including web-based education, interactive CDs, and so forth. Keep in mind that people tend not to understand probability and risk, and they do not understand concepts like expressivity, penetrance, and latency. Consequently, genetic counseling is highly complex.

Another potential source of malpractice liability is the failure to provide warnings to at-risk relatives. A few years ago, the American Society of Human Genetics issued a statement that it would be permissible for physicians and non-physician geneticists to warn at-risk relatives when a patient's refusal to warn could result in imminent harm.¹⁴ It is not clear whether this advice remains valuable in light of the Privacy Rule promulgated under the Health Insurance Portability and Accountability Act (HIPAA).¹⁵

It also remains to be seen whether personal injury lawsuits based on alleged failure to properly prescribe, dose, dispense, and administer medications will increase as a result of the growing availability of pharmacogenomic based drugs. If so, there could well be a significant increase in the potential liability of pharmacists and nurses as well as physicians. Of course, no plaintiff is going to sue a nurse rather than a physician unless the nurse's wrongdoing means liability for a hospital. After all, pharmacogenomics is unlikely to change the need for a malpractice plaintiff to find a deep pocket.

As in other aspects of health care, concerns about liability may prove to be a key factor that drives the adoption of pharmacogenomic tests and medications. Consider the following

14. ASHG Social Issues Subcommittee on Familial Disclosure, Professional Disclosure of Familial Genetic Information, 62 *Am. J. Hum. Genet.* 474 (1998).

15. 45 C.F.R. pts. 160, 164 (2005).

example: the adoption of non-ionic contrasts in IVPs¹⁶ and other imaging procedures. It is well known that a small percentage of the population is allergic to iodine-based (“ionic”) solutions and a small number of individuals have even gone into anaphylactic shock and died. Moreover, when first introduced to the market in the 1980s, non-ionic contrasts cost about one hundred dollars for a sixty cc. bottle, whereas ionic contrasts cost about six dollars.¹⁷ Why, then, would there be an immediate move to adopt the more expensive contrasts? Imagine a courtroom and a radiologist is being sued for the wrongful death of a patient who died after a severe reaction to an ionic contrast. The plaintiff’s lawyer’s questioning of the defendant might go something like this: “Now, Dr. Jones, isn’t it a fact that Mr. Smith would be alive today if you spent an additional ninety-four dollars to give him the safest available contrast solution? Do you think Mr. Smith’s life was worth ninety-four dollars?” The point is clear. Obviously, physicians don’t want their patients to suffer adverse reactions, but they also don’t want to be in the position of defending their failure to provide the best care because of a relatively small difference in cost for each patient, notwithstanding the aggregate effect on health care expenditures. I think it is easy to extend this thinking to new, presumably more expensive, pharmacogenomic therapies.

I want to close by emphasizing the importance of not losing sight of the big picture. First, we would be remiss if we allowed liability concerns to paralyze either drug development or the clinical introduction of safer and more effective pharmacogenomic medications. Although the liability issues I have mentioned are potential impediments, they are not insurmountable. Second, we must remember the overall state of access to prescription medications. We are in the process of creating potentially more exotic and more expensive medications at a time when millions of people in the United States and billions of people worldwide lack access to the cheap, off-patent medications that have been around for years. We must continue to work to ensure that people everywhere have access to medications that make a significant, proven difference in human health while simultaneously researching pharmacogenomics.

16. An intravenous pyelogram is an x-ray examination of the kidneys, ureters, and urinary bladder. Radiological Society of North America, Intravenous Pyelogram (IVP) Radiography (X-Ray), www.radiologyinfo.org/content/ivp_radiology.htm.

17. Frank E. James, *Doctors Debate Use in Tests of Safer but Costlier Dyes*, Wall St. J., Dec. 2, 1988.