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INCENTIVIZING THE UTILIZATION OF PHARMACOGENOMICS IN DRUG DEVELOPMENT

VALERIE GUTMANN KOCH*

I. INTRODUCTION

The last decades have witnessed remarkable advancements in the fields of genetics and genomics, highlighted by the successful completion of the map of the human genome in 2003.¹ With this achievement came scientific possibilities that, only a few decades earlier, seemed more science fiction than reality. Of these developments, pharmacogenomics is hailed by many as a panacea for problems associated with pharmaceutical drug use and development.² The Human Genome Project (HGP) and associated research have demonstrated that all human beings share 99.9 percent of their DNA.³ Pharmacogenomics focuses on the 0.1 percent differences between individuals and promises to allow physicians to tailor a patient's prescription according to his or her genetic profile, reducing painful and sometimes deadly side effects, ensuring appropriate dosage decisions, and targeting specific disease pathways.⁴

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1. The Human Genome Project "sequenced a single genome" for about 4 billion dollars, and Craig Venter, a leader in the field of biotechnology, did it for 100 million dollars. *Getting Personal: The Promise of Cheap Genome Sequencing*, *ECONOMIST* (Apr. 16, 2009), http://www.economist.com/node/13437974.?story_id=13437974.

2. See Michael J. Meurer, *Pharmacogenomics, Genetic Tests, and Patent-Based Incentives*, in *PERSPECTIVES ON PROPERTIES OF THE HUMAN GENOME PROJECT* 399, 403 (F. Scott Kieff ed., 2003) (acknowledging the promise of "tailored medicine"); see also Allen D. Roses, *Pharmacogenetics and the Practice of Medicine*, 405 *NATURE* 857, 857, 863 (2000) (foreseeing the ability to use DNA to predict drug reactions). But see John A. Robertson et al., *Pharmacogenetic Challenges for the Health Care System*, *HEALTH AFF.*, July–Aug. 2002, at 155, 157 (questioning whether genetic effects are significant or predictable enough to alter drug therapy).

3. Press Release, Nat'l Human Genome Research Inst., Whole Genome Ass'n Studies (Feb. 8, 2006), <http://www.genome.gov/17516714>.

4. See *id.* (detailing the 0.1 percent difference between individuals); see also Meurer, *supra* note 2, at 403 (outlining the benefits of pharmacogenomics).

However, pharmacogenomics is unlikely to fulfill the promise of providing “miracle drugs” to all.⁵ The pharmaceutical industry may be reluctant to pursue pharmacogenomics because of the costs associated with developing products for a segmented patient population,⁶ and the current regulatory and legal system may be ill-prepared to deal with the practical, economic, legal, and ethical issues associated with genetic discoveries.⁷ This article explores a number of dimensions of the problems associated with pharmacogenomic discoveries and considers the future of this exciting and complex field.

A. *The History and Promise of Pharmacogenomics*

Genomics can be defined as “the study of the function and structure of genes and gene products.”⁸ *Pharmacogenomics*, a field within genomics, refers to the study of how an individual, based on his or her genetic makeup, responds to drugs, focusing on one’s susceptibility to disease and response to drug therapies.⁹

The history of pharmacogenomics started in the early twentieth century with a scientific concentration on Mendelian effects on drug response.¹⁰ The discipline of *pharmacogenetics* predated pharmacogenomics, and was first articulated by Arno Motulsky in 1957,¹¹ who asserted that “otherwise innocuous genetic traits” might underlie variation among individuals in drug response, based on individual differences in enzyme structure and function.¹² Although the field of pharmacogenetics is relatively well-established, it has only recently had a significant impact on the pharmaceutical industry.¹³

5. See *infra* notes 67–68 and accompanying text (explaining that the benefits of individually-tailored drugs are overstated).

6. Meurer, *supra* note 2, at 401 (explaining the private returns and social costs associated with advancements in pharmacogenomics).

7. See Robertson et al., *supra* note 2, at 159–64 (reviewing a variety of regulatory challenges associated with pharmacogenomics).

8. Meurer, *supra* note 2, at 402.

9. David Housman & Fred D. Ledley, *Why Pharmacogenomics? Why Now?*, 16 NATURE BIOTECH. 2, 2 (Supp. 1998). It is important to ensure that pharmacogenomics is distinguished from predisposition or predictive testing, the latter of which “provide[s] statistical inferences concerning the risk of a disease or its prognosis.” *Id.* More specifically within pharmacogenomics, pharmacokinetics is defined as the study of the variation in drug metabolism, while pharmacodynamics is the mechanism of a drug on its target. Andrew Marshall, *Laying the Foundations for Personalized Medicines*, 16 NATURE BIOTECH. 6, 6–7 (Supp. 1998).

10. David B. Goldstein et al., *Pharmacogenetics Goes Genomic*, 4 NATURE REV. GENETICS 937 (2003). Gregor Mendel “discovered” the laws of genetics in 1865 with his famous studies of the heredity of traits in pea pod plants. Salvatore Giorgianni, *Solving the Mysteries of Inheritance*, PFIZER J., Summer 1998, at 1, 1. His discoveries were generally ignored until the next century, when they were “rediscovered” and applied over a number of disciplines. *Id.*

11. Goldstein et al., *supra* note 10, at 937.

12. Arno G. Motulsky, *Drug Reactions, Enzymes, and Biochemical Genetics*, 165 JAMA 835, 835 (1957).

13. See Housman & Ledley, *supra* note 9, at 2 (explaining recent developments contributing to the significance of pharmacogenetics).

The terms pharmacogenetics and pharmacogenomics are often used interchangeably;¹⁴ however, it is necessary to understand that a distinction exists. Some merely define pharmacogenomics as the ensuing broadening of pharmacogenetics.¹⁵ While pharmacogenetics applies to the reaction of genetically diverse patients to a particular medicine (“one drug across many genomes”),¹⁶ pharmacogenomics encompasses pharmacogenetics, but also applies at earlier phases of drug development, in determining which compounds will be most effective for a particular genome (“many drugs across one genome”).¹⁷ Pharmacogenetics is most useful for already-available drugs, in that it can be applied to existing drugs and development programs; in contrast, “pharmacogenomics will exert its impact at the drug discovery stage and will thus appear in products over the long term.”¹⁸

Regardless of their definitional distinctions, the goals of both pharmacogenomics and pharmacogenetics are identical:

[T]o improve the diagnosis of genetic disease; to develop drugs to fight genetic disease; to make clinical testing of drugs more efficient by identifying populations in which the drugs are likely to be especially efficacious . . . and, using genetic information about patients, to maximize therapeutic benefit and minimize harmful side effects by prescribing drugs to targeted patient populations.¹⁹

In the area of drug discovery and development, pharmacogenomics promises to offer better matching between patients and the appropriate drugs and to reduce or

14. NUFFIELD COUNCIL ON BIOETHICS, PHARMACOGENETICS: ETHICAL ISSUES 4 tbl.1.1 (2003).

15. *Id.*

16. *Id.*; Jai Shah, *Concept and Putative Application of Pharmacogenetics and Pharmacogenomics*, HEALTH L. REV., no. 2, 2004 at 3, 4.

17. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at 4 tbl.1.1; Shah, *supra* note 16, at 3, 4. The World Health Organization provides the following distinction:

Pharmacogenetics refers to the study of DNA sequence variation as it relates to differential drug response of individuals, i.e., the use of genomics to determine an individual’s response. Pharmacogenomics refers to the use of DNA-based genotyping in order to target pharmaceutical agents to specific patient populations in the design of drugs.

World Health Organization, *Progress in Pharmacogenetics and Pharmacogenomics*, 16 WHO DRUG INFO. 17, 17 (2002). Other commentators state that “[p]harmacogenetics is the application of single gene sequence or a limited set of multiple gene sequences to study variation in DNA sequences related to drug action or drug disposition,” while “[p]harmacogenomics is the application of genome-wide single-nucleotide polymorphism maps and genome-wide gene expression analysis to study variations that influence drug action.” Jack E. Urquhart et al., *The Duty to Use Pharmacogenetics and Pharmacogenomics to Reduce the Risk of Idiosyncratic Drug-Induced Liver Injury*, FINDLAW (Mar. 2004), <http://library.findlaw.com/2004/Feb/27/133310.html> (citing Lawrence Lesko et al., *Pharmacogenetics and Pharmacogenomics in Drug Development and Regulatory Decision Making: Report of the First FDA-PWG-PhRMA-DruSafe Workshop*, 43 J. CLINICAL PHARMACOLOGY 342, 343–44 (2003)).

18. Shah, *supra* note 16, at 4.

19. LORI B. ANDREWS ET AL., GENETICS: ETHICS, LAW AND POLICY 423 (2002).

eliminate adverse effects,²⁰ enabling correct dosage according to one's particular metabolism.

1. *Designer Drugs, Adverse Drug Reactions, and Metabolism*

The promise most commonly associated with pharmacogenomics is the advancement of new “designer drugs” that may be developed to meet an individual's particular health needs, thereby increasing a drug's effectiveness.²¹ The completion of the HGP was accompanied by the potential for the development of “individualized medicine,”²² and it has been suggested that applying genetic knowledge to drug development is as simple as “start[ing] backwards and build[ing] a drug that addresses the problem.”²³ Clinical researchers identify drug targets or pathway proteins as potential objectives for pharmacogenomic drug development.²⁴ For example, variations in one gene (GNB3) are associated with a response to antidepressants, while variations in another (AGT) are associated with reduction of blood pressure with anti-hypertensive treatment.²⁵

Dr. Craig Venter, one of the major players behind the HGP, has predicted that eventually each of us “might carry something similar to a bar code that identifies our genotype, and this would help us make healthcare decisions.”²⁶ For example, since the late 1990's, pharmacogenetics has been used to predict the effectiveness of Herceptin, a drug for metastatic breast cancer.²⁷ Herceptin is especially effective in shrinking tumors and extending lives for approximately thirty percent of breast cancer patients—those whose tumors have unusually high amounts of the HER2/neu protein.²⁸ The use of Herceptin illustrates the ability to identify drugs according to an individual's genetic profile; it is now considered the standard of

20. Meurer, *supra* note 2, at 401.

21. *See id.* at 401 (noting the potential for individualized drugs from pharmacogenomics); *see also* D.C. Wertz, *Ethical, Social and Legal Issues in Pharmacogenomics*, 3 PHARMACOGENOMICS J. 194, 194 (2003) (discussing the promise of designing drugs for custom medicines). Currently, most drugs have an average effectiveness rate of 50 percent. Lawrence J. Lesko & Issam Zineh, *DNA, Drugs & Chariots: On a Decade of Pharmacogenomics at the US FDA*, 11 PHARMACOGENOMICS 507, 511 (2010).

22. Henry T. Greely, *Pharmacogenomics: Promise, Prospects, and Potential Problems*, MED. ETHICS, Winter 2002, at 2.

23. DEAN HAMER & PETER COPELAND, *LIVING WITH OUR GENES: WHY THEY MATTER MORE THAN YOU THINK* 303–04 (1998). The authors state, “[i]ndividual DNA sequences, combined with existing computer modeling techniques, would allow drugs to be as precise as a key in a lock.” *Id.*

24. *See* Goldstein et al., *supra* note 10, at 940 tbl.1a (providing examples of common drug targets and pathway proteins that are associated with drug response).

25. *Id.*

26. J. Craig Venter, *The Genome Project – From Microbes to Man*, PFIZER J., Summer 1998, at 7, 11.

27. *The Making of the Pharmacogenomic Prescription*, GENE LETTER (Jan. 27, 2010), <http://www.geneletter.com/the-making-of-the-pharmacogenomic-prescription-22/> (“[T]ests are performed to predict whether it will work in a particular patient prior to drug prescription.”).

28. Shah, *supra* note 16, at 6.

care for that particular form of breast cancer.²⁹ Pharmacogenomics is also currently used in Alzheimer's disease research.³⁰ For instance, one study investigated the relationship between Alzheimer's patients' genotypes and their response to certain already-existing drugs, and found that a certain gene is a good predictor of response to tacrine, a cholinesterase inhibitor.³¹

The second promise of pharmacogenomics is the reduction of adverse drug reactions (ADRs). Fatal ADRs are considered to be between the fourth and sixth leading causes of death,³² accounting for approximately three percent of all deaths in the general population.³³ Moreover, it is estimated that ADRs cost society over 100 billion dollars per year.³⁴ Applying pharmacogenomics to drug development and prescription could potentially reduce the risk of adverse drug reactions such as venous thrombosis, which is associated with the factor V Leiden allele.³⁵ Because the use of oral contraceptives by women with the factor V Leiden allele greatly increases the risk of venous thrombosis, it might be possible to test women for the allele before making prescription decisions.³⁶ Likewise, would-be abacavir users for the treatment of HIV infection could be tested for the HLA-B*5701 allele, so as to reduce the incidence of hypersensitivity reactions to the use of the drug.³⁷

29. Penelope K. Manasco & Teresa E. Arledge, *Drug Development Strategies*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 83, 96 (Mark A. Rothstein ed., 2003).

30. See Roses, *supra* note 2, at 860 (identifying gene mutations associated with Alzheimer's disease).

31. Andrew Marshall, *Getting the Right Drug into the Right Patient*, 16 NATURE BIOTECH., 9, 9 (Supp. 1998) (citing Judes Poirier et al., *Apolipoprotein E4 Allele as a Predictor of Cholinergic Deficits and Treatment Outcome in Alzheimer's Disease*, 92 PROC. NAT'L ACAD. SCI. 12260 (1995)).

32. Jason Lazarou et al., *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-analysis of Prospective Studies*, 279 JAMA 1200, 1202 (1998) (using data collected from 1994 to find that ADRs are responsible for 100,000 drug-related deaths and 2.2 million hospitalizations each year in the U.S.). See also Karin Wester et al., *Incidence of Fatal Adverse Drug Reactions: A Population Based Study*, 65 BRIT. J. CLINICAL PHARMACOLOGY 573, 576 (2008) (finding that fatal ADRs was the seventh most common cause of death in Sweden).

33. Wester et al., *supra* note 32, at 576.

34. Faith Lagay, *Pharmacogenomics: Revolution in a Bottle?*, VIRTUAL MENTOR (Mar. 2002), <http://virtualmentor.ama-assn.org/2002/03/gnth1-0203.html>. See also SAM TETLOW, CAMBRIDGE HEALTHTECH INST., SUCCESSFUL PHARMACOGENOMICS BUSINESS MODELS 4 (2002) (estimating that the computed ADR cost in 1992 was 76.6 billion dollars); David J. Wu, *A Pharmacogenomics Standard for FDA Drug Approval: Arbitrary and Capricious or Safe and Effective?*, 23 BIOTECH. L. REP. 733, 733 (2004) (citing annual cost estimates for ADRs at 30.1 to 136.8 billion dollars).

