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The Regulatory, Economic, and Privacy Implications of Pharmacogenomics

PATRICIA M. FESTIN†

ABSTRACT

The Human Genome Project was a seminal achievement that launched a revolution in science. This revolution is significantly impacting the pharmaceutical industry and drug discovery research. Pharmacogenomics—the study of how genetic differences influence the variability in patients' responses to drugs—complicates our understanding of the economic, regulatory, and policy issues that plague both the pharmaceutical industry and the social and legal mechanisms governing drug-related health care. This Article surveys the debate surrounding these challenges.

† Associate with the Fish & Neave Intellectual Property Group at Ropes & Gray in New York. J.D., Duke University School of Law, 2004. M.A. in English, Duke University, 2004. B.S. in Biochemistry, B.A. in Chemistry, B.A. in English, North Carolina State University, 1998. Research Associate with GlaxoSmithKline from 1998-2001.

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I. INTRODUCTION

¶ 1 The pharmaceutical industry's business practices are undergoing a drastic change that will significantly impact medical care in this country. Across the board, pharmaceutical companies are consolidating[1] in order to meet ever-increasing shareholder expectations in a highly competitive industry. This competition comes not only from large peer corporations but also increasingly from small biotechnology companies—companies that have dismantled big pharma's pipeline and found faster, cheaper, and better methods of performing particular subcomponents of the drug development process.[2] Technology transfer offices in Research I universities[3] across the country have become more savvy to the benefits of Bayh-Dole reform[4] and now exploit their faculty members' intellectual contributions through patent protection instead of freely sharing information with colleagues and corporate partners.[5] To further complicate matters, the intellectual property landscape has seen better days. A once-rich source of additional rents has been blunted by an increase in upstream research tool patenting that has created a patent "thicket,"[6] which makes it almost impossible to employ colleagues' techniques to push development forward.

¶ 2 This marked increase in upstream research patenting arguably finds its cause in

1. ERNST & YOUNG, RESILIENCE: AMERICA'S BIOTECHNOLOGY REPORT 5-6 (2003).
2. *Big Trouble for Big Pharma*, ECONOMIST, Dec. 6, 2003, at 56.
3. Research I universities, as defined by the Carnegie Foundation for the Advancement of Teaching classification system published in 1994, include universities that receive at least $40 million in federal funding per year and award at least fifty doctorate degrees. *See Carnegie Research I Universities*, *available at* http://www.washington.edu/tools/universities94.html (last visited Jan. 10, 2005).
4. The Bayh-Dole Act allows institutions to exert control over inventions funded by federal grant money. *See* Pub. L. No. 96-517, § 6(a), 94 Stat. 3015, 3019-28 (1980) (codified as amended at 35 U.S.C. §§ 200-212 (2004)). *See also The Bayh-Dole Act*, *at* http://www.cptech.org/ip/health/bd/ (last visited Jan. 10, 2005).
5. *See* Margaret Cronin Fisk, *Ivory Towers Fire Back over Patents*, 25 NAT'L L.J. A1 (2002) (highlighting several litigation suits between universities and corporate partners over intellectual property rights and collaborations).
6. *See generally* Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard-Setting*, *available at* http://haas.berkeley.edu/~shapiro/thicket.pdf (last visited Jan. 10, 2005) (discussing market solutions to patent anticommons problems).

Craig Ventor's (i.e., Celera's) recent race to beat Francis Collins and the Human Genome Project[7] in decoding the human genome and in establishing proprietary rights over human gene sequences.[8] Not only did this seminal achievement launch a cultural change in the scientific community's patent practices, the substantive results of the project launched a platform for new drug discovery. Instead of the largely serendipitous ways in which drugs are matched to patients, the elucidation[9] of the human genome enables pharmaceutical companies to determine ex ante whether or not a drug will be effective for a certain segment of the population through a process called pharmacogenomics or pharmacogenetics.[10] "Pharmacogenetics is the study of how genetic differences influence the variability in patients' responses to drugs."[11] The hope is that this additional genetic information will streamline and improve the accuracy with which drugs are matched to patients, in contrast to the current situation, where thousands of patients who exhibit disease symptoms for which a drug is indicated can realize none of its treatment benefits due to genetic incompatibility.

¶ 3 The transition in drug treatment to a pharmacogenomics-focused regime raises several significant issues for an industry already overwrought with economic, regulatory, and policy hurdles. This Article intends to tease out the issues from these different perspectives. Part I provides a brief overview of the practices that pharmaceutical companies currently employ and how these practices will change with a pharmacogenomics program. Part II focuses on the intellectual property issues that will arise from a pharmacogenomics research and development effort. Part III scrutinizes the regulatory arena. The regulatory barriers faced by drug and pharmaceutical companies are already significant; the implementation of pharmacogenomic strategies will only further complicate that process. Part IV discusses the economic implications of incorporating pharmacogenomic technologies into the market. From a purely market-oriented point of view, the effects of pharmacogenomics will serve to expand the drug market and capture niche markets that have heretofore remained neglected. Finally, Part V assesses what market economics and regulatory policies will ultimately fail to address: the privacy rights of the individual patient. While patients will benefit from this new technology, there are also significant costs, primarily in the form of upholding legal rights, and it is difficult to say who will bear the burden of protecting the rights of the patient.

