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## LEGAL ISSUES STEMMING FROM THE ADVANCEMENT OF PHARMACOGENOMICS

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### TABLE OF CONTENTS

I.	Pharmacogenomics Background .....	35
A.	Pharmacogenomics: A Historical Perspective .....	35
1.	Pharmacogenomics in the Pre-Biotechnology Era.....	35
2.	Pharmacogenomics in the Biotechnology Era and the Modern Science Behind It.....	36
B.	The Pharmaceutical Industry's Cry for Pharmacogenomic Help .....	39
1.	The FDA Process .....	39
2.	Pharmaceutical Failures .....	41
3.	Pharmacogenomics to the Rescue? .....	43
II.	Legal Issues .....	45
A.	Pharmaceutical Manufacturer's Potential Liability .....	46
1.	Design Defects .....	46
2.	Failure to Warn .....	48
3.	Cassidy v. SmithKline Beecham.....	52
B.	Physician's Possible Liability .....	53
1.	Medical Malpractice.....	54
2.	Lack of Informed Consent .....	58
C.	Pharmacists .....	60
1.	Common Law Changes in Pharmacists' Immunity from Duty to Warn Suits.....	61
2.	Omnibus Budget Reconciliation Act of 1990 (OBRA) .....	62
III.	Conclusion.....	65

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*“If it were not for the great variability among individuals, medicine might as well be a science and not an art.” – Sir William Osler*

## Introduction

Although in 2001 both *Science*<sup>1</sup> and *Nature*<sup>2</sup> published preliminary results of the human genome project, pharmacogenomics<sup>3</sup> predates this milestone. In fact, some scientists observed hereditary variability in pharmaceutical metabolism among individuals<sup>4</sup> even before Watson and Crick’s seminal “Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid.”<sup>5</sup> Shortly after the modern view of genes and inheritance began to take shape, initial landmark studies in the 1950s and 1960s established a concrete connection between heritable traits and drug safety and efficacy.<sup>6</sup> In 1962, Professor Kalow of the University of Toronto provided pharmaceutical researchers with the first relatively complete account of a new discipline, pharmacogenetics.<sup>7</sup> Over

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<sup>1</sup> J. Craig Venter et al., *The Sequence of the Human Genome*, 291 *SCI.* 1304, 1304 (2001).

<sup>2</sup> Eric S. Lander et al., INT’L HUM. GENOME SEQUENCING CONSORTIUM, *Initial Sequencing and Analysis of the Human Genome*, 409 *NATURE* 860, 860 (2001).

<sup>3</sup> It should be noted that although pharmacogenomics and pharmacogenetics are closely related, they are not synonymous terms. Pharmacogenetics is the interaction of a particular gene with a pharmaceutical. Pharmacogenomics, on the other hand, is the whole genome application of pharmacogenetics – the study of the entire genome’s response to a pharmaceutical. Thus, the differences between these two disciplines can be thought of in terms of scale. This paper uses these two terms interchangeably.

<sup>4</sup> See Archibald E. Garrod, *The Incidence of Alkaptonuria: A Study in Chemical Individuality*, ii *LANCET* 1616, 1616 (1902).

<sup>5</sup> J.D. Watson & F.H.C. Crick, *Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid*, 171 *NATURE* 737, 737 (1953).

<sup>6</sup> WENDELL W. WEBER, *PHARMACOGENETICS* 7 (1997).

<sup>7</sup> W. KALOW, *PHARMACOGENETICS – HEREDITY AND THE RESPONSES TO DRUGS* (1962).

the last half-century, numerous researchers have repeatedly reported causal connections between gene polymorphisms and differential drug responses for several different conditions.<sup>8</sup>

In spite of these numerous studies reporting a connection between genetic traits and drug metabolism, health care has yet to truly adopt a pharmacogenomics approach to prescription drug dispensing. Current estimates of drug efficacy and side effects reveal some shocking trends. Only about 60% of prescriptions produce the desired therapeutic effects.<sup>9</sup> On top of that ineffectiveness, in 2007 Americans spent \$227.5 billion on prescription drugs.<sup>10</sup> When these two values are combined, it reveals that Americans wasted about \$90 billion on prescription drugs in 2007.

On top of this staggering amount of economic waste, Americans also suffer physical harm from drugs. A meta-analysis of nearly forty adverse drug reaction studies illustrated the serious consequences that arise when ill-suited drugs are prescribed to the wrong individuals.<sup>11</sup> This meta-analysis revealed that serious adverse drug reactions arose with nearly 7% of prescriptions and deadly adverse reactions in 0.32% of the studied population.<sup>12</sup> Although these numbers may not seem large, this means that nearly 2.3 million people experienced adverse drug reactions and more than 100,000 died as a result of their adverse drug reaction in the United States.<sup>13</sup> Overall, both the financial waste and, more importantly, the human toll arising from ineffective and inappropriately prescribed pharmaceuticals must serve as a signal to health care providers that a pharmacogenomics-related plan must be implemented to reduce these statistics.