35. Muin J. Khoury & Jill Morris, *Pharmacogenomics and Public Health: The Promise of Targeted Disease Prevention*, OFFICE OF PUB. HEALTH GENOMICS, CTRS FOR DISEASE CONTROL & PREVENTION, <http://web.archive.org/web/20090421103558/http://www.cdc.gov/genomics/training/perspectives/factsheets/pharmacofs.htm> (last updated Nov. 17, 2007) (explaining that while genetic testing to locate V Leiden allele would be medically and scientifically useful, it would also be very costly).

36. *Id.*

37. Kathy L. Hudson, *Genomics, Health Care, and Society*, 365 NEW ENG. J. MED. 1033, 1036-37 tbl.2 (2011); Simon Mallal et al., *Association Between Presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and Hypersensitivity to HIV-1 Reverse-Transcriptase Inhibitor Abacavir*, 359 LANCET 727, 731

The study of genetics could also clarify why people respond differently to medications and how a person's body metabolizes particular compounds.³⁸ The manner by which an individual metabolizes certain drugs may depend on a set of genes separate and unrelated from those correlated to any particular illness that is present throughout the population.³⁹ Simply put, certain genes have an impact on metabolic rates.⁴⁰ Because of genetic variations in metabolism, pharmacogenomic discoveries may cause the drug prescription process to change.⁴¹ Instead of determining dosages by weight, age, and other proxies, physicians will be able to prescribe according to an individual's genetic makeup, thereby "maximiz[ing] the therapy's value and decreas[ing] the likelihood of overdose."⁴²

For example, the D₂ receptor gene, DRD2, is associated with the metabolism of certain antipsychotics.⁴³ Likewise, if an individual carries the variant cytochrome P450 gene, CYP2D6, which encodes a metabolic liver enzyme, he or she cannot metabolize certain compounds, which could therefore allow lethal amounts of a drug to accumulate in his or her body.⁴⁴ It is claimed that "[u]p to 30% of patients do not respond optimally to certain drugs."⁴⁵ If an individual's rate of metabolism is too high, a patient will be undertreated because the drugs will not be delivered in an efficacious manner.⁴⁶ If metabolism is too low, it could lead to an overdose

(2002); Seth Hetherington et al., *Genetic Variations in HLA-B Region and Hypersensitivity Reactions to Abacavir*, 359 LANCET 1121, 1121 (2002).

38. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at 12 tbl.2.1.

39. As the Nuffield Council on Bioethics, an independent charitable body based in the UK, explains, these genes do not necessarily have an effect on an individual's susceptibility to disease, but how the person absorbs, metabolizes, and excretes compounds. *Id.*

40. *See, e.g.*, Goldstein et al., *supra* note 10, at 941 tbl.1b (providing a table of pharmacogenetic variants and their impacts on metabolism).

41. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at 18.

42. Devesh D. Gosavi & Ganapat J. Pawar, *Pharmacogenomics: Promises and Challenges*, 2 INT'L J. RES. PHARMACEUTICAL BIOMED. SCI. 1444, 1445 (2011).

43. Yoshio Yamanouchi et al., *Effect of DRD2, 5-HT2A, and COMT Genes on Antipsychotic Response to Risperidone*, 3 PHARMACOGENOMICS J. 356, 356, 358–59 (2003). One—perhaps now outdated—table on genetic polymorphisms of human drug-metabolizing enzymes and transporters (those genetic variations that are currently known to be susceptible to drug variations) is available online. William E. Evans & Mary V. Relling, *Pharmacogenomics: Translating Functional Genomics into Rational Therapeutics*, 286 SCI. 487, 489 tbl.1 (1999), available at <http://www.sciencemag.org/content/286/5439/487.full.pdf>.

44. Wu, *supra* note 34, at 733. Other examples of prescribing particular dosages according to one's metabolism in order to reduce adverse events include risk reduction strategies such as HIV resistance testing and optimized dosing for HCV. *See* Jianming Tang & Richard A. Kaslow, *Pharmacogenomic Perspectives of Chronic Hepatitis C Virus (HCV) Infection*, 4 PHARMACOGENOMICS J. 171, 172 (2004) (reviewing the use of pharmacogenomics to improve dosing for HCV treatment); *The Making of the Pharmacogenomic Prescription*, *supra* note 27 (discussing how pharmacogenomics is used for HIV resistance testing).

45. Nusrat Khaleeli & Dennis Fernandez, *Patent Prosecution in Pharmacogenomics*, 88 J. PAT. & TRADEMARK OFF. SOC'Y 83, 88 (2006) (claiming that almost a third of patients respond less than ideally to some pharmaceuticals).

46. Greely, *supra* note 22, at 1.

because the site will be overdelivered.⁴⁷ In other words, the ultra-rapid metabolism of a drug can cause it to be ineffective and slow, or non-metabolism of a drug can result in the accumulation of toxic amounts of the compound in the body.

Thus, physicians could modify an individual's prescription according to multiple sets of genes and their interactions,⁴⁸ in order to increase the probability of optimal dosage.⁴⁹ According to Janet Woodcock, Director of the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER), the variability in how individuals metabolize compounds is "a huge problem, because what's considered a normal dose of a drug can be toxic for some people."⁵⁰ She praises the advantages of using pharmacogenomics to determine dosages according to a patient's genetic profile.⁵¹

2. *Diagnosis, Treatment, and Categorization of Disease*

Further, pharmacogenomics promises that our knowledge of the biology underlying illness will increase through the identification of susceptibility genes, which might lead to a better understanding of gene products.⁵² This, in turn, will trigger greater awareness of the role of individual proteins in causing illness, thereby leading to further appreciation of the interaction of these proteins with other substances, as well as the effect of the environment on protein levels and function.⁵³ These developments may result in new forms of diagnosis, treatment, and possibly prevention of many illnesses and disorders.⁵⁴

Although this article primarily focuses on the intersection of pharmacogenomics and the drug development process, diagnosis is another area in which genetic discoveries may have a significant impact. Currently, the process of diagnosis can be quite haphazard, and the trial-and-error method common in the experience of most physicians and patients can take its toll.⁵⁵ Take, for instance,

47. *Id.*

48. See DAVID MELZER ET AL., MY VERY OWN MEDICINE: WHAT MUST I KNOW: INFORMATION POLICY FOR PHARMACOGENETICS 53 (2003) (according to one study, 59 percent of drugs are "metabolised by at least one enzyme that has a variant allele known to cause poor metabolism"); see also NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at 88 (expressing concerns that doctors will group individuals by ethnicity and will refuse to prescribe medications just because they were found to be ineffective in others of the same ethnic group).

49. See Khaleeli & Fernandez, *supra* note 45, at 87–88 (finding that a goal of pharmacogenomics is to identify individual patients and ensure appropriate medication dosages).

50. Tracy Hampton, *FDA Seeks Genome-Based Drug Data*, 291 JAMA 32, 32–33 (2004).

51. *Id.*

52. Nick Craddock & Ian Jones, *Genetics of Bipolar Disorder*, 36 J. MED. GENETICS 585, 592 (1999).

53. *Id.*

54. *Id.*

55. See, e.g., Maree L. Inder et al., "I Really Don't Know Whether it is Still There": Ambivalent Acceptance of a Diagnosis of Bipolar Disorder, 81 PSYCHIATRIC Q. 157, 157 (2010) (describing the haphazard diagnosis among individuals with bipolar disorder).

bipolar disorder, a mental illness that affects 3.9 percent of the American population in their lifetime, with an average age-of-onset of 25 years.⁵⁶ It is one of the most fatal of all illnesses, with a suicide rate of up to 20 percent.⁵⁷ One survey found that although 26.2 percent of adults may have some sort of mental illness within a given year, only 12 percent receive minimally adequate treatment.⁵⁸ This low rate of success is telling of the historical “needle-in-a-haystack” process of diagnosis. The isolation of genes that predispose certain individuals to particular illnesses will lead to an improvement in the understanding of the causes and mechanisms of the illnesses themselves.⁵⁹ For example, mental health physicians began to see this improvement during the revisions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) in the 1980’s, as the definitions shifted away from psychoanalytic assumptions toward a more standardized biology-based approach.⁶⁰

Moreover, the process of identifying the right dosage and combination of medications can be extraordinarily slow and discouraging, and it can take months, or even years, to determine the most effective treatment regimen for many diseases.⁶¹ For example, the Surgeon General’s Office reported that approximately 30 to 50 percent of patients diagnosed with major depressive episodes do not respond to their original medication.⁶² It has been argued that genetic discoveries will allow us to develop a “molecular taxonomy of disease,”⁶³ or “a rational, aetiology-based classification of . . . disorders which will almost certainly provide a much better guide to treatment and prognosis than do current classifications.”⁶⁴

56. *Bipolar Disorder Among Adults*, NAT’L INST. MENTAL HEALTH, http://www.nimh.nih.gov/statistics/1BIPOLAR_ADULT.shtml (last visited Feb. 14, 2012); Liberty Fajutrao et al., *A Systematic Review of the Burden of Bipolar Disorder in Europe*, 5 *CLINICAL PRAC. & EPIDEMIOLOGY MENTAL HEALTH* 3 (2009), <http://w09.biomedcentral.com/content/pdf/1745-0179-5-3.pdf>.

57. Peter M. Brigham, *The Psychopharmacology of Bipolar Disorder*, http://home.comcast.net/~pmbbrig/BP_pharm.html (last visited Jan. 3, 2012).

58. *Any Disorder Among Adults*, NAT’L INST. MENTAL HEALTH, http://www.nimh.nih.gov/statistics//1ANYDIS_ADULT.shtml (last visited Jan. 11, 2012).

59. Nicholas J. Schork, *Genetics of Complex Disease: Approaches, Problems, and Solutions*, 156 *AM. J. RESPIRATORY & CRITICAL CARE MED.* S103, S105 (Supp. 1997) (describing that the study of genetics could lead to investigations into: “(1) the frequency of the deleterious gene in the population, (2) the effect of the gene in the presence of other factors . . . [and] (3) the impact of public health and health economics of the gene if its effects were ameliorated”).

60. See Rick Mayes & Allan V. Horwitz, *DSM-III and the Revolution in Classification of Mental Illness*, 41 *J. HIST. BEHAV. SCI.* 249, 264 (2005) (detailing how the DSM-III help diagnosticians move away from psychoanalysis to the more dominant symptom-based approach to diagnosing mental disorders).

61. P.C. Carder et al., *Negotiating Medications: Patient Perceptions of Long-Term Medication Use*, 28 *J. CLINICAL PHARMACY & THERAPEUTICS* 409, 412 (2003).

62. DEP’T OF HEALTH AND HUMAN SERVS., *MENTAL HEALTH: A REPORT OF THE SURGEON GENERAL-EXECUTIVE SUMMARY* 263 (1999).

63. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at xvii.

64. Craddock & Jones, *supra* note 52, at 592.

Indeed, the discovery of genes that confer vulnerability to an illness could establish multiple and distinct biological causes for the same symptoms, thus creating new categories of an overarching illness.⁶⁵ These subcategories could have diverse molecular and environmental causes, while being manifested in similar physical or behavioral symptoms.⁶⁶ Thus, in the future, diagnosis could be categorized by the individual's biological interactions or one's predetermined reactions to certain medications. For example, the current categories of cancer—based on location and type of tumor—may become obsolete, as the understanding of the molecular biology of illness improves.

B. *The Complexity of Pharmacogenomics*

An important disclaimer is necessary: pharmacogenomics is not as simple as analyzing one's genetic makeup to make drug dosage and prescription decisions.⁶⁷ Pharmacogenomics does not promise perfectly individualized medicine; it will only accelerate the process of tailoring treatment decisions to one's genetic predispositions.⁶⁸ As researchers have focused on the probabilistic nature of genetics, it is becoming clearer that the most common illnesses, if genetic, are compounded by drug interactions and environmental and physiological factors such as nutrition, aging, and liver and kidney function.⁶⁹ Thus, the application of

65. Many believe that "it is likely that some conditions which are now considered to be single disorders, with a common set of symptoms, will be discovered to be more heterogeneous, with several different biochemical disorders leading to a common set of clinical features." NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at xviii.

66. *See generally id.*

67. *See generally* Daniel W. Nebert & Elliot S. Vessell, *Advances in Pharmacogenomics and Individualized Drug Therapy: Exciting Challenges that Lie Ahead*, 500 EUR. J. PHARMACOLOGY 267 (2004) (describing the many challenges and factors effecting the success of pharmacogenomics).

68. *See, e.g.,* TANYA M. LUHRMANN, OF TWO MINDS: THE GROWING DISORDER IN AMERICAN PSYCHIATRY 48 (2000) (discussing the problem of genetic predispositions and the uncertainty of non-individualized medicine).

69. *See* MELZER ET AL., *supra* note 48, at 53; *see also* Pat Buckley & Ross A. McKinnon, *Pharmacogenomics, Ethics, and the Community*, 23 PHARMACIST 23, 23 (2004) ("The probabilistic nature of pharmacogenomics needs to be appreciated when considering whether its application will increase inequalities in the provision of health care. Pharmacogenomic tests are unlikely to indicate that a particular medicine will definitely be effective or ineffective in a particular patient. Rather, they are likely to provide probabilistic information . . ."). The FDA guidance to industry regarding the submission of pharmacogenomic data is clear on the interaction between genes, the environment, and other assorted factors, stating, "[i]n most instances, a genotype or particular gene expression profile is likely to be one of a number of factors that affects the probability of an adverse event or a favorable response. For this reason, pharmacogenomic biomarkers can ordinarily be handled like other non-genomic predictive markers in the clinical arena." FOOD & DRUG ADMIN., U.S. DEP'T OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS 16 (2005) [hereinafter 2005 FDA GUIDANCE]. *See also* Marshall, *supra* note 9, at 7 ("More often than not, several genes, rather than one, interact with environmental factors to result in a particular variation in drug action.").

pharmacogenomics is likely much more complicated than some members of the media and public hope and claim.⁷⁰

The ultimate promise of effective, personalized, tailor-made medicine, with fewer side effects and more appropriate dosage, is tantalizing. However, there are a number of issues that must be considered to proactively approach and anticipate potential innovations and their implications rather than “trying to implement retroactive changes.”⁷¹

Many of the problems encountered when considering the impact of pharmacogenomics on society are multilayered and complex, and involve a myriad of ethical, legal, and policy-related considerations. This article focuses on the role of industry in furthering pharmacogenomic developments and the dimensions of current regulatory and legislative decision-making in the discipline.⁷² The discussion of the impact of pharmacogenomics would be incomplete without addressing how theories of liability may change, or be changed, by pharmacogenomic developments.⁷³

II. PHARMACOGENOMIC DRUG RESEARCH AND DEVELOPMENT

A. Industry Reluctance to Pursue Pharmacogenomics

Pharmaceutical companies may be reluctant to use pharmacogenomics to develop potentially beneficial drugs and therapies because of the limited financial benefit associated with drug development for smaller stratified patient populations. These companies may be hesitant to pursue pharmacogenomics at all due to its inherently unprofitability.⁷⁴ Some critics assert that companies that sell the most products that are *ineffective* for many consumers/patients have the least incentive to do research to identify more effective drugs that will draw market share away from their one-size-fits-all drugs.⁷⁵ Companies with successful blockbuster drugs may be cautious about pursuing pharmacogenomic research because alternative drugs may only benefit a small portion of the population.⁷⁶ Pharmacogenomic developments

70. For example, one commentator, in a critique of the Nuffield Council on Bioethics' report on pharmacogenetics, concluded that “expert opinion is less optimistic as the complexities of gene/gene, and gene/environment interaction have become more apparent.” Oonagh Patricia Corrigan, *Pharmacogenetics, Ethical Issues: Review of the Nuffield Council on Bioethics Report*, 31 J. MED. ETHICS 144, 146 (2005).