II. BACKGROUND

¶ 4 When I was soon-to-be a college graduate, I interviewed with the man who would

7. The Human Genome Project was the successful effort to decode the entire human genome. The project was coordinated by the U.S. Department of Energy and the National Institutes of Health (NIH). *See generally* U.S. Department of Energy, *Human Genome Project Information*, *available at* http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml (last visited Jan. 10, 2005).

8. Eliot Marshall, *Sharing the Glory, Not the Credit*, 291 SCIENCE 1189, 1189 (2001).

9. To use the term "elucidation" here is relative—even though the sequence of the human genome has been elucidated, the genes and their functions from this sequence data are far from reaching elucidation.

10. While Allen Roses, *infra* note 11, distinguishes the terms, I will use them interchangeably here.

11. Allen D. Roses, *Pharmacogenetics and the Practice of Medicine*, 405 NATURE 857, 857 (2000).

later become my supervisor at GlaxoSmithKline.[12] In response to my question about what exactly it was that his R&D group did, he replied that they developed and ran screening assays. I had never heard of screening before. I was surprised to learn that with an army of employees, including some of the best scientists in the world, pharmaceutical companies still employed a serendipitous process for developing drugs. They do not take a disease, learn it inside out, and design a drug to address the aberrant proteins in the biochemical process implicated. Rather, pharmaceutical companies know relatively little about diseases. They know enough to identify active groups on small molecules that will affect active sites on the target receptors participating in the disease process, and they hope that these small molecules—agonists and antagonists[13]—will trigger some sort of reaction.

¶ 5 Scientists screen hundreds of thousands of these small molecules against cell receptors that play a crucial role in a disease. Once they identify small molecules that affect the receptor, scientists push these "hits" down the drug development pipeline, first testing for toxicity *in vitro*, followed by testing *in vivo* in animal models, and once they establish proof of concept, eventual testing in humans.[14] As they progress down the pipeline, successful hits become "leads" and successful leads become "candidates." The lion's share of hits fall off the development pipeline along the way due to inefficacy,[15] toxicity, or because they are not orally bioavailable.[16] Only a scant few make it to clinical trials. Even though candidate drugs go through a significant number of obstacles to reach the clinical trial stage, there is no guarantee that they will be effective against the intended disease in human subjects. Some patients may experience miraculous, life-changing results, while others might see no change at all or experience adverse events. Sometimes the potential benefit of a drug for thousands of patients is completely eclipsed by a few adverse cases, particularly if a trial participant dies as a result of the trial.[17] In order to protect the public, the Food and Drug Administration (FDA) often pulls such a drug off the market completely, even when it confers significant life-changing benefits to a large portion of the population.[18]

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12. At the time of the interview in the spring of 1998, the company was then GlaxoWellcome, the result of a recent merger between Glaxo and Burroughs Wellcome.

13. Agonists mimic the action of an endogenous (i.e., naturally-occurring) substance, whereas antagonists block the action of the endogenous substance by inhibiting the normal process of binding to the relevant receptor.

14. *In vitro* refers to artificial experimental environments, such as cell cultures or isolated protein-protein interactions. *In vivo* means the experiment occurs within a natural living environment, such as a plant or animal, including humans.

15. Efficacy refers to the maximum effect able to be produced by a drug. Efficacy is different from potency, which is used when describing the relative effects of two drugs. If Drug A produces a greater effect than Drug B at a particular dosage level, then Drug A is more potent.

16. Bioavailability refers to the degree to which a substance, such as the active ingredient in an orally-administered pill, is absorbed into the body and subsequently made available to perform its intended function.

17. *See, e.g.*, Press Release, GlaxoSmithKline, Glaxo Wellcome Withdraws Lotronex from the US Market (Nov. 28, 2000), *available at* http://www.gsk.com/press_archive/mn_PR975485699.htm (last viewed Jan. 10, 2005) (discussing the incidence of rare fatalities that occurred with use of Lotronex for irritable bowel syndrome, where Lotronex otherwise brought life-changing beneficial results to thousands of women plagued with the disease).

18. *Id.*

¶ 6 What has confounded the pharmaceutical industry for so long is why one segment of a given test group responds favorably to a drug while another segment exhibiting the same exact disease symptoms experiences no change or adverse reactions to that same drug. If companies were somehow able to parse out the differences between these populations, companies would be better able to understand the disease and to deliver the appropriate drug to the appropriate patient. The industry believes that pharmacogenomics is the solution to this puzzle.

¶ 7 One way of determining the source of discrepancy in reactions to a drug among patients lies in understanding at the genetic level. One of the holy grails that pharmaceutical companies are pursuing is the ability to profile a patient and determine ex ante whether or not a putative drug will be efficacious for their particular variation of the target disease. This would enable researchers to exclude patients likely to experience no benefit or even adverse events from a clinical trial. Similarly, patients whose disease symptoms class them in a general group could be further classified into a more specific subgroup where a drug may be particularly suited to their genetic makeup. The drug companies hope the result is that the right medicine will get to the right patients and that the patients who would not benefit from a medicine would be spared the cost of purchasing a drug that does not work for them.