In spite of these pressing concerns with adverse drug reactions, only limited implementations of

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<sup>8</sup> WEBER, *supra* note 6, at 9-13.

<sup>9</sup> Tim Peakman & Steve Arlington, *Putting the Code to Work: The Promise of Pharmacogenetics and Pharmacogenomics*, 2 DRUG DISCOVERY WORLD 35, 36 (2000).

<sup>10</sup> CTRS. FOR MEDICARE AND MEDICAID SERV. U.S. DEP'T OF HEALTH & HUMAN SERVS., NATIONAL HEALTH EXPENDITURES: 2007 HIGHLIGHTS 1 (2007), 1  
<http://www.cms.hhs.gov/NationalHealthExpendData/downloads/highlights.pdf>.

<sup>11</sup> Jason Lazarou et al., *Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies*, 279 JAMA 1200, 1200 (1998).

<sup>12</sup> *Id.* at 1202.

<sup>13</sup> *See id.*

pharmacogenomics-based strategies have occurred. To date, many studies have demonstrated a relationship between a genotype and a drug response.<sup>14</sup> Although several published studies report a verifiable connection between a genotype and drug-metabolizing phenotype, relatively few reported connections have been translated into action.<sup>15</sup> Because of the reported advancements in basic research and increased incentives for development of pharmacogenomics strategies,<sup>16</sup> hopefully a trend of translating these developments into clinical practice will escalate, to further ease the problems of adverse drug reactions and inefficient or non-effective pharmaceuticals.

Although pharmacogenomics-related drug treatment strategies are not yet main stream in the health care profession, early consideration of legal issues surrounding pharmacogenomics' use in the medical profession could ease the transition. Important questions surround issues of informed consent, products liability, and general medical malpractice claims. These potential legal liabilities touch not only the physician-patient relationship, but also pharmaceutical manufacturers, and interestingly enough, potentially pharmacists.

The main thrust of this article is the above-described liability issues. Part I of this paper contains a detailed background on pharmacogenomics, including a deeper analysis of why pharmacogenomics is needed, and how it can play a role in the drug development process to produce the best pharmaceuticals for genetically identified patients. Part II contains analysis of the potential legal issues present with implementation of pharmacogenomics from the point of view of the physician, pharmacist, and manufacturer.

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<sup>14</sup> See Mary V. Relling & Thierry Dervieux, *Pharmacogenetics and Cancer Therapy*, 1 NATURE REV. 99 (2001); Farhad Kamali & Hilary Wynne, *Pharmacogenetics of Warfarin*, 61 ANN. REV. MED. 63 (2010); and Elizabeth B. Daily & Christina L. Aquilante, *Cytochrome P450 2C8 Pharmacogenetics: a Review of Clinical Studies*, 10 PHARMACOGENOMICS 1489 (2009).

<sup>15</sup> But see Penelope K. Manasco and Teresa E. Arledge, *Drug Development Strategies*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 90-91 (Mark A. Rothstein ed., 2003).

<sup>16</sup> Lawrence J. Lesko & Janet Woodcock, Opinion, *Translation of Pharmacogenomics and Pharmacogenetics: A Regulatory Perspective*, 3 NATURE REV. 763, 765-67 (2004).

## I. Pharmacogenomics Background

### A. Pharmacogenomics: A Historical Perspective

The “biotechnology revolution,” although ever-advancing in our modern age, truly began in a twenty-year time span between the late 1950s and the late 1970s. This time span evolved from when Watson and Crick published their landmark article on the structure of DNA<sup>17</sup> to when Cohen and Boyer reported their observations leading to the birth of modern molecular biology.<sup>18</sup>

Separating pharmacogenomics advancements into the pre- and post-biotechnology revolution is important for two reasons. First, it is important to realize that physicians and other scientists observed the need for *heritable* input into pharmaceutical usage long before researchers hypothesized genes as the *heritable* unit. This further emphasizes the pressing need for the use of pharmacogenomics in drug development and usage. Second, the pre-biotechnology era observations have important societal implications. Because of the lack of gene-based knowledge and social constructs of race that pervaded society and science in the pre-biotechnology era (and still do to some extent, unfortunately), observations from that time period were used to characterize races in certain ways. And, although this debate about race-based medicine still rages,<sup>19</sup> society in general has grown more accepting of different populations.