71. 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, 104 (2003).

72. See *infra* Parts II–III.

73. See *infra* Part III.C.

74. Karen Peterson-Iyer, *Pharmacogenomics, Ethics, and Public Policy*, 18 KENNEDY INST. ETHICS J. 35, 39 (2008).

75. Barbara J. Evans et al., *Creating Incentives for Genomics Research to Improve Targeting of Therapies*, 10 NATURE MED. 1289, 1291 (2004).

76. See Peterson-Iyer, *supra* note 74, at 39; see also *Pharmacogenomics: Medicine and the New Genetics*, HUMAN GENOME PROJECT INFO.,

could lead to market segmentation by increasing research and development (R&D) costs without raising profits.⁷⁷ Income estimates for smaller, targeted patient markets run 300 to 500 million dollars rather than the one billion dollars generally associated with blockbuster drugs.⁷⁸ Thus, companies may bypass the use of pharmacogenomics to develop potentially beneficial drugs and therapies because of the perceived limited financial benefit.⁷⁹

However, if a rival company manufactures a drug that is obviously more effective than the current blockbuster drug, people may stop buying the ineffective one, thereby forcing sponsors of big-name drugs to focus on targeted drug development in order to compete in the market. In other words, differentiating drugs according to effectiveness in subpopulations may lead to increased competition among companies.⁸⁰

Even as it might fight it, industry is anticipating change, admitting that “[t]he era of the blockbuster is ending.”⁸¹ However, it is unclear how “the drug industry will metamorphose itself.”⁸² In fact, the configuration of the industry may shift so much that Robert Freeman, the former Executive Director of Public Policy at AstraZeneca, acknowledged, “[w]e simply don’t know what kind of business model is necessary to commercialize personalized medicine.”⁸³ Some pharmaceutical companies have actively begun pursuing pharmacogenomic research.⁸⁴ For example, GlaxoSmithKline “has played a prominent role in

http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml (last visited April 12, 2012) [hereinafter HUMAN GENOME PROJECT INFO].

77. Corrigan, *supra* note 70, at 145.

78. Wu, *supra* note 34, at 743.

79. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at 29.

80. Commentators have noted big pharmaceutical companies’ reluctance to enter the pharmacogenomics market, but have conceded that although “[i]ncreased attention to cost effectiveness tends to reward well-targeted therapies for their low rates of treatment failure . . . drugs need only outperform a standard or reference drug, which could itself be poorly targeted.” Evans et al., *supra* note 75, at 1290.

81. Pamela Sherrid, *Is There a Market for Personal Medicine?*, U.S. NEWS & WORLD REP., Jan. 20, 2003, at 56, 56. Six of the ten most successful blockbuster drugs are scheduled to go off-patent in the near future, including Pfizer’s Lipitor. Chris Woolston, *Blockbuster-Drug Prices to Drop as Patents Expire*, L.A. TIMES, July 25, 2011, <http://articles.latimes.com/2011/jul/25/news/la-heb-generics-drug-prices-20110725>.

82. Sherrid, *supra* note 81.

83. *Id.*

84. Amber L. Beitelshes & David L. Veenstra, *Evolving Research and Stakeholder Perspectives on Pharmacogenomics*, 306 JAMA 1252, 1252 (2011) (citing recent studies including one by GlaxoSmithKline investigators, which “has identified major histocompatibility complex genetic variants associated with liver damage in response to lapatinib, which is already Food and Drug Administration (FDA) approved for the treatment of breast cancer,” another in which the “epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors erlotinib and gefitinib recently [was] shown to be more effective in patients with non-small cell lung cancer (NSCLC) who have certain EGFR tumor mutations,” and a third by Pfizer to develop a drug “(crizotinib) for NSCLC, which is projected to be indicated for 3% to 5% of patients with an EML4-ALK fusion gene variation”). By 1998, three major

promoting pharmacogenetics, with company scientists producing a number of scientific papers in high profile science and medical journals urging the uptake of pharmacogenetics.”⁸⁵

B. Advantages of Using Pharmacogenomics in Drug Development

1. Potential Cost-Saving Measures

Drug R&D is expensive and relatively haphazard. In 2010, industry spent an estimated 67.4 billion dollars on pharmaceutical R&D.⁸⁶ The Pharmaceutical Research and Manufacturers of America (PhRMA), the pharmaceutical trade association, estimates the average cost to develop a drug at 1.3 billion dollars.⁸⁷ It currently takes an average of ten to fifteen years for a company to develop a drug.⁸⁸ Since most drugs do not make it to market, the profits from one product must make up for the losses incurred for failed compounds.⁸⁹

Furthermore, only one of “60,000 compounds synthesized by pharmaceutical companies” can be considered “highly successful.”⁹⁰ Success is currently measured by the amount earned; “highly successful” blockbuster drugs have annual global sales over one billion dollars.⁹¹

A study by the Boston Consulting Group asserts that companies that are hesitant to enter the “genomics revolution head on” will suffer the consequences, rendering them unable to compete in the market with those that do.⁹² According to one estimate, the incorporation of pharmacogenomics into drug development could

companies—Genset, Celera Genomics, and Incyte Genetics—had already begun preparations to undertake systematic searches of the genome for variants or single-nucleotide polymorphisms (SNPs), and a number of other companies had been created in order to develop molecular diagnostics. Jeanette J. McCarthy & Rolf Hilfiker, *The Use of Single-Nucleotide Polymorphism Maps in Pharmacogenomics*, 18 NATURE BIOTECH. 505, 505 (2000).

85. Corrigan, *supra* note 70, at 145.

86. PHARM. RESEARCH & MFRS. OF AM., 2011 PROFILE 10 (2011).

87. *Id.* This estimate is highly contentious. See, e.g., Donald W. Light & Rebecca Warburton, *Demythologizing the High Cost of Pharmaceutical Research*, 6 BIOSOCIETIES 34, 36, 38–39 (2011) (critiquing the high costs associated research and development of new drugs).

88. PHARM. RESEARCH & MFRS. OF AM, *supra* note 86, at 12 fig.4.

89. “Only about one in six drug candidates that enter clinical trials are ultimately submitted to and approved by the FDA, according to a study of the 50 largest companies.” *Id.* at 10.

90. C.E. Reeder & W. Michael Dickson, *Economic Implications of Pharmacogenomics*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 229, 230 (Mark A. Rothstein ed., 2003).

91. Michael N. Liebman, *Personalised Medicine: End of the Blockbuster?*, 9 PHARMA FOCUS ASIA, no. 9, 2008 at 4, 8.

92. PETER TOLLMAN ET AL., BOSTON CONSULTING GRP., A REVOLUTION IN R&D: HOW GENOMICS AND GENETICS ARE TRANSFORMING THE BIOPHARMACEUTICAL INDUSTRY 21 (2001).

lead to a reduction in the cost and time of drug development, saving up to 45 percent of clinical drug development costs.⁹³

Pharmacogenomics can be applied at every phase in the drug development process, and companies may be able to save substantial R&D costs and speed up the drug approval process because of the ability to reduce the population in which the drug is tested, leading to more reliable findings, ostensibly faster institutional review board (IRB) review and approval, and safer trials.⁹⁴ Individuals for whom the drug in question is less likely to be effective, or those for whom the drug may have deleterious side effects, can be excluded from the various stages of clinical trials, thereby improving the protection of participants in human research.⁹⁵ Moreover, the “selection of smaller groups of genetically homogenous participants in clinical trials may be advantageous, leading to more robust and reliable scientific findings regarding the group of patients who might eventually be prescribed the medicine.”⁹⁶

Reducing the failure rate could “far outweigh the negatives of market segmentation,” according to Nicholas Dracopoli, the former Vice President of Clinical Discovery Technologies at Bristol-Myers Squibb.⁹⁷ A drug guaranteed to work on the percentage of the population “for whom other drugs are ineffective or cause harmful side effects will return steady revenue at a premium price”—resulting in the development of reliable “mini-busters.”⁹⁸ Currently, blockbusters are the biggest source of revenue for many drug companies, but “mini-busters”

93. Reeder & Dickson, *supra* note 90, at 231 (estimating 45 percent savings of clinical drug development costs). Another group estimates the cost of developing a new medicine to be reduced to about 60 percent of the cost. TOLLMAN ET AL., *supra* note 92, at 12 (estimating a savings of 300 million dollars from an average 880 million dollars in costs).

94. Marshall, *supra* note 31, at 12 (asserting several rewards of pharmacogenomics such as quicker development and increased financial pay-offs for pharmaceutical companies). Goldstein et al., states:

One motivation for pharmacogenetic testing during drug development is that the stratification of patients by genotype might allow the identification of responses that would have been missed in an unselected cohort. This could allow efficacy for subgroups to be shown in drugs that might not have been considered effective in general populations, which could potentially improve the success rate of compounds. Because of the huge costs per patient of clinical trials, it has also been suggested that such streamlining might reduce the average cost of developing new compounds.

Goldstein et al., *supra* note 10, at 945.

95. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at xiv.

96. *Id.*

97. Sherrid, *supra* note 81.

98. Lagay, *supra* note 34 (asserting that such drugs will return a steady revenue at a premium price); Evans et al., *supra* note 75, at 1289 (asserting that tailored treatments could generate new avenues for income); Catherine Schaffer, *Pfizer Explores Rare Disease Path*, 28 NATURE BIOTECH. 881, 881 (2010) (defining “mini-busters” as drugs which treat a small population by pharma standards, but can be charged at a premium due to the demand).

could replace the blockbusters with new, more genome-specific drugs.⁹⁹ For example, pharmacogenomic discoveries “threaten[] to shake up the lucrative 26 billion dollar market for Statins—the big-selling products that help lower cholesterol in the blood and reduce the risk of heart attacks and strokes.”¹⁰⁰

However, the view that pharmacogenomics will lead to more efficacious, reliable, and safe clinical trials because of more targeted trial studies is not without its detractors.¹⁰¹ For example, some believe that “the small size of pharmacogenetics studies renders them unconvincing.”¹⁰² In addition, the restricted trial populations will limit the claims a company can make on a drug to the FDA.¹⁰³ This may affect the licenses FDA may grant, because approval will only be related to the particular population in the pivotal trials.¹⁰⁴ The restriction of FDA approval to specific patient groups could implicate a significant problem already plaguing FDA, that of off-label prescription.¹⁰⁵

2. *Saving Shelved Drugs*

Pharmacogenomics may also enable the re-marketing of “shelved” drugs that are rarely, if ever, prescribed because of an inability to determine for whom the drugs work or because they cause adverse reactions in some patients.¹⁰⁶ Between January 1, 1971 and May 31, 2006, over three percent of drugs approved by FDA were withdrawn due to unacceptable side effects.¹⁰⁷ Genetic tests may be able to revive such drugs that were withdrawn from the market.¹⁰⁸ The identification of a

99. See Javier Barrios-González & Roxana U. Miranda, *Biotechnological Production and Application of Statins*, 85 APPLIED MICROBIOLOGY & BIOTECH. 869, 869 (2010) (stating that the two highest selling drugs in the United States in 2006 were statins).

100. *Genes Play Role In Who Benefits From Statin—In Boost to ‘Personalize Medicine,’ Study Links Patient Genetics with Efficacy of Cholesterol Drug*, WALL ST. J., June 16, 2004, at D1. In one study, “[p]atients with a certain common genetic variant had a 22% smaller drop in total cholesterol and a 19% smaller drop in LDL or ‘bad’ cholesterol than those patients without the variant.” *Id.*

101. See MELZER ET AL., *supra* note 48, at 33 (questioning the generalizability of pharmacogenomics in pre-licensing drug trials).

102. *Id.*

103. *Id.* at 34–35 (assessing the issues created by a smaller target population in detecting unusual adverse events).

104. See *id.* (detailing the uncertainty surrounding the regulatory guidelines for pharmacogenetic products).

105. See *infra* Part III.A.2.b.

106. Greely, *supra* note 22, at 2.

107. CTR. FOR DRUG EVALUATION & RES., FOOD & DRUG ADMIN., REPORT TO THE NATION 2005: IMPROVING PUBLIC HEALTH THROUGH HUMAN DRUGS 49 (2005) [hereinafter REPORT TO THE NATION].

108. Meurer, *supra* note 2, at 401. One commentator highlighted the anti-epileptic drug felbamate in order to clarify the use of pharmacogenomics to reduce ADRs. Goldstein et al., *supra* note 10, at 945. The drug was approved in 1993, after it was demonstrated that it helped control seizures. *Id.* During a clinical investigation, there was no evidence of clinically significant blood or liver disorders related to use of the drug. *Id.* However, 34 cases of aplastic anaemia and 23 cases of hepatic failure, with 18 reported fatalities, were reported in the first year after licensing. *Id.* It is believed that these ADRs and associated deaths were related to the metabolism of the drug. *Id.* The authors contend that “[t]he ability

“unique population . . . that benefits from a drug that once experienced lagging sales because of its ineffectiveness in the larger overall population” could mean that “the postmarketing use of pharmacogenomic data may be quite useful to a drug company.”¹⁰⁹

Moreover, like those products that were shelved *after* FDA approval, drugs that had not made it through the approval process or were abandoned during development may also be given a second chance.¹¹⁰ Companies may take advantage of “Lazarus” programs in which drugs that have failed to receive FDA approval due to high rates of ADRs or low efficacy can be “resurrected and used to treat genetically selected responders.”¹¹¹ Thus, “[p]reviously failed drug candidates may be revived as they are matched with the niche population they serve.”¹¹² In particular, drugs in Phase III trials may be “rescued” due to a new ability to reduce the rate of toxicity or adverse events in the identified testing population.¹¹³ It has been predicted that although the big pharmaceutical companies may continue to abandon these drugs (“why try to rescue a failed compound when pipelines are overflowing with leads?”), such drugs may present desirable opportunities for smaller biotech companies who choose to pursue licensing.¹¹⁴

3. Avoiding Scandal (and Harm to Patients)

Companies may also be able to avoid scandals like that associated with the antiarthritic drug Vioxx. In 2004, Merck & Co. initiated the biggest voluntary drug recall in history due to evidence that Vioxx raises the risk of heart attack and stroke.¹¹⁵ The recall incensed FDA critics, who have accused the FDA of lacking aggressiveness and “foot-dragging” once a drug has entered the market.¹¹⁶ Agency

to reliably predict which patients might be at risk of such reactions to felbamate might allow greater confidence in its use, and again make available a potentially valuable AED [anti-epileptic drug] for patients with epilepsy that can itself be life-threatening.” *Id.* This example is illustrative of the optimism many have for FDA-approved drugs that have been shelved due to adverse reactions. The authors claim that the economic incentives for “unshelving” the drug could be well worth it, explaining that “[i]f pharmacogenetic predictors of adverse events could prevent the exposure of genetically vulnerable patients and so preserve even a single drug, the costs of any large-scale research effort in pharmacogenetics could be fully recovered.” *Id.*

109. Binzak, *supra* note 71, at 126.

110. Andrew Marshall, *One Drug Does Not Fit All*, 16 NATURE BIOTECH. 1, 1 (Supp. 1998) (discussing “Lazarus” programs in which products that had been shelved after not making it through the approval process).