¶ 8 Patients will also benefit from pharmaceutical companies' ability to streamline their drug development process and illuminate variations on diseases so that concurrent therapies can be developed.[19] This will save a significant amount of time and money and will presumably deliver effective drugs to the marketplace more quickly and for a lower price. Pharmacogenomics streamlines the drug development process on two levels. First, it determines whether or not a patient has a genetic makeup conducive to metabolizing the drug candidate in the trial. In addition to the active ingredient that works directly on the intended indication, there are ingredients in a drug that render it orally bioavailable to the patient. Ideally, a drug is taken orally, survives the digestive enzymes in the stomach, and stays intact long enough to reach the bloodstream.[20] Once the drug reaches the bloodstream, the biochemical processes that actually break it down, or *metabolize* it, determine whether or not the drug will be effective. It may be that the active ingredient in a drug works in any given patient, but if she cannot metabolize the drug into the active compound, then the drug passes right through without being metabolized into the active compound. Genetics plays an important role in determining whether or not a patient has the requisite genes that encode for the enzymes essential to that metabolic process. Implementing an initial screening for these requisite genes would help drug companies determine whether or not the patient is capable of accessing the active form of the drug.

¶ 9 Secondly, at a fundamental, more complex level, scientists will use genetics to determine variations within diseases themselves. Instead of identifying and classifying

19. Roses, *supra* note 11, at 857.

20. Other delivery mechanisms include inhalation, injection, and topical application, and depending on the type of drug and the condition to be treated, these may be advantageous or disadvantageous drug delivery systems.

diseases based on their symptoms, also known as phenotypes, they would look to diseases' genes, or genotypes, since "many of the diseases that we classify clinically may be syndromes with several distinct contributing pathogenic mechanisms."[21] For example, Type II diabetes is an exceedingly complex disease with innumerable possible metabolic points of breakdown. Multiple biochemical pathways are implicated in diabetes; any given reaction of the many that occur along these pathways may serve as the break in the chain that leads to diabetes. Two 7TM receptors[22] implicated in diabetes are glucagon and GLP-1.[23] A potential diabetes drug may be selective for the glucagon receptor and thus be ineffective against the GLP-1 receptor. Of two diabetic patients signed up for a study testing the glucagon-selective drug, one may have diabetes resulting from a malfunctioning glucagon receptor and have an otherwise fully-functioning GLP-1 receptor, while the other may have diabetes resulting from a malfunctioning GLP-1 receptor but have an otherwise fully-functioning glucagon receptor. Assuming no adverse reactions, the glucagon-selective drug would be effective in the former but not the latter. If a drug company could screen the two patients to determine whether or not the problem stemmed from a glucagon receptor malfunction, it could target those individuals with faulty glucagon receptor production and exclude other individuals for whom the drug would not work. Accordingly, "[p]harmacogenetics will enable individuals to be classified according to their likely response to a medicine. . . . [This] will expand the population to those who can be helped but might have otherwise been missed because their clinical syndrome did not fit neatly into a traditional disease category."[24] Moreover, pharmacogenomics will aid in uncovering multiple indications for a particular drug.[25] Essentially, diseases that appeared to be unrelated could be found to share underlying causes and mechanisms through understanding the genetic basis of patient response to treatment.[26]

¶ 10 There are two practical ways a pharmaceutical company would conduct this kind of research. "Discovery *genetics* uses human disease populations to identify disease-related susceptibility genes."[27] In contrast, "[d]iscovery *genomics* uses the increasing number of databases of DNA sequence information to identify genes and families of genes for tractable or screenable targets that are not known to be genetically related to disease."[28] As Allen Roses distinguishes the terms, genetics is the traditional study of population genetics, while genomics involves mining DNA information, an effort called *in silico* testing, which marks the evolutionary trend of the industry to go exclusively from *in vivo* studies to including *in vitro* studies.[29]

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21. Roses, *supra* note 11, at 860.

22. 7TM, or seven-transmembrane, receptors are integrated G-proteins that cross the cell membrane 7 times.

23. GLP-1 is one of a group of "Glucagon-Like Proteins." Despite its similar name to "glucagon," it is a wholly different protein.

24. Roses, *supra* note 11, at 860.

25. *See id. See also* Barbara Ann Binzak, *How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process*, 58 FOOD & DRUG L.J. 103, 113 (2003).

26. Roses, *supra* note 11, at 860.

27. *Id.* at 858 (emphasis added).

28. *Id*. (emphasis added).

29. *Id.*

¶ 11 The Human Genome Project makes the entire human genome available for extensive computative analysis. Thus, creating algorithmic models that mine databases of DNA sequence information—a crude definition for the field of *bioinformatics*[30]—will be much cheaper and less resource-intensive than working with *in vitro* cell models and *in vivo* animal models to gather the same data. These traditional models will not drop out altogether, since at some point, a drug must be tested in relatively simplified environments before being tested in humans. However, the need for testing in cells and animals will markedly decrease if most of the preliminary data can be gathered via bioinformatics research efforts.

III. PHARMACOGENOMICS AND INTELLECTUAL PROPERTY

¶ 12 The pharmaceutical industry is highly dependent on intellectual property law.[31] Small molecules are a largely imitable product[32] and the cost of R&D is astronomical in proportion to the handful of drugs that make it to market. Strong intellectual property rights, specifically patents, are necessary to prevent an otherwise abysmal likely rate of return on investment.[33] Without patent protection, the incentive to invest in innovation or to continue to bring drugs to the market would be undermined, since someone else could easily reap the rewards for seeds that he has not sown (i.e., free ride).[34]

¶ 13 Usually a drug patent has only a few years remaining in its term of exclusivity by the time the drug actually goes to market. For a blockbuster drug, this period is usually enough to recoup the pharmaceutical company's investment and make enough profit in order to keep its R&D programs going. Because this model of extracting monopoly rents from the marketplace has been so successful, we have witnessed an increasing incidence of patenting farther and farther upstream in basic research.[35] In the pharmaceutical industry, one of the forms of upstream research is gene patenting. A pharmaceutical company with a patent on a gene or the DNA sequence of part of a gene can easily coordinate all the research efforts regarding the study of that gene and ensure that there are no duplicative efforts.[36] However, this upstream research is often fundamental to an

30. For a general discussion of bioinformatics, see David S. Roos, *Bioinformatics–Trying to Swim in a Sea of Data*, 291 SCIENCE 1260 (2001).