#### 1. Pharmacogenomics in the Pre-Biotechnology Era

Pharmacogenomics is a rapidly advancing field. Newly discovered associations between genotypes and drug metabolism phenotypes are reported on a regular basis. However, relative to

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<sup>17</sup> Watson & Crick, *supra* note 5.

<sup>18</sup> Stanly N. Cohen et al., *Construction of Biologically Function Bacterial Plasmids In Vitro*, 70 PROC. NAT’L ACAD. SCI. 3240, 3244 (1973).

<sup>19</sup> See B. Séguin et al., *Bidil: Recontextualizing the Race Debate*, 8 PHARMACOGENOMICS J. 169, 169, 172 (2008); C. Weijer & P.B. Miller, *Protecting Communities in Pharmacogenetic and Pharmacogenomic Research*, 4 PHARMACOGENOMICS J. 9, 9 (2004); M. Tamaoki et al., *Pharmacogenomics in Japan*, 4 PHARMACOGENOMICS J. 288, 288 (2004); and Henry T. Greely, *Genome Research and Minorities*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 67 (Mark A. Rothstein ed., 2003).

other modern biological innovations, the field of pharmacogenomics is surprisingly old. In fact, initial reports detailing the impact of heritable factors on drug metabolism date back to the turn of the century—the turn of the twentieth century!<sup>20</sup> A half century later, a German researcher coined the term “pharmacogenetics”<sup>21</sup> and an important field was named.

Initial discoveries of a relationship between heritable factors and drug metabolism came from a wide variety of fields in the years leading up to the biotechnology revolution between the late 1950s and late 1970s. Interestingly, efforts to protect soldiers from malaria during the Korean War in the mid-1950s led to an important pharmacogenetics observation. Some soldiers of African descent taking the anti-malarial drug, primaquine, suffered hemolysis as a result of a heritable factor combined with the drug.<sup>22</sup> Later, researchers determined glucose-6-phosphate dehydrogenase deficiency gave rise to this phenotype.<sup>23</sup> Other major observations from the pre-biotechnology era include evidence that neuropathy occurs in certain individuals when given isoniazid, an anti-tuberculosis pharmaceutical,<sup>24</sup> and evidence of a relationship between prolonged muscle relaxation and a drug when a patient exhibited an inherited plasma cholinesterase deficiency and was given the drug suxamethonium.<sup>25</sup> Overall, before a more advanced understanding of genetics and molecular biology’s key principles became commonplace, observations of altered drug responses originated largely from pedigree studies and information gleaned from ethnic generalizations.<sup>26</sup>

## 2. Pharmacogenomics in the Biotechnology Era and the Modern Science Behind It

The biotechnology era began in the mid-1970s. The modern advances in biotechnology,

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<sup>20</sup> See Garrod, *supra* note 4.

<sup>21</sup> F. Vogel, *Moderne problem der Humangenetik*, 12 ERGEBNISSE INNEREN MEDIZIN UND KEINDERHEILKUNDE 52 (1959).

<sup>22</sup> Charles B. Clayman et al., *Toxicity of Primaquine in Caucasians*, 142 JAMA 1563, 1568 (1952).

<sup>23</sup> Paul E. Carson et al., *Enzymatic Deficiency in Primaquine-Sensitive Erythrocytes*, 124 SCL. 484, 484-85 (1956).

<sup>24</sup> Hettie B. Hughes et al., *Metabolism of Isoniazid in Man as Related to the Occurrence of Peripheral Neuritis*, 70 AM. REV. TUBERCULOSIS 266 (1954).

<sup>25</sup> W. Kalow, *Familial Incidence of Low Pseudocholinesterase Level*, 268 LANCET 576, 576-77 (1956).

<sup>26</sup> Relling & Dervieux, *supra* note 13, at 99.

including an ever-growing knowledge base and more precise and cheaper equipment, presents an easier environment in which scientists can make pharmacogenomic advances. These advances include the development of DNA cloning techniques,<sup>27</sup> DNA sequencing methods,<sup>28</sup> and the polymerase chain reaction (PCR).<sup>29</sup> These molecular biology innovations led to the one of the greatest endeavors humanity set out to accomplish, the Human Genome Project (HGP). Although the HGP continues to evolve over its nearly twenty years of existence, current estimates state that there are 20,000-25,000 genes in the human genome.<sup>30</sup> This range of values, combined with the enormous amount of variation between geographically distinct human populations<sup>31</sup> creates a large list of potential pharmacogenomic-related genes.