111. *Id.*

112. HUMAN GENOME PROJECT INFO, *supra* note 78.

113. MELZER ET AL., *supra* note 48, at 31.

114. Marshall, *supra* note 110, at 1.

115. *See Recall of Merck Arthritis Drug Vioxx Recall Leads to New Questions on FDA Effectiveness*, KAISER HEALTH NEWS (Oct. 4, 2004), <http://www.kaiserhealthnews.org/Daily-Reports/2004/October/04/dr00026061.aspx?p=1> (reporting concerns surrounding the FDA approval process for pharmaceuticals).

116. *Id.*

response to the Vioxx debacle has included a focus on pharmacogenomics. Steven Galson, then-Acting Director of CDER, said that, among other things, FDA would “promot[e] research on pharmacogenetics to help identify people who might react adversely to drugs.”¹¹⁷ Thus, with an increase in pharmacogenomic research, drugs companies like Merck may be less likely to lose money late in trials due to safety and efficacy problems (even after FDA has already approved the drug), and will therefore be able to avoid withdrawing a drug from the market and the concomitant negative press and profit loss.¹¹⁸

C. *The Public and Private Sectors: Shifts and Collaborations*

Identifying resources for R&D is of primary significance to encouraging pharmacogenomic advancement. Generally, “[f]ederal subsidies and public sector research . . . play significant roles stimulating the development of the first generation of genetic tests designed to customize drug therapy.”¹¹⁹ Going forward, pharmacogenomics will continue to require public sector funding to encourage the private sector to develop tests for existing drugs.¹²⁰ It may be necessary to either incentivize private sponsorship of drug development, or the government will need to provide greater federal subsidies.¹²¹ In particular, alternative sources of funding may be most needed where genetic tests “are not widely adopted, when tests are designed for use with substitute drugs manufactured by different companies, or when the private cost of test development is high because of licensing costs.”¹²²

117. *Id.*

118. Evans et al., *supra* note 75, at 1289.

119. Meurer, *supra* note 2, at 401, 425 (“Thus far, public sector funding and R&D have been critical to the creation and deployment of pharmacogenomic innovations.”).

120. *Id.* at 401, 425–26 (suggesting that funding from the public sector will further the goals of pharmacogenomics).

121. A Pharmaceutical Research and Manufacturers of America (“PhRMA”) report explained: [A]ccording to the National Institutes of Health (NIH), public dollars are not funding the research leading to new medicines. In fact, only 4 of the 47 top-selling drugs considered by NIH in its study to determine if American public investments were funding new drug development were developed in part with NIH funding, and none [were] developed solely with public funds.

PHARM. RESEARCH & MFGS. AM., PHARMACEUTICAL INDUSTRY PROFILE 5 (2004).

122. Meurer, *supra* note 2, at 425–26. Meurer concludes by recommending a number of options for the type of public subsidies that should be offered, stating:

Presently, federal grants directly support public sector pharmacogenomic research, and indirectly support pharmacogenomics through subsidies encouraging the production of research inputs (like gene data) that are used in the development of genetic tests. The government can encourage adoption of genetic tests through drug law and health insurance regulation. Finally, the drug laws may be used to subsidize the development of drugs designed to treat “orphan genotypes.”

Id. at 426.

However, data supports the conclusion that some R&D support for pharmacogenomics must shift from the public to the private sector.¹²³

Critics argue that economic considerations could lead to a differentiation between the research focus in the industrial and academic sectors.¹²⁴ They recommend that the appropriate regulatory mechanisms ensure cooperation between sectors to facilitate the transfer of information and the development of pharmacogenomic technology.¹²⁵ There are a few public-private collaborations already underway.¹²⁶ The SNP Consortium, a non-profit foundation, was founded to provide public genomic data online, thereby facilitating genomic research.¹²⁷ Pharmaceutical and technology companies, academic research centers, and the Wellcome Trust have entered into a partnership “to publish a high-density SNP map of the human genome.”¹²⁸ The database of over 3.1 million SNPs is maintained by Cold Spring Harbor Laboratory.¹²⁹

There have also been a number of agreements between pharmaceutical and biotech companies.¹³⁰ A 2003 survey indicated an interest in pharmacogenomic collaborations by both small biotech companies that are generally involved in providing test kits and other technological innovation, and large pharmaceutical companies.¹³¹ In 1997, two other collaborations between companies involved a 25 million dollar deal between Incyte Genomics and GlaxoSmithKline to form diaDEXUS, and a 42.5 million dollar agreement between Genset and Abbott to

123. *See id.* at 425 (“If pharmacogenomics fulfills its promise, then we should expect that, as this sector of the pharmaceutical industry matures, most of the R&D on genetic tests will shift to the private sector.”); *see also* Beitelshes & Veenstra, *supra* note 84, at 1252 (“The pharmaceutical industry is increasingly using pharmacogenomic strategies to identify patient subgroups with improved benefit-risk profiles.”).

124. Goldstein et al., *supra* note 10, at 945.

125. Likewise, the Nuffield Council on Bioethics recommends that public-private partnerships be encouraged. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at xiv.

126. *See* Arthur L. Holden, *The SNP Consortium: Summary of a Private Consortium Effort to Develop an Applied Map of the Human Genome*, 32 *BIOTECHNIQUES* S22, S22, S23 (Supp. 2002) (describing partnerships between private entities like the Wellcome Trust and public universities).

127. *Id.* at S22.

128. Celia M. Henry, *Pharmacogenomics*, *CHEMICAL & ENGINEERING NEWS*, Aug. 13, 2001, at 37, 39. In phase I of the HapMap project, “[over] 1.1 million SNPs were genotyped in 270 individuals from 4 worldwide populations.” Gudmunder A. Thorisson et al., *The International HapMap Project Web Site*, 15 *GENOME RES.* 1592, 1592 (2005).

129. Int’l HapMap Consortium, *A Second Generation Human Haplotype Map of Over 3.1 Million SNPs*, 449 *NATURE* 851 (2007). *See also* *Groups Participating in the International HapMap Project*, INT’L HAPMAP PROJECT, <http://snp.csh.org/groups.html> (last visited Apr. 12, 2012).

130. *See, e.g.*, Corrigan, *supra* note 70, at 145 (providing the example of a 20 million dollar alliance between the biotech company Genset and the pharmaceutical company Abbott Laboratories “to analyze variations in patient responses to particular drug therapies”).

131. Adam Hedgecoe & Paul Martin, *The Drugs Don’t Work: Expectations and the Shaping of Pharmacogenetics*, 33 *SOC. STUD. SCI.* 327, 342–43 (2003).

develop pharmacogenomics tests for gauging drug response.¹³² In 1998, deCODE Genetics and Roche entered into a 200 million dollar agreement “to identify disease genes through genetic analysis of the uniquely homogenous Icelandic population.”¹³³ Pharmaceutical companies have also been encouraged to enter into agreements with biotech companies to develop test-drug combinations.¹³⁴ Such arrangements are financially desirable because “[w]here tests and drugs are intimately linked, as is in the case of new pharmacogenetic products, their evaluation needs to be co-ordinated and any licensing approval issued in concert” rather than separately.¹³⁵

Even if smaller companies do not enter into collaborations with “big pharma,” the “existence of ‘niche’ therapeutic categories will present opportunities for smaller, genetics-based biotechnology firms to enter the market and produce the drugs.”¹³⁶ It has been hypothesized that the pharmaceutical industry may bifurcate into two separate sectors: those big pharmaceutical companies that will continue to pursue “blockbuster” drugs for “high-prevalence polymorphisms” and a “second ‘cottage’ sector that serves the ‘orphan drug’ market.”¹³⁷

It will be interesting to see how the pharmaceutical industry adapts and changes with pharmacogenomic advances. The industry has been “in a consolidation and merger phase, with ever larger corporations emerging at a steady pace.”¹³⁸ Since blockbuster drugs may no longer be the preferred treatment, companies may hone in on “mini-busters,” thereby decreasing their size and the way they work with one another.¹³⁹

132. Allen C. Nunnally et al., *Intellectual Property and Commercial Aspects of Pharmacogenomics*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 109, 127–28 (Mark A. Rothstein ed., 2003).

133. *Id.* at 128. deCODE Genetics is an Icelandic company that endeavored to set up an Icelandic Health Sector Database (HSD) containing the medical records and genealogical and genetic data of all Icelanders. David E. Winickoff, *Genome and Nation: Iceland's Health Sector Database and its Legacy*, INNOVATIONS, 80, 80–81 (2006).

134. Companies have “jumped on the technology, many of them merging with biotech companies that suddenly see a profitable product in the near future for the first time.” Lagay, *supra* note 35.

135. MELZER ET AL., *supra* note 48, at 40. Herceptin is one example of a linked test-drug combination, as it requires administration of a test before it can be prescribed. However, “[t]he test is not a true pharmacogenetic test, because it measures protein expression in a tumor rather than the underlying genetic makeup of the patient, but it shows the power of such tests.” Henry, *supra* note 128.

136. Reeder & Dickson, *supra* note 90, at 233.

137. *Id.*

138. Laviero Mancinelli et al., *Pharmacogenomics: The Promise of Personalized Medicine*, 2 AAPS PHARMSCI 1, 2 (2000), available at <http://www.aapsj.org/articles/ps0201/ps020104/ps020104.pdf>.

139. *See id.* (explaining that the “one drug fits all” approach could evolve into more individualized efforts, although this may not be a realistic goal); Bryn Williams-Jones & Oonagh Patricia Corrigan, *Rhetoric and Hype: Where's the 'Ethics' in Pharmacogenomics?*, 3 AM. J. PHARMACOGENOMICS 375, 379 (2003).

III. REGULATORY AND LEGAL ISSUES

The utilization of pharmacogenomics in drug development has repercussions for diverse areas of the law. This section considers the FDA guidance on pharmacogenomic data submission as well as other FDA measures taken to ensure the safety and efficacy of pharmacogenomic advancements.¹⁴⁰ The impact of the Orphan Drug Act (ODA) is explored in light of the creation of drug compounds for small targeted populations.¹⁴¹ This article concludes with a consideration of legal liability for both physicians and the pharmaceutical industry.¹⁴²

A. *The FDA*

Pharmacogenomics introduces new complexities to the already complicated system of drug development and approval, and it has been argued that pharmacogenomics will lead to a “major, technology-driven restructuring” which would require “bold leadership from relevant regulatory agencies worldwide.”¹⁴³ The FDA encourages the incorporation of pharmacogenomics into the drug development process, and currently the agency has approved 114 drugs with pharmacogenomic information in their labels.¹⁴⁴

The Food, Drug, and Cosmetic Act (FDCA)¹⁴⁵ authorizes the FDA to ensure that human and animal drugs, biological products, and therapeutic devices are safe and effective.¹⁴⁶ The drug amendment to the FDCA of 1962 authorized the FDA to take a more preemptive approach to drug development, requiring premarket approval for every new drug.¹⁴⁷ Thus, a new drug application (NDA) will only be approved once the Center for Drug Evaluation and Research (CDER), which is responsible for approving NDAs, is convinced of the drug’s safety and

140. *See infra* Part III.A.

141. *See infra* Part III.B.

142. *See infra* Part III.C.

143. Evans et al., *supra* note 75, at 1290.

144. *Table of Pharmacogenomic Biomarkers in Drug Labels*, FOOD & DRUG ADMIN, <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm> (last updated Feb. 29, 2012). However, critics have noted that the current labeling process may be inadequate, as the information provided on the labels “is probably of limited use to most physicians and patients” because it does not contain “clear and comprehensive drug labeling that informs about genetic tests relevant to the safety or efficacy of use is critical to enhancing patient care.” Hudson, *supra* note 37, at 1036.

145. 21 U.S.C. §§ 301–399 (2006).

146. The FDA’s mission is to “protect public health . . . by helping to speed innovations that make medicines more effective, safer, and more affordable.” *What We Do*, FOOD & DRUG ADMIN, <http://www.fda.gov/aboutfda/whatwedo/default.htm> (last visited Apr. 12, 2012).

147. Drug Amendments of 1962, Pub. L. No. 87-781, §101, 76 Stat. 780, 781. *See also* John J. Smith, *Regulation of Medical Devices in Radiology: Current Standards and Future Opportunities*, 218 RADIOLOGY 329, 330 (2001) (explaining the premarket approval process).

effectiveness.¹⁴⁸ In order to demonstrate safety and efficacy, drug companies spend millions of dollars and many years enrolling individuals in a series of clinical trials to generate the necessary data.¹⁴⁹ The Office of Clinical Pharmacology in CDER is charged with reviewing biopharmaceutic, pharmacokinetic, and pharmacodynamic data in Investigational New Drug (IND) applications and NDAs.¹⁵⁰ After the pioneer drug's patent has expired, FDA can approve abbreviated new drug applications (ANDAs), for which a generic drug sponsor may establish that the drug is a bioequivalent to the original product.¹⁵¹

In general, the FDA has taken a wait and see approach to regulating new technologies. In the late 1990's, in response to developments in pharmacogenomics, the FDA indicated that it planned to maintain the "drug approval process as it currently exists," explaining that there is "no problem with the promise of pharmacogenomics," and that they were waiting for "data to evaluate the results."¹⁵² As of 1998, the FDA still had no plans to focus any guidance solely on pharmacogenomics.¹⁵³ Moreover, the FDA and other agencies thought it unlikely that pharmacogenomic information would be required for all drugs.¹⁵⁴

1. Voluntary Genomic Data Submissions

Only five years later, in November, 2003, the FDA released its draft guidance to industry regarding the submission of pharmacogenomic data to the agency.¹⁵⁵

148. *How Drugs are Developed and Approved*, FOOD & DRUG ADMIN, <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/default.htm> (last visited Apr. 12, 2012).

149. See, e.g., Thomas Bodenheimer, *Uneasy Alliance: Clinical Investigators and the Pharmaceutical Industry*, 342 NEW ENG. J. MED. 1539, 1539 (explaining that the FDA mandates that manufacturers demonstrate their products meet efficacy and safety tests, and the entire process can range from 300 million to 600 million dollars).

150. *Office of Clinical Pharmacology (OCP)*, FOOD & DRUG ADMIN, <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm106189.htm> (last updated Nov. 16, 2011).