31. *See* Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 LAW & CONTEMP. PROBS. 289, 290 (2003).

32. For a general discussion on the implications of imitability in a "knowledge economy," see DAVID J. TEECE, MANAGING INTELLECTUAL CAPITAL: ORGANIZATIONAL, STRATEGIC, AND POLICY DIMENSIONS 3-26 (2000).

33. *Id.*

34. *See generally* Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1024-25 (1989).

35. *See* Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J.L. & ECON. 265, 265-71 (1977) (arguing the need to allow patents on upstream research and detailing the advantages of allowing upstream research patent holders to coordinate downstream efforts). *But see* Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 698 (1998), *available at* http://www.sciencemag.org/cgi/content/full/280/5364/698 (last viewed Jan. 10, 2005) (presenting the proposition that allowing excessive upstream research will lead to a freeze on innovation in the biotechnology industry).

36. *See generally* Kitch, *supra* note 35, at 266.

exponential number of downstream techniques and products. Hence, the patent owner will have exclusive control over the downstream progeny of that upstream patent.[37] But what if the owner does not have adequate resources to best coordinate research efforts on that gene? What if he does not wish to commercialize the subject matter of a patent that could impact life-saving technology? A patent owner who has rights on such a fundamental tool or fundamental information could easily thwart a significant cross-section of scientific innovation across disciplines and industries. There are many moral and ethical considerations that flow from the idea of patent holders having this kind of control over genetic material or genetic information. The impact on individual citizens will be discussed in Part V, *infra*.

¶ 14 A specific manifestation of the problem of upstream patenting arises in the case of "blocking" patents. Often, a small biotechnology company has a patent on a single nucleotide polymorphism (SNP)[38] or an expressed sequence tag (EST)[39] but lacks the resources to commercialize it. Instead, the company extracts value by licensing it to a licensee with commercializing capabilities. If a potential licensee is willing to enter such an agreement, then an upstream patent would pose no problem. However, sometimes one company has a patent on an EST that is part of a specific gene, and another company has a patent on an overlapping EST of the same gene. Both have the ability to commercialize their ESTs into drug therapies but, because their patents cover the same sequence component, they "block" each other from being able to practice their inventions. When the companies are rivals and thus unwilling to enter into a cross-licensing agreement, neither party can conduct research on that gene. This scenario is the primary example of what Rebecca Eisenberg and Michael Heller have called the Tragedy of the Anticommons.[40] If scientists are allowed to pursue of the practice of upstream patenting, ownership over research tools will be fragmented, blocking patents will abound, and research efforts will stall.

¶ 15 The pharmaceutical industry is no stranger to the tragedy of the anticommons. In anticipation of the impending patent thicket[41] resulting from multiple companies engaging in similar genetic research programs, a group of pharmaceutical companies and public organizations formed the SNP Consortium.[42] While consortium members will continue with their individual SNP programs, they have agreed to inject any gene SNPs they discover into the public domain to allow access for all.

¶ 16 Such genetic information is instrumental in getting pharmacogenomic programs off the ground. Though the SNP Consortium mimics responsible citizenship by relinquishing ownership rights over SNP information, this does not mean that the individual members will relinquish rights to lucrative downstream products, nor does it mean that SNPs are the sole means to block patentable downstream genetic subject

37. *See id.*
38. SNPs are variations in genes that are implicated in disease.
39. ESTs are unique regions of genes that can be used for mapping full-length genes.
40. Heller & Eisenberg, *supra* note 35, at 698.
41. *See* Shapiro, *supra* note 6, at 1-2.
42. For a list of participating members and their policies on the release of SNP information, see http://snp.cshl.org (last visited Jan. 10, 2005).

matter. So how will patenting downstream products work? Conceivably, patents on pharmacogenomic diagnostic tests will function similarly to drug patents. However, the objective of pharmaceutical companies is to widen the pipeline at the later stages of drug development, thereby reducing the currently atrocious amount of hits that are eventually unsuccessful. Evidence suggests that the pharmaceutical industry will generate huge amounts of data from innumerable samples, giving them the ability to produce approximately 10,000 drug targets in the next few years.[43] Thus, drug companies will create an even greater backlog of patent applications at the United States Patent and Trademark Office (USPTO), with both product (the diagnostic test kit) and process (method of treating and whom with what genetic makeup) inventions.[44]

IV. PHARMACOGENOMICS AND THE REGULATORY PROCESS

¶ 17 Given the potential benefits, it seems that the pharmaceutical industry is barreling forward with the promise of pharmacogenomics. Are regulatory bodies such as the FDA and Institutional Review Boards (IRBs)[45] prepared to meet this challenge? Signs suggest that they are not. Barbara Ann Binzak believes that the FDA needs to begin planning now to meet the barrage of drugs coming down the pharmacogenomic pipeline.[46] Nevertheless, as of last year, the FDA believed the process currently in place would be sufficient to deal with pharmacogenomics.[47] Perhaps more alarming, however, is that the FDA is unlikely to approve a drug for a narrow population when a greater population can benefit.[48] Looking at IRBs, many currently do not have genetics expertise represented; Binzak suggests that institutions populate their IRBs with at least one geneticist to meet the challenge of approving genetics-intensive studies.[49]

¶ 18 At first blush, it appears that both drug companies and regulatory agencies will benefit from the streamlined, focused clinical trial participant group that pharmacogenomics promises. "DNA from patients who experienced the adverse event [can] be extracted and compared with DNA from control patients who received the drug

43. Michael J. Malinowski, *Law, Policy, and Market Implications of Genetic Profiling in Drug Development*, 2 HOUS. J. HEALTH L. & POL'Y 31, 40 (2002).