151. *Abbreviated New Drug Application (ANDA): Generics*, FOOD & DRUG ADMIN, <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandgenerics/default.htm> (last updated Jan. 3, 2012). One author has maintained that pharmacogenomics will facilitate the way generic drugs are approved. Lars Noah, *The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients' Genetic Profiles*, 43 JURIMETRICS 1, 18 (2002) ("Pharmacogenomic information could, therefore, provide a better basis for making comparative judgments about bioavailability and facilitate the approval and use of generic drugs in the future.").

152. Binzak, *supra* note 71, at 105.

153. See John Hodgson & Andrew Marshall, *Pharmacogenomics: Will the Regulators Approve?*, 16 NATURE BIOTECH. 243, 243 (1998).

154. *Id.* at 243.

155. FOOD & DRUG ADMIN., DEP'T OF HEALTH & HUMAN SERVS., DRAFT GUIDANCE FOR INDUSTRY ON PHARMACOGENOMIC DATA SUBMISSIONS (2003) [hereinafter FDA DRAFT GUIDANCE].

Lawrence Lesko, the former Director of the Office of Clinical Pharmacology, stated that the agency has been atypically proactive in issuing its guidance.¹⁵⁶

Although industry often prefers a hands-off approach, the private sector sought guidance from the FDA regarding the use of pharmacogenomics in its R&D.¹⁵⁷ Stephen Friend, a Senior Vice President at Merck, explained that both patients and pharmaceutical companies need “ground rules because the correct use of this data . . . is going to be critical for it to be of benefit.”¹⁵⁸ In response, the FDA encouraged drug companies to conduct pharmacogenomic tests during drug development and to submit resulting data to the FDA, while maintaining an appropriate level of safety and efficacy for consumers.¹⁵⁹ The draft guidance was considered quite “pro-pharmacogenomics,” and the FDA stated that the nonbinding recommendations were intended to “facilitate,” and “not impede, the use of pharmacogenomic tests during drug development.”¹⁶⁰ In discussing the draft guidance, then-FDA Commissioner Mark B. McClellan explained that it was:

[I]ntended to ensure that evolving regulatory policies and study designs are based on the best science; provide public confidence in this new field where scientifically appropriate; facilitate the use of such tests during drug development; and clarify for industry what types of pharmacogenomic data to submit to FDA.¹⁶¹

The guidance sought to remedy pharmaceutical sponsors’ hesitancy in using pharmacogenomic technologies in drug development by clarifying how the FDA will use and interpret in the drug application review process.¹⁶²

156. Lawrence Lesko, Dir. of the Office of Clinical Pharmacology, Ctr. Drug Evaluation & Res., Luncheon Keynote Address at the Scientific American Present: Targeted Medicine: From Concept to Clinic (Nov. 11, 2004) (transcript available in the Fair Disclosure Wire) [hereinafter Lesko Keynote Address].

157. Anna Wilde Mathews, *FDA Will Issue Rules on New Era of ‘Personalized Medicine’*, WALL ST. J., Nov. 3, 2003, at B1 (“Major drug companies are likely to welcome a firm signal from the FDA that will reduce the questions surrounding the new field. They are also likely to applaud the agency’s promise that voluntarily submitted information won’t be used in decisions about drug approvals.”).

158. *Id.*

159. See FDA DRAFT GUIDANCE, *supra* note 155 (“The draft guidance is intended to facilitate scientific progress in the area of pharmacogenomics, which should enable the FDA to use pharmacogenomic data in regulatory policies and decision making.”); see also Hampton, *supra* note 50.

160. Letter from Joanna Waugh, Regulatory Grp. Dir., Hoffman-La Roche, Inc., to the Dockets Mgmt. Branch (HFA-305) of the Food & Drug Admin. (Feb. 2, 2004) (on file with the Journal of Health Care Law & Policy).

161. Frank S. Zollmann, *FDA Issues Guidance on Pharmacogenomics Data*, HUM-MOLGEN (Nov. 5, 2003, 16:28), <http://hum-molgen.org/NewsGen/11-2003/000015.html>. The draft guidelines were intended to balance the thin line between: “(a) accepting correlative data on genotype and drug response . . . and (b) ensuring that the first experiences evaluating this data will not act as a disincentive for drug companies embarking on existing and future drug research and development programs.” Shah, *supra* note 16, at 5.

162. Zollmann, *supra* note 161.

In March 2005, the FDA issued its final guidance, which did not vary significantly from the draft version.¹⁶³ The fact that the final guidance had been so delayed led to some skepticism among those that it affects.¹⁶⁴ In late 2004, Lesko denied that the wait for the final draft was due to a “big, big problem,”¹⁶⁵ and attributed the delay to the 2004 political elections, which impeded the collaboration necessary to issue the final guidance.¹⁶⁶ He also explained that the guidance had been postponed because it would be released with companion documents, including a “roadmap for the voluntary submission process.”¹⁶⁷

The guidance provides a number of examples of places in which the field of pharmacogenomics has yet to be established or generally accepted by the scientific community.¹⁶⁸ The guidance is therefore intended to motivate the pharmaceutical industry to pursue pharmacogenomic R&D, allowing industry and the FDA to become comfortable with novel pharmacogenomic approaches as they develop and to establish consensus around pharmacogenomics standards and policies.¹⁶⁹

The FDA’s guidance also provides a “safe harbor,” which asks companies to voluntarily submit their pharmacogenomic data (“voluntary exploratory data submissions” or VXDSs), in return for the assurance that the agency will not make premature regulatory decisions based on these submissions.¹⁷⁰ This assurance was a reaction to companies’ concerns that data would be used against them to keep their products off the market or to “limit [their] approval to a small subpopulation of

163. Press Release, Food & Drug Admin., FDA Works to Speed the Advent of New, More Effective Personalized Medicine (Mar. 22, 2005). Although there is little obvious difference between the draft and final guidance, the final version did attempt to resolve ambiguities in the draft version. See FOOD & DRUG ADMIN., U.S. DEP’T. OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS—COMPANION GUIDANCE (2007) (clarifying voluntary genomic data submissions). In 2007, FDA released companion guidance to the 2005 guidance. *Id.* The addendum includes recommendations on gene expression data from microarrays, genotyping, genomic data in clinical study reports, genomic data from nonclinical toxicology studies, and data submission formats. *Id.*

164. See Lesko Keynote Address, *supra* note 156; Mark Ratner, *FDA Pharmacogenomics Guidance Sends Clear Message to Industry*, 4 NATURE REVS. DRUG DISCOVERY 359, 359 (2005) (explaining that companies awaited the final guidance document for some time).

165. Lesko Keynote Address, *supra* note 156.

166. *Id.*

167. *Id.* Others attributed the delay in part to Mark McClennan’s departure from his position as Commissioner of FDA in March 2004. Malorye A. Branca, *FDA Issues PGX Guidance*, BIO-IT WORLD (Apr. 15, 2005), http://www.bio-itworld.com/BioIT_Article.aspx?id=39242.

168. See 2005 FDA GUIDANCE, *supra* note 69, at 3–4 (explaining the scientific uncertainty of pharmacogenomic test results which make regulatory decision-making difficult, such as probable or known valid biomarkers, as well as other less well-developed tests that are “insufficient for making regulatory decisions”).

169. See Press Release, Food & Drug Admin., *supra* note 163.

170. Federico M. Goodsaid et al., *Voluntary Exploratory Data Submissions to the US FDA and the EMA: Experience and Impact*, 9 NATURE REVS. DRUG DISCOVERY 435, 435 (2010). VXDSs were formerly referred to as “voluntary genomic data submissions” or VGDSs. *Id.*

patients.”¹⁷¹ The FDA’s policy is aimed at encouraging drug companies to share pharmacogenomic results without fear of the FDA demanding more research.¹⁷² The agency plans to use submitted pharmacogenomic information to “gain a better understanding of the field.”¹⁷³

The Institutional Pharmacogenomics Review Group (IPRG) was created by the FDA to set a scientific and regulatory framework for reviewing VXDSs.¹⁷⁴ If it is unclear whether a submission is voluntary or mandatory, the IPRG is responsible for convening a meeting with the sponsor and representative(s) from the relevant review division to help determine the status of the submission in question.¹⁷⁵ The IPRG reviews voluntary data submissions and also, upon request, consults with FDA review staff regarding genomic data submissions that are required (per the relevant regulations) to be submitted to, or as part of, an existing application that will be used during the regulatory process.¹⁷⁶

The FDA guidance clarifies how submitted data will be utilized in regulatory decision-making, setting out three classifications of biomarkers: exploratory, probable valid, and known valid biomarkers.¹⁷⁷ What differentiates the categories is “their validity or degree of validity,” or “their degree of uncertainty.”¹⁷⁸ Lesko

171. Hampton, *supra* note 50, at 32. The FDA lists the following as advantages of voluntarily submitting pharmacogenomic data, including the opportunities for industry to: (1) have informal meeting with FDA pharmacogenomics experts; (2) “[r]eceive and benefit from informal peer-review feedback” on pharmacogenomics issues and/or questions; (3) “[g]ain insight into current FDA thinking” about pharmacogenomics that may assist in reach strategic decisions; and (4) familiarize FDA with pharmacogenomics experiments, data analysis and interpretation approaches. *Genomics: Frequently Asked Questions*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083893.htm> (last visited April 13, 2012).

172. See Mathews, *supra* note 157 (noting that the FDA may ask “companies to voluntarily submit more general research in pharmacogenomics”); see also Richard Fisler, *Biomarkers in Clinical Development: Implications for Personalized Medicine and Streamlining R&D*, ADVANCES LIFE SCIENCES REPORT 16 (2005) (explaining that many companies fear a delay in approval of their product due to FDA questioning).

173. Such knowledge is “important, because there’s a lot of uncertainty about the significance of data in these areas,” according to the director of regulatory affairs of a large pharmaceutical company. Mathews, *supra* note 157.

174. *Interdisciplinary Pharmacogenomics Review Group (IPRG)*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083889.htm> (last updated July 27, 2010).

175. CTR. FOR DRUG EVALUATION & RESEARCH, FOOD & DRUG ADMIN., MANUAL OF POLICIES AND PROCEDURES: MANAGEMENT OF THE INTERDISCIPLINARY PHARMACOGENOMICS REVIEW GROUP (IPRG) 1–3 (2005) [hereinafter MANUAL OF POLICIES AND PROCEDURES].

176. *Id.* at 2–3.

177. 2005 FDA GUIDANCE, *supra* note 69, at 4 (explaining “when the data will be considered sufficiently reliable to serve as the basis for regulatory decision making; when it will be considered only supportive to a decision; and when the data will not be used in regulatory decision making.”).

178. Lesko Keynote Address, *supra* note 156. See 2005 FDA GUIDANCE, *supra* note 69, at 4 (distinguishing between known valid biomarkers, which are accepted in the broad scientific community,

explained that “the function is driven by the classification, and then the function in turn drives the submission process, whether it is voluntary or required and whether it is a full report, abbreviated or synopsis.”¹⁷⁹ The guidance informs drug sponsors on when and how to submit pharmacogenomic data “during the drug or biological drug product development and review processes,” what format and content must be submitted, and how the data will, or will not, be used in regulatory decision making.¹⁸⁰ Moreover, although the submission of pharmacogenomic data is generally voluntary, the FDA guidance recommends that tests and drugs be co-developed, and all information submitted to the agency;¹⁸¹ this way a drug sponsor can “fully integrate pharmacogenomic data into the drug development program.”¹⁸²

Thus, in issuing its pharmacogenomics-related guidance, the FDA sought to remain consistent with existing agency policy.¹⁸³ Mandatory genomic data submissions continue to be processed according to standard processing for routine application submissions.¹⁸⁴ Moreover, the FDA provides detailed instructions for determining when a drug company is required to submit pharmacogenomic data for an IND.¹⁸⁵ For example, if data is submitted to a known valid biomarker, the information must be submitted pursuant to 21 C.F.R. § 312.23.¹⁸⁶ The FDA guidance provides a unique submission algorithm for each category because FDA regulations enunciate different requirements for INDs, unapproved NDAs and Biologics License Applications (BLAs), and approved NDAs and BLAs.¹⁸⁷

and probable valid biomarkers, which appear to have predictive value but may not yet be widely accepted).

179. Lesko Keynote Address, *supra* note 156.

180. 2005 FDA GUIDANCE, *supra* note 69, at 1.

181. *Id.* at 6.

182. *Id.*; see Hampton, *supra* note 50, at 33 (explaining that collaboration between the FDA and the pharmaceutical industry is important from a clinical perspective).

183. 2005 FDA GUIDANCE, *supra* note 69, at 3.

184. MANUAL OF POLICIES AND PROCEDURES, *supra* note 175, at 2.

185. 2005 FDA GUIDANCE, *supra* note 69, at 19–20. A company must submit a full report if:

1. The test results are used for making decisions pertaining to a specific clinical trial, or in an animal trial used to support safety (e.g., the results will affect dose selection, entry criteria into a clinical trial safety monitoring, or subject stratification).

2. A sponsor is using the test results to support scientific arguments pertaining to, for example, the pharmacologic mechanism of action, the selection of drug dosing or the safety and effectiveness of a drug.

3. The test results constitute a known, valid biomarker for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in humans, or is a known valid biomarker for a safety outcome in animal studies or a probable valid biomarker in human safety studies. If the information on the biomarker (example, human CYP2D6 status) is *not* being used for purposes 1 or 2 above, the information can be submitted to the IND as an abbreviated report.

Id.

186. *Id.* at 24.

187. *Id.* at 8–12 (explaining the algorithms in Section IV of the report).

Lesko predicted that the relation between submission format and which definition will apply to biomarkers within the “hierarchy” the guidance provides would be one of the most contentious issues with the guidance.¹⁸⁸ Many claimed that the definitions in the guidance were unclear, and “you need[ed] a lot of specific examples to walk through them, either with a sponsor or with a review division at FDA.”¹⁸⁹ Most likely in response, the FDA published *Quick Reference* materials, which contain a series of decision trees to make the process as clear as possible.¹⁹⁰ The guide provides a simple table for determining when data is required to be submitted and when it may be submitted voluntarily.¹⁹¹ To clarify further, the FDA also issued an attachment to the guidance, providing prototypical examples of voluntary and required submissions.¹⁹²

Reactions to the guidance have been generally positive.¹⁹³ In the first five years after its release, the agency received more than 40 VXDSs, resulting in more than 35 meetings between the FDA and industry sponsors.¹⁹⁴ However, FDA representatives assert that “[i]ndustry sponsors have not fully embraced the [VXDS] concept as evidenced by the fact that numerous major pharmaceutical and biotechnology companies have never submitted a [VXDS] to the FDA.”¹⁹⁵

2. Other FDA Approaches

Pharmacogenomics has impacted the way entities that determine licensing and prescription of new drugs interact with entities that regulate and approve linked

188. Lesko Keynote Address, *supra* note 156.

189. *Id.*

190. See 2005 FDA GUIDANCE, *supra* note 69, at 19–24.

191. *Id.* at 24.

192. See FOOD & DRUG ADMIN., U.S. DEP’T OF HEALTH & HUMAN SERVS., ATTACHMENT TO GUIDANCE ON PHARMACOGENOMIC DATA SUBMISSIONS: EXAMPLES OF VOLUNTARY SUBMISSIONS OR SUBMISSIONS REQUIRED UNDER 21 CFR 312, 314, OR 601 (2005). However, some issues were not clarified—for example, how pharmacogenomics may affect how drugs will be classified as orphan drugs under the Orphan Drug Act of 1983. NAT’L INST. HEALTH, NIH COMMENTS ON FDA’S DRAFT GUIDANCE FOR INDUSTRY PHARMACOGENOMIC DATA SUBMISSION 2 (2004).

193. Goodsaid et al., *supra* note 170, at 435 (VXDSs have “a positive impact on the content of biomarker data in subsequent regulatory applications” and “industry is successfully integrating novel biomarker data in drug development.”).

194. *Id.* at 435. Goodsaid et al. note:

VXDS meetings have led to mutually beneficial and effective interactions between the FDA, the [European Medicines Agency], and sponsors of VXDSs (pharmaceutical companies, technology providers and academic researchers). Because of the importance of biomarker strategies and pharmacogenetics in drug development, as enumerated by the FDA’s Critical Path Initiative, the VXDS process is likely to adapt to meet the changing and growing needs of both the regulatory agencies and VXDS sponsors.

Id. at 444.

195. Lesko & Zineh, *supra* note 21, at 508 (explaining this reluctance may be based on “residual apprehension about the FDA review of voluntary genomic data, confusion over the requirements of a voluntary submission versus a required submission or the perception that it is not worth the time or effort to prepare and submit a [VXDS]”).

tests and other medical devices.¹⁹⁶ For example, the FDA established the Office of Combination Products to “streamline the processing of complex drug-device, drug-biologic, and device-biologic combination products that play an increasingly significant role in health care.”¹⁹⁷ Moreover, as part of the Critical Path Initiative, an effort to “stimulate and facilitate the modernization of the sciences through which regulated products are developed, evaluated, and manufactured,” the FDA has attempted to clarify co-development of pharmacogenomic-based therapeutic drugs and associated diagnostic tests.¹⁹⁸ In April 2005, the FDA released its draft *Drug-Diagnostic Co-Development Concept Paper*, which directly addresses drugs that require a genetic test before the drug is administered.¹⁹⁹ It provides guidance regarding whether the therapy and diagnostic are required to be co-developed, approved together, or considered a combination product.²⁰⁰

There are a number of additional ways in which the FDA could address the various implications of pharmacogenomics. The FDA’s 2005 guidance indicates that the agency is committed to educating the pharmaceutical industry about how pharmacogenomic data can be submitted to help a drug through the approval process.²⁰¹ The FDA has set up a number of workshops focusing on the integration of genomics and diagnostics into the drug development process.²⁰² Moreover, because the agency is concerned that FDA officials may not be prepared to deal with the number of INDs and NDAs containing genomic information that may be submitted, the FDA has sponsored a number of internal educational programs.²⁰³

196. Shah, *supra* note 16, at 7.

197. Press Release, Food & Drug Admin., FDA Establishes Office of Combination Products (Dec. 31, 2002).

198. *Pharmacogenomics and its Role in Drug Safety*, 1 FDA DRUG SAFETY NEWSLETTER (Food & Drug Admin., Silver Spring, MD), Winter 2008, <http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm119991.htm>.

199. Food & Drug Admin., *Drug-Diagnostic Co-Development Concept Paper 1* (Apr. 2005) (unpublished draft), www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM116689.pdf.

200. *Id.* at 1–5.

201. See 2005 FDA GUIDANCE, *supra* note 69, at 2–3, 14–16 (noting that with the guidance the FDA hopes to “clarify” its policy in terms of how pharmacogenomic testing will be used in the drug application review process).

202. See *id.* at 3 (indicating that in May 2002, the Agency and pharmaceutical industry groups held workshops to discuss the important issues surrounding “the application of pharmacogenetics and pharmacogenomics to drug development”).

203. See Lesko Keynote Address, *supra* note 156. In his keynote address, Lesko indicated that:

[The FDA has sponsored] a number of educational programs for people in the center to raise their awareness level and better prepare them for the applications they’re going to see. And they are going to see them because already we can see a significant increase in the number of INDs and NDAs coming in that contain genomic information, and we have to get a readiness in the staff.

Id.

The FDA also has hosted a lecture series designed for scientists and created a new training program on genomics for review staff.²⁰⁴

Instituting more safeguards throughout the FDA approval process—for example, by requiring genetics experts on IRBs—may ensure that the increasing use of pharmacogenomics is encouraged while ensuring appropriate research participant protections.²⁰⁵ Another option is to build in-house regulatory expertise to monitor evolving regulations and to help the FDA determine how the regulatory process should apply to pharmacogenomics.²⁰⁶

a. Increased Phase IV Monitoring

In order to further regulate pharmacogenomics, the FDA may also require increased monitoring during phase IV trials, which take place after the drug or treatment has been licensed and marketed.²⁰⁷ The use of pharmacogenomics in premarketing studies may call for a greater focus on postmarketing surveillance.²⁰⁸ Since the premarket trial population will likely be small relative to current clinical studies, potential ADRs may not be identified as readily.²⁰⁹ Thus, continued post-marketing monitoring would allow a larger trial population than in the premarketing clinical trials, although use of the drug after FDA approval is not as controlled as during the approval process.²¹⁰

204. *Presentations on Genomics: FDA Genomics Group Presentations in 2010-2011*, FOOD & DRUG ADMIN, <http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085427.htm> (last updated Sept. 27, 2011).

205. Binzak, *supra* note 72, at 115–16.

206. See SEC’Y’S ADVISORY COMM. ON GENETICS, HEALTH & SOC’Y, U.S. DEP’T OF HEALTH & HUMAN SERVS., *REALIZING THE POTENTIAL OF PHARMACOGENOMICS: OPPORTUNITIES AND CHALLENGES* 78 (2008) (explaining that because limited awareness about the impacts of pharmacogenetics by health care decision-makers could harm the advancement of the technologies, regulating bodies like the FDA must have adequate in-house expertise in pharmacogenetics).

207. Phase IV clinical trials are conducted in order to glean additional information regarding the drug’s risks, benefits, and optimal use. See 21 U.S.C. § 356a(b) (2006) (providing authority for monitoring the progress of post-marketing studies that drug and biologic applicants have agreed to conduct).

208. Noah, *supra* note 151, at 24 (“Because of the inherent limitations of clinical trials, pharmacogenomic interventions will not alter the existing need for postmarket surveillance . . .”). One author recommends a more formal (and therefore more costly) phase IV system because of the smaller premarketing trials that will be a result of pharmacogenomics. Shah, *supra* note 16, at 7.

209. See Binzak, *supra* note 71, at 125–26 (noting the difficulty in detecting adverse drug responses in a phase III trial, in which only several thousand people may be included).

210. *Postmarketing Surveillance Programs*, FOOD & DRUG ADMIN, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm090385.htm> (last visited Mar. 24, 2012) (noting that postmarketing surveillance is critical because all of a drug’s possible side effects cannot be determined based on preapproval studies that involve a maximum of several thousand patients and sometimes only several hundred). See also OFFICE OF TECH. ASSESSMENT, *POSTMARKETING SURVEILLANCE OF PRESCRIPTION DRUGS* 18 (1982) (noting that while clinical trials are conducted under strict rules, effects of a drug administered by a regular physician or outpatient clinic is not as controlled and cannot be fully assessed).

As phase IV trials become more indispensable for ensuring safety and efficacy, the Office of Post-Marketing Drug Risk Assessment, which is responsible for conducting epidemiological studies involving possible adverse outcomes, might be in the best position to regulate postmarketing surveillance.²¹¹ Critics argue that the FDA must be more “proactive” in “considering how it is going to regulate the new pharmacogenomic drugs already being developed.”²¹² However, increased focus on phase IV trials may stretch the FDA’s scarce resources even further.²¹³ In 2002, the FDA reported that, of its 2400 postmarketing NDA commitments, only 882 had been completed.²¹⁴

Alternatively, the FDA may consider requiring drug developers that, in postmarketing surveillance, find that the number of ADRs is above a certain threshold set by FDA to perform pharmacogenomic studies of the drug or submit to withdrawal from the market.²¹⁵ One critic claims that this could benefit drug manufacturers as well, because:

ADR studies could serve as an additional revenue stream in which the manufacturer could secure intellectual property rights in any pharmacogenetics test derived from its ADR studies and may avoid a complete withdrawal of its drug from the market by labeling changes that would permit the screening out of patients at risk from the drug.²¹⁶

However, one concern with shifting the focus to greater surveillance *after* FDA approval is that it might be dangerous to leave adverse event surveillance and reporting until a drug is already on the market. Doing so might potentially defeat the FDA mandate to ensure safety and efficacy by allowing the product onto the market before it has been fully demonstrated to be safe.²¹⁷

211. Mark A. Rothstein, *Epilogue: Policy Prescriptions*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 319, 324 (Mark A. Rothstein ed., 2003). FDA has authority to withdraw a drug from the market due to postmarketing study results. *Id.* at 325.

212. Binzak, *supra* note 71, at 107.

213. Charles Steenburg, *The Food and Drug Administration’s Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 FOOD & DRUG L.J. 295, 380 (2006) (noting that the resources of the agency “are limited . . . particularly in the case of postapproval activities”).

214. FOOD & DRUG ADMIN., REPORT TO CONGRESS: REPORTS ON POSTMARKETING STUDIES 10 (2002), available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071529.pdf>.

215. Wu, *supra* note 34, at 745–46.

216. *Id.* at 746.

217. See Rena Steinzor & Margaret Clune, *The Hidden Lesson of the Vioxx Fiasco: Reviving a Hollow FDA*, CTR. FOR PROGRESSIVE REFORM WHITE PAPER NO. 514, Oct. 2005, at 11, 17–18 (highlighting the importance of pre-market drug safety reviews and how speeding up drug approvals can increase post-marketing risks).

b. Off-Label Use

An issue of major concern to the FDA is the problem of off-label prescription.²¹⁸ Drugs are only FDA-approved for use in the permitted population, and drug companies are prohibited from encouraging off-label use.²¹⁹ However, physicians are not subject to the FDA prohibition, because the agency does not regulate the practice of medicine.²²⁰ Thus, physicians are allowed to prescribe drugs for off-label use,²²¹ which arguably ensures “clinical freedom” and fosters innovation, leading to the development of new treatments.²²² The use of smaller, more targeted trial samples in clinical studies may have enormous implications once the drug is on the market, because the number of individuals for whom use of the drug would be off-label would potentially increase as the approved population shrinks.²²³ Further, because off-label use might be more dangerous for compounds developed via pharmacogenomics research than for other one-size-fits-all blockbuster drugs due to the risk of adverse drug reactions, it might be necessary to require more safeguards for off-label usage in the future.

Potential solutions to the augmented problem of off-label use exist and could be implemented alone or jointly. One option would require study groups to encompass more varied genotypes.²²⁴ This would extend required clinical studies on special populations *prior* to a drug’s approval, because small premarket targeted studies will mean that those with dissimilar genomes will not otherwise have been tested for adverse events.²²⁵ However, increasing the size of trial populations might directly counteract the benefit that pharmacogenomics presents for clinical trials,

218. The FDA has released multiple guidance documents on the topic. *See, e.g., “Off-Label” and Investigational Use of Marketed Drugs, Biologics and Medical Devices – Information Sheet*, FOOD & DRUG ADMIN, <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm> (last updated Aug. 20, 2011) [hereinafter *Information Sheet*]; Office of the Comm’r, Food & Drug Admin, *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (Jan. 2009), <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm> [hereinafter *Good Reprint Practices*]; *see also Off-label but Not Unregulated*, L.A. TIMES, Nov. 7, 2011, at A14 (discussing the government’s approach to off-label uses).

219. *Good Reprint Practices*, *supra* note 218.

220. *Information Sheet*, *supra* note 218.

221. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 369 (2007).

222. MELZER ET AL., *supra* note 49, at 51.

223. *Id.* at 12; *see also* Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427–28 (2008) (noting that there has been no formal evaluation of off-label uses of drugs and evidence for a clinical situation might not apply to other situations).

224. MELZER ET AL., *supra* note 48, at 41 (recommending that a larger safety file than just the genotypic subgroup be required).

225. *Id.*

thereby negating the efficiency and safety advantages offered by the field.²²⁶ Some critics have also recommended that DNA samples be collected as part of adverse event reporting.²²⁷ This information could then be made available to the academic community for further research and analysis, to gauge if the compound is safe for use in the broader population. Alternatively, the FDA could offer a new class of conditional approvals for drugs targeted to particular subpopulations.²²⁸

Moreover, physician education might be necessary regarding the dangerous consequences of off-label prescription for genetically-targeted drugs, while maintaining the legality of off-label prescribing.²²⁹ A final option, which will be discussed in more depth in section III.C, is to impose stricter liability on physicians who prescribe pharmacogenomics products off-label, resulting in harm to the patient.²³⁰

B. The Orphan Drug Act

The often-cited “orphan drug problem” refers to industry’s reluctance, in light of financial limitations, to develop drugs for diseases that affect small segments of the patient population.²³¹ Pharmacogenomics intensifies this problem because it divides patient populations into smaller subpopulations, thereby disincentivizing the development of new drugs for these discrete groups.²³² Thus, economic “incentives for research may be weakest precisely where improved targeting is most needed.”²³³

In 1983, Congress passed the Orphan Drug Act (ODA) to provide incentives for developing drugs for small markets.²³⁴ The ODA focuses on the 25 to 30

226. *Id.* at 46 (noting that pharmacogenomics will allow the more efficient and quicker development of compounds because of smaller trial samples and more predictable outcomes).

227. *Id.* at 53.

228. *Id.* at 41 (“[A] more flexible approach offering ‘conditional’ approvals could be appropriate here.”).

229. The education of physicians will be discussed in more detail in the section on physician liability. *See infra* Part III.C.1.

230. *See infra* note 296 and accompanying text.

231. Richard Y. Cheung et al., *Orphan Drug Policies: Implications for the United States, Canada, and Developing Countries*, 12 HEALTH L.J. 183, 184 (2004) (identifying the increased cost of drug development as the reason for the pharmaceutical industry’s focus on drugs addressing common diseases). The problem has also been described as “the possibility of focusing on ‘easier to treat’ subsets of the population and excluding from trials those with unfavourable, or simply unusual, genetic constitutions.” Goldstein et al., *supra* note 10, at 945.

232. Buckley & McKinnon, *supra* note 69, at 23. *See also* Thomas Morrow, *Orphan Drug Act Treatments Deserve Full Insurance Coverage*, MANAGED CARE MAG. (Sept. 2004), <http://www.managedcaremag.com/archives/0409/0409.biotech.html> (exclaiming that, because of this stratification “[w]e may all soon be orphans”).