44. *See id.* at 41. Supposing that drug companies clear the backlog hurdle that they have created, what are the implications of patenting not the treatment itself but rather the diagnostic screen to determine safety (or, conversely, toxicity)? Not only will doctors and pharmacists have to work with insurance companies on formulary-approved drugs, but part and parcel with the drug will be a diagnostic test that would be almost unethical not to employ if one intends to prescribe its companion drug. In a way, this patent arrangement arguably creates an antitrust problem of bundling products, which is exacerbated by the context of health, which consumers find to be sensitive.

45. IRBs are formed to ensure compliance with FDA requirements experiments involving human subjects. *See generally* U.S. Food and Drug Administration, *Guidance for Institutional Review Boards and Clinical Investigators 1998 Update: Frequently Asked Questions*, *available at* http://www.fda.gov/oc/ohrt/irbs/faqs.html#IRBOrg (last visited Jan. 10, 2005).

46. Barbara Ann Binzak, *How Pharmacogenomics Will Impact the Federal Regulation of Clinical Trials and the New Drug Approval Process*, 58 FOOD & DRUG L.J. 103, 107 (2003).

47. *Id.* at 105.

48. *Id.* at 106.

49. *Id.* at 115.

but did not experience the adverse event."[50] Thus, the group on whom the drug will be tested can be screened both for safety and likely efficacy. Despite these advantages, however, there is a chance that searching for highly focused groups will yield too few trial participants to give statistically significant results.[51]

¶ 19 Binzak suggests numerous improvements to the regulatory process. In addition to adjusting the make-up of IRBs, she suggests that there must be full disclosure of all relevant SNP data at the preclinical research stage.[52] Next, at the Pre-IND[53] meeting and IND submission/approval stage, she argues that the government should mandate an FDA sponsor meeting, convene a pharmacogenomics group, and require genetic data on the population.[54] Doing so would minimize the risk of selecting too small a sample population for clinical trials, which harms the larger population as a whole.

¶ 20 Binzak makes a compelling argument for rethinking our notion of what is "healthy." This concept is implicated during Phase I of clinical trials, when drug companies test "healthy" subjects for "the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness."[55] She suggests that we must distinguish between "phenotypic" health and "genotypic" health.[56] Since there are multiple variables to consider in this alternative connotation of health, there are numerous combinations of the two types of health; these combinations are further complicated by the nature of the gene itself.[57] Selecting candidates for a Phase I clinical trial will no longer be as easy as allowing any volunteer off the street who passes a simple clinical exam and blood work screen. Instead, companies will also look at the individual's genetic makeup to determine whether or not he possesses SNPs or alleles that might lead to an adverse reaction.[58]

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50. Roses, *supra* note 11, at 862.

51. *Id*. *See also* Mark Rothstein & Phyllis Griffin Epps, *Ethical and Legal Implications of Pharmacogenomics*, 2 NATURE REVS.: GENETICS 228, 228 (2001) (noting the difficulty of identifying the range of potential adverse side effects with a smaller group of test subjects).

52. Binzak, *supra* note 46, at 116.

53. An IND, or Investigational New Drug Application, represents the point at which a molecule has been tested *in vitro* and *in vivo*, and the drug manufacturer would like to obtain permission to test it in humans.

54. Binzak, *supra* note 46, at 118.

55. *Id*. at 119-120 (citing 21 C.F.R. §§ 312.21(a)(1) (2004)).

56. *Id.* at 120.

57. *See id.* at 120-123, Table 1 at 127 (outlining the implications of phenotypic versus genotypic health in a study for the butyrylcholinesterase (BCHE) gene).

58. What I find confusing about this complicated initial screen is that it seems to beg the very question being studied in the clinical trial. Clearly, in cases where the trial is meant to determine whether or not the drug for the disease gene proper is dangerous for someone with an unfavorable genetic makeup, then this pre-screening is logical. But what kind of validation procedures do we have for testing a diagnostic test? We must test a diagnostic test for accuracy, so presumably it too will undergo some sort of clinical trial. The enhanced notion of "healthy" would not seem to apply in this instance because if we could screen out patients who would not be healthy in terms of this diagnostic test, there would be no need for the diagnostic test. Presumably, there are no health risks associated with administration of a diagnostic test (since no drug is being administered), but validating it is a challenge if we do not know how to find our target population in the first place. Finding the target population is the purpose of this diagnostic test. Therefore, traditional notions of "healthy" must be employed at the stage of testing diagnostic tests.

¶ 21 Ultimately, what Binzak argues, and what I suspect, is that there will be a need for greater levels of review throughout the regulatory process. Not only will there be a spike in the number of patent applications and issued patents, there will also be a more complex regulatory process emerging in order to meet the intricacy of pharmacogenomics-based medicine.

V. MARKET IMPLICATIONS OF PHARMACOGENOMICS

¶ 22 As with any market strategy, there are both advantages and disadvantages to retooling one's business. We can derive what the advantages and disadvantages will be from two viewpoints: that of the supplier (e.g., drug companies) and that of the consumer (e.g, patients). I believe that most of the economic advantages will be conferred on drug companies while consumers will experience a merely marginal economic advantage compared to the overall societal economic disadvantages they will have to bear.[59] The economic advantages of introducing pharmacogenomic techniques into the marketplace will putatively benefit drug companies in the following ways: 1) reduction in the costs associated with drug development and clinical trials, and 2) further refinement of their ability to identify target markets. As Allen Roses, head of GlaxoSmithKline's Genetics division, observes:

> [T]here are . . . enormous economical costs associated with searching huge lists of genes for 'the right disease for the available gene.' It is correct to state that target validation is a major challenge to the pharmaceutical industry, but it is also critical to realize that the core problem for drug development is poor target selection. . . . Each failure is very expensive in lost time and money.[60]

According to the Boston Consulting Group, drug companies are estimated to save "an average of $300 million and two years per new drug as a result of increased efficiency,"[61] a significant figure.

¶ 23 The primary disadvantage I identify for drug companies is, as noted above, increased complexity in the regulatory process, which can result in significant costs in and of itself. However, drug companies can easily pass on this cost to the consumer. Alternatively, the increased regulatory costs can be counterbalanced by the $300 million saved via greater efficiency at the preclinical stage.

¶ 24 The primary benefit of pharmacogenomics to the consumer is more precise matching of drug to patient. This benefit will translate into greater efficacy and fewer incidents of inefficacy or adverse events, and will thereby lower the cost (economic and physical) to the consumer. "By focusing clinical trials on patients who are most likely to respond, drug development resources could be targeted to those patients with continued

59. *See generally* Rothstein & Epps, *supra* note 51, at 228.
60. Roses, *supra* note 11, at 859.
61. Binzak, *supra* note 46, at 113.

unmet medical need."[62]

¶ 25 However, the costs to the consumer are numerous and sobering. While the ability to match drugs to patients will be enhanced, perfect matches will not result every time. What will happen to the false positives that are inadvertently included and harmed? If the point of pharmacogenomics is to reduce the segment of the population for whom the drug will be ineffective or even harmful, we may find ourselves back at square one if a pharmacogenomics-based clinical trial experiences a single fatality. What will happen to the false negatives that are wrongfully excluded and deprived of the drug? In addition to the litigation that would occur if a patient were to discover that she had been wrongfully excluded, a new kind of social prejudice would likely emerge from the rise of the untreatable patient—patients who were properly excluded but are now left out to dry because drug companies will have little to no incentive to develop drugs since they will have already captured a population that exhibits efficacy for an existent drug. There would be no need to invest new resources into an orphan disease if a company can capture adequate revenue from a well-resourced disease research program they have in place. Thus, drug companies may limit their research and development efforts to genotypes of high incidence in the greater population.[63]

¶ 26 It will also be strategic for companies to capture a market with a high willingness to pay. A well-resourced disease research program has no doubt benefited from pharmaceutical companies' marketing departments who have identified lucrative markets. Marketing departments can identify such markets by identifying a known disease population, as discussed above. However, marketing departments can also identify a lucrative market by redefining perceptions about a symptom set. Perhaps the most well-known example of this tactic is drug treatment for male erectile dysfunction. Only in the last ten years has this disorder really gained momentum as a bona fide disease. Prior to this period, people merely accepted the condition as a consequence of age, diabetes, or testicular or prostate cancer. There was no outcry on the travesty of this debilitating disease.

¶ 27 Another compelling example of discovering new markets comes, anecdotally, from my time at GlaxoSmithKline. In conjunction with work on a receptor implicated in urinary incontinence, the company's marketing department had generated mind-boggling numbers on how much families would save, as well as what the country would save in terms of our health care system. Generally, monies saved from projects such as this could be redirected back to drug R&D: "As treatment and prevention of chronic and common diseases improves, a significant proportion of money saved by reducing hospitalization and long-term care costs could be transferred to well-tolerated and effective medicines."[64] Furthermore, "[e]ffective and well-tolerated medicines with predictive medicine response profiles will obviate the need for formulary restrictions on prescribing and new policies to mandate cost-effectiveness to be proved in a broad

62. Roses, *supra* note 11, at 863.
63. *Id*.
64. *Id*.

population of patients."[65]

¶ 28 Evidence shows that one of the primary reasons a family will resort to putting an elderly loved one in the hospital or a nursing home is urinary incontinence. Eliminating that element of a symptom set makes it more likely that family members will keep their loved one at home and care for them themselves. The money saved from avoiding nursing home costs would be significant and would far outweigh the cost of the drug used to treat the incontinence. Profits generated from the sale of the incontinence drug could then be reinvested into other drugs. Even where families purchase multiple pharmacogenomically-derived drugs, the cost of the drugs will be significantly less than the cost of hospitalization or nursing homes.