233. Evans et al., *supra* note 75, at 1289.

234. *See* 21 U.S.C. §§ 360aa, 360bb, 360cc, 360dd (2006) (codifying the Orphan Drug Act); 21 C.F.R. § 316 (2011); *see also* Morrow, *supra* note 232 (crediting the Orphan Drug Act with incentivizing pharmaceutical companies to research and develop drugs for small populations); Enrique

million Americans with one of almost 7,000 rare—or “orphan”—diseases.²³⁵ Currently, orphan drug status applies to drugs that are effective for fewer than 200,000 patients or those that affect a greater number, but for which “there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.”²³⁶ Patient population is determined by the total number of individuals with clinical symptoms, rather than those who would actually be eligible for use of the drug.²³⁷ This definition has great implications for products developed using pharmacogenomics.

Specifically, the ODA: (1) grants the sponsoring organization seven years of marketing exclusivity, beginning on the date of FDA approval for the designated orphan indication;²³⁸ (2) gives a 50 percent tax credit toward the financing of clinical trials in humans;²³⁹ and (3) provides grants up to 150,000 dollars for phase I studies and up to 300,000 dollars for Phase II and III studies.²⁴⁰ Through exclusivity incentives, drug developers may recover the costs of investing in expensive orphan genotypes.²⁴¹ The FDA often grants priority review for orphan drugs, and therapies may also be considered for a rapid approval under the special accelerated process.²⁴²

Seoane-Vazquez et al., *Incentives for Orphan Drug Research and Development in the United States*, 3 ORPHANET J. RARE DISEASES 33, 33 (2008) (stating that the Orphan Drug Act was enacted to facilitate development and marketing of orphan drugs). In October 2011, HHS proposed modifications to the ODA regulations. See *Orphan Drug Regulations*, 76 Fed. Reg. 64868 (proposed Oct. 19, 2011) (proposing changes to the Orphan Drug Act like specific subsets of orphan designations).

235. PHARM. RESEARCH & MFG. AM., 2011 REPORT: ORPHAN DRUGS IN DEVELOPMENT FOR RARE DISEASES I (2011).

236. 21 U.S.C. § 360bb(a)(2) (2006).

237. Buckley & McKinnon, *supra* note 69, at 23.

238. 21 U.S.C. § 360cc(a)(2) (2006). See also OFFICE OF THE INSPECTOR GEN., DEP’T OF HEALTH & HUMAN SERVS., *THE ORPHAN DRUG ACT: IMPLEMENTATION AND IMPACT 1* (2001) [hereinafter *THE ORPHAN DRUG ACT*]. This contrasts with the five years granted by the Hatch-Waxman Act of 1984. Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 189 (1999).

239. 26 U.S.C. § 45C(a) (2006). See also *THE ORPHAN DRUG ACT*, *supra* note 238, at 1.

240. 21 U.S.C. § 360ee (2006). See also *THE ORPHAN DRUG ACT*, *supra* note 238, at 1; Morrow, *supra* note 240,

241. Wu, *supra* note 34, at 745 (“Exclusivity may include barring other drug developers from submitting competing drug applications. Moreover, exclusivity may include extending prescription drug benefits to cover drugs for orphan genotypes while denying or limiting coverage for competing drugs.”). See also Paul V. Buday, *Hints on Preparing Successful Orphan Drug Designation Requests*, 51 FOOD & DRUG L.J. 75, 76–77 (1996) (detailing the incentives for developing orphan drugs).

242. Buday, *supra* note 241, at 76 & n.11 (discussing approval times for orphan drugs). In 1997, Congress waived the usual drug application fee charged by the FDA for orphan drugs, amounting to approximately 500,000 dollar savings to drug developers. Morrow, *supra* note 232.

The ODA, sometimes called one of most successful laws Congress has ever written,²⁴³ enabled FDA not only to oversee drug development, but to take an active role.²⁴⁴ The Act is responsible for the largest single source of clinical grants from the FDA: in 2010, FDA awarded approximately 14 million dollars in grants for orphan drugs, funding 22 new grants and approximately 40 other ongoing clinical study projects.²⁴⁵ Since the passage of the ODA, 350 drugs for orphan diseases have received FDA approval.²⁴⁶ In contrast, in the decade before the ODA's passage, less than ten drugs and biological products for rare diseases were brought to market.²⁴⁷ Further, "orphan drug product designations more than doubled" in the first decade of the twenty-first century.²⁴⁸ Notably, approximately 50 percent of the biologics approved for marketing in the U.S. since 1982 have been designated orphan drugs.²⁴⁹

Not all pharmacogenomic products will attain orphan drug status under the ODA. Although it is "anticipated by industry that subgroups of patients, defined by genotype would qualify," orphan status may not be certain, "particularly where the target population is only a subgroup of the disease indication."²⁵⁰ A drug's patient population is generally defined according to the *total expected treatment* population, not just those whom the pharmaceutical company identifies as eligible for clinical trials.²⁵¹ Thus, Herceptin, which is often cited as a rational model for pharmacogenomics, was refused orphan status by the FDA for metastatic breast cancer because the agency disagreed with the drug sponsor's interpretation of the size of the target population.²⁵² The Office of Orphan Products Development

243. Marlene E. Haffner et al., *Two Decades of Orphan Product Development*, 1 NATURE REVS. DRUG DISCOVERY 821, 821 (2002).

244. Morrow, *supra* note 232.

245. FOOD & DRUG ADMIN., FY 2011 CONGRESSIONAL BUDGET REQUEST 120, 122 (2010).

246. Office of Orphan Prod. Dev., *Developing Products for Rare Diseases & Conditions*, FOOD & DRUG ADMIN., <http://www.fda.gov/orphan/designat/allap.rtf> (last updated March 20, 2012).

247. *Id.*

248. Tufts Ctr. for the Study of Drug Dev., *U.S. Orphan Product Designations More Than Doubled from 2000-02 to 2006-08*, 12 IMPACT REP., no. 1, 2010 at 1.

249. Morrow, *supra* note 232. However, managed care organizations have been hesitant to cover drugs approved via the orphan drug process, suggesting that the drugs are "less 'proven' than those developed through traditional pathways." *Id.* One reason they cite is that double blind randomized controlled studies are often not possible because of the dearth of patients. *Id.* One alternative to such studies is historic-control trials. Morrow cites the approval of an enzyme which demonstrated efficacy in treating severe combined immunodeficiency (SCID) as a prime example of a historic-control study, which only had six patients enrolled in its pivotal trial. *Id.*

250. MELZER ET AL., *supra* note 48, at 41.

251. Mignon Fogarty, *Up for Adoption: Pharmacogenetics and the Orphan Drug Law* (Dec. 11, 1998), http://acor.org/sgreene/hmsbeagle/html/content/44/people/op_ed.htm.

252. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at 52 (indicating that the FDA considered Herceptin's limited patient population of approximately 165,000 U.S. women with metastatic breast cancer as insufficient and opining that the FDA tries to restrict those drugs that obtain orphan designation to prevent pharmaceutical companies from dividing the market for economic benefit).

(OOPD) defended its decision not to grant the drug orphan drug status and explained that pharmacogenomic products would not be treated differently than other orphan drug submissions.²⁵³

However, many support the expansion of the ODA to apply to subpopulations identified via pharmacogenomic discoveries.²⁵⁴ To rectify the possibility that stratification of patients by their genetic makeup will lead to a dearth of treatments for those groups, the British Nuffield Council on Bioethics recommends that regulatory agencies prepare guidance that “use existing orphan medicine legislation, or any other policy instrument with equivalent effect, to provide incentives for development.”²⁵⁵ It has been suggested that Congress be encouraged to consider making the ODA more flexible and extending resources to the FDA to support the development of drugs for orphan genotypes.²⁵⁶

Application of the ODA, although incentivizing pharmacogenomic research by drug companies, gives rise to distributive justice questions related to the allocation of scarce research resources between different orphan disease groups.²⁵⁷ One critic recommends supplementing “moral theory with transparent, well-reasoned political debate” and advocates cost-benefit analysis in order to give preferential treatment to those drugs that are considered cost-beneficial.²⁵⁸

C. Legal Liability

As pharmacogenomic discoveries enter the market, higher diagnostic and prescription precision will likely lead to better matching between patients and the appropriate drugs, a reduction or elimination of adverse effects, and more targeted dosaging according to one’s individual metabolism.²⁵⁹ However, because of these advances, adverse events or ineffective treatments will be scrutinized. Who will bear the liability for side effects or unsuccessful therapies? Increased liability may encourage more diligence on both physicians and pharmaceutical manufacturers’

253. Jai Shah, *Economic and Regulatory Considerations in Pharmacogenomics for Drug Licensing and Healthcare*, 21 NATURE BIOTECH. 747, 749 (2003). Note that regardless of orphan drug status, Herceptin has become profitable. NUFFIELD COUNCIL ON BIOETHICS, PHARMACOGENETICS: ETHICAL ISSUES CONSULTATION PAPER 10 (2003). However, it is not clear that this will be true for other drugs with smaller patient populations. *Id.*

254. See Greely, *supra* note 22, at 8.

255. NUFFIELD COUNCIL ON BIOETHICS, *supra* note 14, at xix.

256. Rothstein, *supra* note 211, at 324 (encouraging increased funding for translational research to facilitate further innovation).

257. Arti K. Rai, *Pharmacogenetic Interventions, Orphan Drugs, and Distributive Justice: The Role of Cost-Benefit Analysis*, 19 J. SOCIAL PHIL. & POL’Y, July 2002, at 246, 248.

258. See *id.* at 270.

259. See Teresa Kelton, *Pharmacogenomics: The Re-Discovery of the Concept of Tailored Drug Therapy and Personalized Medicine*, 19 HEALTH LAWYER, Jan. 2007, at 1, 3 (describing the benefits of pharmacogenomic-based diagnostics).

parts. Often, the choice of defendant depends on who has the deeper pockets.²⁶⁰ Additionally, in the pharmacogenomic context, the choice of defendant may depend on whether advertising is direct-to-consumer or whether there is a third party intermediary.

There is currently little liability attached to mistakes related to drug prescription due to the presumption in law and ethics that medicine is “inherently imprecise” compared to other types of science.²⁶¹ This presumption may have a deterrent effect on drug companies from developing targeted, more precise pharmacogenomic products. Because the law’s “special rules” regarding medicine may be based on outdated presumptions, they may necessitate evolution and modification.²⁶²

One hindrance to holding a physician or drug company liable for deleterious drug effects or lack of efficacious treatment is the problem of demonstrating causation.²⁶³ Causation of an adverse event by a particular drug may be difficult to prove because of the complexities of environmental interactions, coupled with other possible causative factors. Moreover, defendants may use genetic discoveries to establish alternative causes for the adverse events for which they are being held responsible, using genetic information to demonstrate that the individual would have developed the illness regardless of the drug’s effect.²⁶⁴ The defendants could use an individual’s genetic susceptibility to an illness to demonstrate that they have no duty to protect “hypersensitive individuals.”²⁶⁵

260. See Steven S. Gensler, *Prejudice, Confusion, and the Bifurcated Civil Jury Trial: Lessons From Tennessee*, 67 TENN. L. REV. 653, 661–62 (2000) (pointing out that courts often instill procedural safeguards to prevent net worth evidence from becoming a factor).

261. Evans et al., *supra* note 75, at 1289 (comparing the implied warranties of appliances to the vague and imprecise nature of medicine). One of the authors’ recommendations to incentivize pharmacogenomic research include reversing state statutes and court doctrines “that have long shielded medical product manufacturers from refund obligations.” *Id.* at 1290.

262. *Id.*

263. “The elements of a negligence claim are: (1) a duty of care owed by the defendant to the plaintiff, (2) breach of that duty through conduct that fails to meet the applicable standard of care, (3) harm or injury, and (4) a causal link between the injury and the breach of duty.” Sharona Hoffman, *Responders’ Responsibility: Liability and Immunity in Public Health Emergencies*, 96 GEO. L.J. 1913, 1926 (2008).

264. See Gary E. Marchant, *Genomics and Toxic Substances: Part II – Genetic Susceptibility to Environmental Agents*, 33 ENVTL. L. REP. 10641, 10648 (2003). For example, a “defendant could also argue that the plaintiff’s disease resulted solely from his or her genetic predisposition, which caused the disease to develop independent of any exposure to the defendant’s product.” *Id.* Genetic test could demonstrate that a person’s predisposition decreased susceptibility to a disease, thereby providing a useful defense against causation. A defendant could also “seek to test the plaintiff for other genetic variants that provide increased resilience to the toxic agent at issue, which would make that person less susceptible than the average person.” *Id.*

265. *Id.* Marchant provides:

In particular, defendants could assert what has sometimes been described as the “idiosyncratic response” defense. This defense protects from liability a defendant whose product or activity is harmless to the general public but may injure a small number of

Further, because of the complexity of genetic information, and the “perils inherent in broad statistical judgments based on science that will be inexact even in the best scenario,” it will often be impossible to demonstrate a simple cause and effect relationship between one’s genetic profile and the disease or side effects one exhibits.²⁶⁶ It is clear that not all tests are completely accurate, and the more complicated the gene interactions, the less accurate any prescription might be.

1. Individual Liability

Pharmacogenomics could be a double-edged sword, where physicians are penalized for either prescribing or withholding pharmacogenomically-developed drugs and treatments.²⁶⁷ It is unclear whether physicians will have an obligation to utilize pharmacogenomic diagnostics to hone an individual’s prescription to his or her genetic profile, or whether doctors can continue to follow the status quo in diagnosing and prescribing medicines.²⁶⁸ For example, a patient could sue his or her doctor for adverse events associated with a prescription given according to currently accepted standards, which may not have kept pace with scientific innovations. Will there be liability for *not* testing for genetic predispositions or using a particular treatment?

A patient could ostensibly sue a physician for medical malpractice claiming that he or she refused to prescribe a drug (perhaps off-label) because it was not approved for his or her exact genetic makeup (i.e., he or she did not have the genetic predisposition of those involved in the clinical studies).²⁶⁹ Under the current liability regime, physicians may be sued for malpractice for negligent prescription of drugs, and courts have found doctors liable for failing to test for and prescribe the most appropriate drug for a particular individual.²⁷⁰ Pharmacogenomic discoveries may therefore render adverse effects more predictable than for other

individuals with a unique and unusual susceptibility. This defense has generally been applied in cases where a plaintiff developed a rare allergenic response to a cosmetic or similar product, but the defense would presumably also apply to cases where a plaintiff was harmed due to a rare genetic susceptibility to a product that is otherwise harmless to the general population.

Id. Marchant continues, “[t]he formal justification for this defense is that the hyper-susceptibility of the plaintiff, rather than some defect in the product, is the proximate cause of the plaintiff’s injury.” *Id.*

266. Evans et al., *supra* note 75, at 1290.

267. See Mark A. Rothstein, *Liability Issues in Pharmacogenomics*, 66 LA. L. REV. 117, 121–22, 124 (2005) (detailing the need to provide the best care to patients while protecting themselves from liability in the new venture of pharmacogenomics).