¶ 29 It is difficult to determine how we as a society view emerging markets and how they affect our perceptions about disease. From a purely economic point of view, there can be no doubt that these market studies are brilliant marketing strategies. As with male erectile dysfunction, it would be fairly easy to believe that urinary incontinence is not a disease but rather a condition that one must live with as a consequence of age. By changing our perceptions about whether or not a condition is a disease or something we should merely endure, companies create markets where they did not exist before. On the one hand, consumer benefits from a better quality of life and a greater number of treatment choices. On the other hand, are drug companies taking advantage of the consumer? Is it really better to expand our perceptions of necessary health care to areas we would not have deemed as necessary in the past? If it is not better, would the response be that this is the desired trajectory of medicine in that our standards keep getting higher and higher?

¶ 30 While people suffer from debilitating or life-threatening diseases, drug companies have chosen to invest in lifestyle therapies rather than life-saving therapies. While a small lifestyle change to one is life-saving to another, the trend is illustrative of the increasingly confirmed fear that the market is becoming grossly and inequitably fragmented. As I have described above, "pharmacogenomic-based drugs will be expensive, because of, for example, the need to recoup the cost of investment in new technologies. The ability to develop specialized drugs that are ultimately approved for smaller populations rather than for general use will *fragment the market for pharmaceuticals*."[66]

¶ 31 Even though Rothstein and Epps have referred to the fragmentation of the market pejoratively, such fragmentation may ultimately work to the economic benefit of the consumer. As I discussed earlier in Part III, pharmacogenomics-generated drugs will result in a greater number of patent applications and issued patents. If we assume that the total market capacity remains constant, the total valuation of overall market willingness to pay will be spread over many drug products rather than over a few. By spreading the costs of medicine more evenly and effectively over the relevant populations, we achieve a better distribution of the R&D costs incurred by pharmaceutical companies. Given that

65. *Id.*
66. Rothstein & Epps, *supra* note 51, at 228 (emphasis added).

R&D costs account for the high price of drugs, the cost per drug would (in theory) be lower than if everyone were paying for the same few drugs.

¶ 32 For example, let us suppose that there are five drugs in the world, each manufactured by one of five drug companies. Let us then suppose that because there is a scarcity of drugs in the marketplace, the profit-maximizing price for each of these drugs is $10 per pill and the average consumer also has a willingness to pay up to $10. We will also assume that a single drug company only needs $10 per pill to recoup its R&D investments and continue producing. If that company were to implement pharmacogenomics programs and suddenly produce five drugs with the same resources instead of the one they have in the marketplace, then they could conceivably begin charging only $2 per pill for their five pills. In this scenario, pharmacogenomics allows the drug company to retain the necessary revenue stream while reducing the cost to the consumer. Since the consumer has in the past exhibited a willingness to pay $10, however, the willingness to pay adjustment in the face of diminished scarcity would probably level out at about $5. Even then, we have a win-win scenario. The drug company will make an extra $15 ($25 for their 5 drugs, at $5 each) while each consumer pays $5 less per pill. Even if they were to know that they should only in theory have to pay $2, that extra premium of $3 would likely be worth the greater efficacy a patient would experience with a correctly matched drug and a significant reduction in price from $10.

¶ 33 Unfortunately, the above scenario is concededly oversimplified and the disadvantages to the consumer still loom. As discussed, along with the potential for genetic drug-compatibility discrimination, revaluing market populations on a genetics-contingent basis allows for even more economic discrimination than already exists. Again, the two populations who stand to gain the most from pharmacogenomics are: 1) large disease populations across whom the cost would be evenly spread, and 2) wealthy disease populations who will always be able to pay the profit-maximizing price. The population that will suffer is the poor, orphan-disease population.

VI. PATIENT RIGHTS & PHARMACOGENOMICS: LEAVING THE PATIENT GENETICALLY AND LEGALLY EXPOSED

¶ 34 As the previous sections illustrate, the transition from traditional to pharmacogenomics-based drug discovery creates many benefits. However, there are also significant costs, and those costs will be transferred to the consumer. What the technological, economic, and regulatory perspectives have inadequately addressed are patients' rights. This anxiety over patients' rights flows primarily from the most fundamental area of concern: the patient's right to privacy regarding genetic information. This issue is a topic in itself. Nevertheless, because genetic information is an essential element to pharmacogenomics-generated drugs, the entire debate must be imported into pharmacogenomics. Determining whether or not a patient may take a pharmacogenomics-generated drug necessarily exposes a portion of a patient's genetic profile. Even if the exposure is incomplete, that scant amount of genetic information can reveal volumes.

¶ 35 The elements of the genetic privacy debate closely track the traditional dialogue on informed consent policies; patients' rights in the pharmacogenomics context will inherit these same problems. Intellectual property law fails to address patients' rights in situations where a physician or researcher claims intellectual property rights over innovations related to a patient's genetic disease.[67] Since pharmacogenomics-based treatment necessitates genetic profile disclosure, individuals who exhibit variants on a drug's target disease could easily become the subject of a next-generation drug study. Here we have a double-edged sword. On the one hand, a drug company may merely relegate such a patient to the margin and not have anything to do with her disease. This is disadvantageous to the patient because she receives no treatment. On the other hand, a drug company may take interest in her for her variant form of the disease. While this interest may be advantageous in terms of her treatment potential, the downside is that a drug company may appropriate the DNA sequence underlying that interesting genotype variant.

¶ 36 Currently, neither the USPTO nor the Court of Appeals for the Federal Circuit recognize an individual's intellectual property rights over her own genetic information, since it was not she who purified the DNA and elucidated its sequence. However, whether or not a patient wishes to have this property right, she may have a personal interest in keeping this information private and outside the realm of a drug company's commercializing capability.[68] At the same time, she may want to find a cure or a treatment for her condition, and she cannot obtain that treatment without disclosing her genetics. Is this a choice at all? Further, as discussed earlier, an additional risk to occupying a rare disease variant group is the possibility of being subject to a new kind of prejudice. The initial screen may determine that a person is not suitable for the study, and these ineligible patients might be labeled as "'difficult to treat,' 'less profitable to treat,' or 'more expensive to treat.'"[69]

¶ 37 Along the lines of a patient's unsuitability for a potential treatment, "[a]n unresolved issue is whether the ethical principles of beneficence and non-maleficence…would preclude the deliberate inclusion of anyone who is not likely to respond favourably to treatment."[70] This issue centers on the inevitability of false positives and false negatives. While it is clear that excluding someone for whom the drug would be dangerous is ethical, situations will arise where a patient *may* respond

67. *Cf.* Moore v. Regents of the University of California, 793 P.2d 479, 480 (Cal. 1990) (suit by patient, John Moore, against physicians and researchers with the University of California-Los Angeles for using cells from his spleen for lucrative medical research without his permission; the patient had a valid cause of action under the theory of breach of fiduciary duty, but not for conversion of property).

68. *See, e.g.*, Margaret Jane Radin, *Property and Personhood*, 34 STAN. L. REV. 957 (1982) (discussing a deontological, non-utilitarian perspective on the concept of property rights).

69. Rothstein & Epps, *supra* note 51, at 229.

70. *Id.* "The principle of nonmaleficence asserts an obligation not to inflict harm on others." TOM L. BEAUCHAMP & JAMES F. CHILDRESS, PRINCIPLES OF BIOMEDICAL ETHICS 113 (5th ed. 2001). "[N]onmaleficence only requires *intentionally refraining* from actions that cause harm." *Id.* at 115. "[R]ules of nonmaleficence (1) are negative prohibitions of action that (2) must be followed impartially, and (3) provide moral reasons for legal prohibitions of certain forms of conduct. By contrast, rules of beneficence (1) present positive requirements of action, (2) need not always be followed impartially, and (3) rarely, if ever, provide reasons for legal punishment when agents fail to abide by the rules." *Id.* at 168.

favorably, but with whom a drug company is not willing to take the risk. Until we have completely mastered genetics, such studies will inevitably generate false negatives. In the interest of ensuring that its drug passes muster in clinical trials, a drug company may exclude someone for whom the drug might be effective. If such a case were to arise in a clinical trial that could serve as the final life-saving measure for a patient, and she were excluded and subsequently died from lack of treatment, could there be a legitimate claim that the principle of non-maleficence was violated? The very basis of pharmacogenomics efforts is to avoid administering the drug to inappropriate candidates, but rarely will that line be so clear—is this illusionary bright-line policy at odds with the ethical principles of beneficence and non-maleficence? Where will the liability for failure to treat fall? Will it fall on pharmaceutical companies, who oversee clinical trials and determine populations for which drugs will be indicated?[71]

¶ 38 We can see this scenario play out in a normal relationship between physician and patient long after clinical trials have proved the concept of a drug. As Rothstein and Epps note:

> Moral and ethical proscriptions against causing harm might require a physician to integrate pharmacogenetics into clinical practice where necessary to minimize risk to a patient. By contrast, budgetary constraints imposed by insurers could slow the acceptance of drugs developed through pharmacogenomics by limiting their use by physicians and their availability to patients.[72]

Thus, a tool such as a diagnostic test might be available somewhere on the market but because an insurance company has not incorporated it into its formulary, it may be inaccessible to the patient. While she may have the option of paying for it herself, she may not be able to afford it. This scenario is by no means new—physicians and patients are constantly in the position of having their treatment options severely limited by insurance company constraints. Pharmacogenomics merely creates yet another situation where this may occur, and given its promise of cleaner and more effective drugs, it dangles a carrot before physicians and patients.

¶ 39 Such limitations on a physician's ability to practice medicine raise the issue of who will bear the burden of liability when a diagnostic test has been improperly administered or not administered at all. One logical place to assign the burden is with doctors and pharmacists.[73] However, if we subject them to this liability, they will have to know the complete medical history of a given patient, particularly her genetic history. Knowing that information raises privacy concerns not only for the patient but also for the patient's family.[74] Further, how do we deal with physicians who are accustomed to the practice of broad off-label discretion?[75] At the end of the day, regardless of who bears the costs of liability—drug company, physician, insurance company, pharmacist—it is

71. Rothstein & Epps, *supra* note 51, at 231.
72. *Id.* at 230.
73. *Id*.
74. *See id.*
75. Malinowski, *supra* note 43, at 39.

the patient who will end up paying: with risk to her health.

VII. CONCLUSION

¶ 40 Pharmacogenomics offers the promise of replacing serendipitous drug discovery with rational drug design. With it comes the promise of safer, more effective, and more accessible drugs. While these technological advances may be intended for the betterment of social welfare, there are many costs the market will have to bear in order to accommodate this technological, economic, and socially revolutionary change. Consumers stand to gain substantially from this bold move into the future of genetics; nevertheless, regardless of whether or not they will ultimately bear liability costs, they will also pay for it with their health. Pharmacogenomics is coming and there is nothing to stop it—but we must not allow it to move forward without engaging in a meaningful dialogue about how to responsibly administer pharmacogenomic treatments.