268. See *id.* at 122 (indicating the possibility of potential liability in the future for failure to utilize newer, more individualized medication).

269. See Rothstein, *supra* note 267, at 122.

270. See Noah, *supra* note 151, at 24 & n.12.

drugs,²⁷¹ and physicians may consequently be subject to stricter medical liability for off-label prescription of pharmacogenomics products.²⁷²

Because of the probabilistic nature of genetics, it is unclear how high a possibility of a drug not working or having deleterious effects would be necessary to justify denial of treatment.²⁷³ If there is only a single available treatment, the threshold for refusing it may be higher than if there are multiple treatments from which to choose.²⁷⁴ Some critics recommend greater liability for negative outcomes or ineffective treatment results, worrying that there is the possibility that “[p]eople receiving a ‘negative’ test result will be denied a (more remote) chance of the drug working for them. Where there are no alternatives this may cause conflict.”²⁷⁵ They have called for new “standards to limit lawsuits against providers who deny treatments based on careful, evidence-based inferences that the therapy, if administered, would not work.”²⁷⁶

2. Liability Against Pharmaceutical Companies

Pharmaceutical companies may also face liability for faulty products or for failure to warn consumers directly of the possible ADRs associated with their products.²⁷⁷ Once a patient is warned of the possibility of ADRs related to one’s genetic predisposition, however, it could be argued that the patient has assumed the risk and may therefore not recover if he or she experiences an adverse reaction.²⁷⁸

To support a product liability claim, a plaintiff could also allege that the failure to use pharmacogenomic technologies resulted in a marketing or design defect.²⁷⁹ Because of the state of the technology, however, the required expert

271. See Giovanni Severino & Maria Del Zompo, *Adverse Drug Reactions: Role of Pharmacogenomics*, 49 PHARMACOLOGICAL RES. 363, 367, 370–71 (2004) (explaining that pharmacogenomics provides a “plausible basis” for predictive testing as well as enhanced understanding of potentially fatal adverse drug reactions).

272. See Tilo Mandry, *Legal Implications of Pharmacogenomics Regarding Drug Trials, Drug Labeling, and Genetic Testing for Drug Prescription: An International Approach*, 59 FOOD & DRUG L.J. 519, 528–29 (2004) (noting that physicians may face liability for prescribing off-label “genotypically-defined drug[s]” when genetic testing could have shown the drugs to be harmful or ineffective).

273. See Greely, *supra* note 22, at 2 (discussing the potential levels of beneficence that will be required by regulatory bodies such as the FDA for approval of drugs that are effective for an identifiable and lesser part of the population or, alternatively, may only harm a particular and trivial part of the population while providing benefits to others).

274. See Evans et al., *supra* note 75, at 1290 (elaborating that although a group may not respond collectively when results are averaged, individuals within that group still have potential for response, and as a result, such individuals may be harmed if denied treatment, particularly when there are no other treatment options).

275. MELZER ET AL., *supra* note 48, at 49.

276. Evans et al., *supra* note 75, at 1290.

277. See Rothstein, *supra* note 267, at 118–19.

278. See Marchant, *supra* note 264, at 10650.

279. See Urquhart et al., *supra* note 17 (explaining that “failure to test” as a cause of action has been rejected as an independent claim by more cogent case law).

opinion may not make it past the gatekeeper, because it could not meet the scientific reliability standards of expert testimony required by *Daubert*.²⁸⁰

Moreover, patients could attempt to hold pharmaceutical companies responsible for failing to incorporate pharmacogenomic technology into their drug development process.²⁸¹ There is a noted lack of legal duty to use pharmacogenomics to discover potential new drugs and reduce major drug adverse reactions—for example, idiosyncratic liver injuries that occur on a rare basis with a number of drugs.²⁸² Some critics, however, assert that individuals should not be able to sue a drug manufacturer for failure to use pharmacogenomics to develop a drug that will reveal an individual's predisposition to deleterious side effects, because “[p]rematurely imposing an actual or de facto duty on drug makers to use these technologies will discourage the cooperative atmosphere needed to overcome the current limitations of pharmacogenetics and pharmacogenomics.”²⁸³

3. *Shifts in the Standard of Care*

Pharmacogenomics may shift physicians' expected standard of care, although it is unclear at what point and to what extent the standard will change to require physicians to conduct genetic tests and prescribe drugs accordingly.²⁸⁴ Critics have expressed concerns about imposing liability for adverse outcomes resulting from the use of pharmacogenomics in diagnosis and treatment decisions.²⁸⁵ In the future, healthcare providers can expect to bear a larger share of the costs when treatment options fail for lack of individualized treatment.²⁸⁶

At the industry level, imposing legal liability may obstruct research by deterring pharmaceutical companies from engaging in pharmacogenomic development for fear of being sued. Greater precision may shift the standard of care such that companies could increasingly be held responsible for ineffective treatment or ADRs. As pharmacogenomics develops, treatment effectiveness and

280. *Daubert v. Merrell Dow Pharm.*, 509 U.S. 579, 589–90 (1993) (holding that the trial judge is the gatekeeper in deciding whether an expert's testimony with respect to “scientific knowledge” meets the standard of evidentiary relevance and reliability). *See also* Urquhart et al., *supra* note 17 (explaining that expert testimony supporting claims of drug-induced liver injury should be excluded by the trial judge because the hypothesis that pharmacogenomics may identify at risk patients has not been tested, has not been supported in peer review materials, has an unknown error rate, and is not generally accepted by the scientific community).

281. *See* Urquhart et al., *supra* note 17 (hypothesizing that patients harmed by certain drugs may claim the drug manufacturer had a duty to implement pharmacogenomic testing techniques to identify possible adverse drug reactions).

282. *Id.*

283. *Id.*

284. *See* MELZER ET AL., *supra* note 48, at 12, 49.

285. *Id.*

286. *See generally* Evans et al., *supra* note 75 (suggesting that policymakers establish incentives to encourage health care providers to develop more targeted therapies and avoid the 65 billion dollars wasted per year on therapies that either did not help or were detrimental to patients).

side effects will become increasingly within drug manufacturers' control.²⁸⁷ One company, Novartis, has "offered customers a money-back guarantee on two of its antihypertensive drugs," demonstrating behavior more like that of other industries than the drug industry.²⁸⁸ However, mandating such action "would be an extreme approach to the desired incentive structure . . . rife with ethical, social, industry and community concerns, even if science were fully ready to support it."²⁸⁹ Thus, the FDA has explored a "safe harbor" from liability provision in any federal regulations involving pharmacogenomics in order to facilitate experimentation.²⁹⁰

The anticipated changes to the standard of care for physicians and drug manufacturers may be, in part, a reaction to lawsuits that have been filed around the country.²⁹¹ One such example are the personal liability suits in which, after taking the vaccine LYMERix, individuals claimed severe health problems akin to those associated with Lyme disease.²⁹² The product was heavily advertised directly to consumers, and physicians expressed the common worry associated with direct-to-consumer genetic testing—that patients would demand prescriptions even when it was medically inadvisable.²⁹³ Additionally, "[o]thers feared vaccinated people would gain a false sense of security and let their guard down against ticks."²⁹⁴

In 1999, a number of affected individuals brought a class action case against the manufacturer of LYMERix, SmithKline Beecham, alleging that it had failed to warn doctors and the public that nearly a third of the general population (those with the HLA-DR4+ allele) is susceptible to developing autoimmune arthritis if they are exposed to the protein that makes the vaccine work.²⁹⁵ In 2000, many of those who participated in the class action suit also filed individually against the manufacturer, asking that it expand its vaccine labeling.²⁹⁶ The plaintiffs' allegations included a failure by the drug company to warn consumers of the potential adverse effects of

287. *Id.* at 1289–90.

288. *Id.* at 1290.

289. *Id.*

290. See Urquhart et al., *supra* note 17.

291. See Rothstein, *supra* note 211, at 326 (noting that the various potential liability theories for suits related to pharmacogenomic claims). Rothstein specifically notes the following liability theories: "failure to order genetic testing, improper interpretation of genetic test results, failure to provide necessary genetic counseling, failure to prescribe the proper medication and dosage, failure to warn the patient of possible adverse events . . . and failure to dispense or administer the medication properly," as well as, perhaps, failure to *not* prescribe a drug. *Id.*

292. Susan Warner, *Patients Sue Over Effects of Vaccine a Medication to Prevent Lyme Disease Made Them Ill, They Say, in Court Filings Against SmithKline*, PHILA. INQUIRER, June 13, 2000, at C1.

293. *Id.*

294. *Id.* (noting the vaccine has a rate of 78 percent effectiveness).

295. Cassidy v. SmithKline Beecham, No. 99-10423, 2003 WL 22216528 (Pa. Com. Pl. July 1, 2003). See also Rothstein, *supra* note 211, at 327 (using the Cassidy case as an example of potential liability for a drug manufacturer could face when there was a failure to warn).

296. Holcomb B. Noble, *3 Suits Say Lyme Vaccine Caused Severe Arthritis*, N.Y. TIMES, June 13, 2000, at F6.

the vaccine.²⁹⁷ In 2002, the drug was removed from the market due to a reduction in sales, likely resulting from the negative publicity surrounding the lawsuits.²⁹⁸ The class action case is particularly interesting because, first, rather than seeking compensation for past injuries, as tort law usually mandates, the plaintiffs sought “protection against the risks of *future* injury.”²⁹⁹ Second, the case is significant because, for maybe the first time, the class was explicitly defined by genotype.³⁰⁰

IV. CONCLUSION

Pharmacogenomics will have far-reaching and diverse effects on drug research and development. It promises to reduce adverse drug reactions and allow physicians to make more accurate diagnoses and prescription and dosage decisions.³⁰¹ We as a society—individually and collectively—must choose the most appropriate regulatory and legal pathways in the effort to establish an adequate and protective system, both for individuals seeking new and effective drugs and society at large. The field of pharmacogenomics and associated genetic discoveries shape, and are shaped by, the current regulatory regime under the guidance of the FDA.³⁰² Legal and policy decision-makers, as well as insurance companies and the pharmaceutical industry, are entrusted with the responsibility of making proper resource allocation decisions. By properly distributing resources through, for example, the Orphan Drug Act, we can ensure that certain historically underserved groups are given access to therapeutic advancements.³⁰³

Each of the various players could positively or adversely affect the role that pharmacogenomics can and will play in providing therapeutic innovations to the

297. *Id.*

298. Emily Sohn, *Lyme Disease: Where's the Vaccine?*, DISCOVERY NEWS (June, 17, 2011), <http://news.discovery.com/human/lyme-disease-ticks-vaccine-110617.html>.

299. Larry I. Palmer, *Medical Liability for Pharmacogenomics*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 187, 200 (Mark A. Rothstein ed., 2003) (emphasis added).

300. *See, e.g.*, Marchant, *supra* note 264, at 10651 (citing court use of genetic heterogeneity as a factor for denying class certification in cases involving toxic injury).

301. *See generally* John A. Robertson et al., *Pharmacogenetic Challenges for the Health Care System*, 21 HEALTH AFF. 155, 159 (2002) (discussing the potential of pharmacogenetic research to enable physicians to prescribe safer and more effective medication). *See also* Mark A. Rothstein & Carlton A. Hornung, *Public Attitudes About Pharmacogenomics*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 3, 3 (Mark A. Rothstein ed., 2003) (noting how pharmacogenomics are likely to develop “new pharmaceutical products . . . that decrease adverse drug reactions and improve the treatment of many serious diseases.”).

302. *See* Rothstein, *supra* note 211, at 328 (specifying four likely approaches the FDA may take with respect to pharmacogenomics, including regulation of test kits in clinical settings for commercial diagnostics, subdivision of target populations to enable better scrutiny, evaluation of clinical trials for safety and efficacy, and consideration of genetic factors when reviewing post-marketing safety data).

303. *See* Cheung et al., *supra* note 231, at 183 (specifying rare disease sufferers as one such historically underserved group).

public.³⁰⁴ The pharmaceutical industry must choose whether to pursue pharmacogenomic research and development, depending on financial and other incentives. Congress and the regulatory agencies must choose whether, and how, to encourage pharmacogenomic innovations while providing equal and fair access to targeted therapies and drugs.³⁰⁵ Policy-makers must also determine, through the patent system, how to balance the promotion of downstream pharmacogenomic research while protecting the rights of innovators.³⁰⁶ Likewise, they must consider the appropriate liability regime for industry, which must avoid discouraging the pharmaceutical industry from pursuing valuable therapeutic advancements.³⁰⁷ Liability laws must also continue to allow physician independence while still protecting the interests of the patient, striking a balance between the conflicting standards of paternalism and patient autonomy.³⁰⁸ In light of these diverse decisions, education regarding the promises and consequences of pharmacogenomics is a basic, but significant, necessity.³⁰⁹ Targeted education is fundamental to different aspects of society, including the public at large, the regulatory bodies that make policy choices, and physicians and health care providers.

The implications that the current legal regime has for pharmacogenomics, and vice versa, have only begun to be explored. However, it is imperative to proactively anticipate the potential dilemmas and issues associated with scientific advancement in order to keep legal and ethical considerations current with technological innovations. Only in this way can we hope to effectively advance, rather than hinder, appropriate technological progress while protecting the rights of individuals and ensuring that they receive the best medical treatment available.

304. See Evans et al., *supra* note 75, at 1291 (emphasizing that if legislators and courts at the federal, state and local levels do not create substantial incentives to promote research in tandem with private industry, a financial crisis may undermine the current therapeutic promise offered by pharmacogenomics).

305. See *id.* at 1289, 1290 (predicting that “bold leadership” will be required by regulatory bodies to guide the private industry through a “wrenching period of transition” towards targeted therapies); see also Rothstein, *supra* note 211, at 331–32 (arguing that leaving pharmacogenomic development and cost-setting completely to free market forces may result in worse health care access outcomes than currently exist and that Congress should tailor the Orphan Drug Act in light of the recent progress in pharmacogenomics).

306. See Nunnally et al., *supra* note 132, at 111, 118–119 (noting that while gene patents are critical for continued industry innovation in pharmacogenomics, legislators may narrow the scope of protection to address concerns that the high cost of licensing fees may be inhibiting other medical research).

307. See Palmer, *supra* note 299, at 188 (arguing that the basic tenets of medical liability must be reexamined to account for “systemic approaches to risk reduction” for parties developing and allocating pharmacogenomics-based products).

308. See *id.* at 189–190 (noting a new “professional-patient dyad” must be developed allow theories of medical liability to accommodate advances in pharmacogenomics).

309. See MELZER ET AL., *supra* note 48, at 12 (specifying that pharmacogenetics must become part of the undergraduate and postgraduate health professional educational programs); see also Rothstein, *supra* note 211, at 326 (describing the necessity for all health professionals to be trained in pharmacogenomics).