In spite of these advances giving humanity a nearly never-ending *playlist* of potential targets for drug-gene/protein interactions, researchers tend to focus their efforts on genes relevant for the pathology being treated. Several peer-review journals, including *The Pharmacogenomics Journal* are dedicated to reporting developments in these fields. Each issue contains several reports on different genotypes interacting with pharmaceuticals or other treatments, and in turn these different genotypes bring about a different response. Although many researchers focus on relatively narrow targets such as specific genes or gene families related to a given malady, other researchers focus on broader gene groups, such as the CYP 450 gene family—this family is known to metabolize nearly 80% of today's

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<sup>27</sup> See Cohen et al., *supra* note 17, at 3240.

<sup>28</sup> See F. Sanger et al., *DNA Sequencing with Chain-Terminating Inhibitors*, 74 PROC. NAT'L ACAD. SCI. 5463, 5463s (1977).

<sup>29</sup> Randall K. Saiki et al., *Enzymatic Amplification of Beta-Globin Sequences and Restriction Site Analysis for Diagnosis of Sickle Cell Anemia*, 230 SCI. 1350, 1350 (1985).

<sup>30</sup> International Human Genome Sequencing Consortium, *Finishing the Euchromatic Sequence of the Human Genome*, 431 NATURE 931,942-43 (2004).

<sup>31</sup> See Louise V. Wain et al., *Genomic Copy Number Variation, Human Health, and Disease*, 374 LANCET 340, 340-41 (2009), and Kelly A. Frazer et al., THE INT'L HAPMAP CONSORTIUM, *A Second Generation Human Haplotype Map of Over 3.1 Million SNPs*, 449 NATURE 851 (2007).

drugs.<sup>32</sup> Significantly, other researchers target specific genotypes of proteins, such as *HER2*, *EGFR*, and *ALK-EML4*.<sup>33</sup> These genes code for proteins found on the surface of tumors that physicians can use to tailor the most effective chemotherapeutic treatment regimen for their patients.

An understanding of how researchers target these genotypes is important. Researchers generally go about targeting genes with potentially important polymorphisms in one of two ways – a candidate gene approach or a genomic approach. The candidate gene approach is analogous to the way geneticists have largely characterized many genes, not only in humans, but in all organisms studied. The researcher, led to investigate some association between a gene and a phenotype, discovers that different alleles of the gene have different phenotypes when exposed to different pharmaceuticals or other environmental stimuli.<sup>34</sup> Then, *hopefully*, researchers and pharmaceutical companies translate these observations into clinical practice. This technique, although well-used by generations of researchers, is not necessarily the most efficient or reliable given the often complex network of gene-product associations needed to create a phenotype.<sup>35</sup>

The genomic approach results in a much broader search than the candidate gene approach. The genomic approach uses information researchers glean from both the HGP and previous pharmacogenetics-based research. Instead of researchers needing an initial indication to study a gene as related to a desired/non-desired phenotype, researchers can scan the whole genome sequence to look for genes related to those already noted to have a given phenotype.<sup>36</sup> Additionally, researchers can look for areas with high concentrations of some of the 3.1 million single nucleotide

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<sup>32</sup> Shu-Feng Zhou et al., *Polymorphisms of Human Cytochrome P450 Enzymes and Its Clinical Impact*, 41 DRUG METABOLISM REV. 89, 241 (2009).

<sup>33</sup> Jocelyn Kaiser, *Looking for a Target on Every Tumor*, 326 SCI. 218, 219 (2009).

<sup>34</sup> Klaus Lindpaintner, *Pharmacogenetics: A Review of Concepts and Contents*, DRUG DISCOVERY WORLD 21, 21-23 (2001).

<sup>35</sup> See Eric E. Schadt, *Molecular Networks as Sensors and Drivers of Common Human Diseases*, 461 NATURE 218, 218 (2009).

<sup>36</sup> Harvey W. Mohrenweiser, *Pharmacogenomics: Pharmacology and Toxicology in the Genomics Era*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS (Mark A. Rothstein ed., 2003).

polymorphisms (SNPs) for areas of high variability.<sup>37</sup>

After identification of a potential target, the genomic approach continues along the same research path as the candidate gene approach—characterizing the gene to ensure its role in a variable response, hopefully coupled with a successful translation to clinical practice. Now, although the genomics approach may still be considered a *fishing expedition*, ever-advancing bioinformatics techniques can help scientists identify potentially relevant genes for further examination.

Overall, pharmacogenomic observations over the past century have helped scientists recognize the important relationship between heritable factors and drug metabolism. As technology progresses, hopefully this trend will continue.

## **B. The Pharmaceutical Industry’s Cry for Pharmacogenomic Help**

*“If new refrigerators hurt 7% of customers and failed to work for another one-third of them, customers would expect refunds.”*<sup>38</sup>

The pharmaceutical industry needs pharmacogenomics. The current manner in which pharmaceutical companies develop drugs and physicians prescribe them leaves *much* to be desired. This section describes the current pharmaceutical approval process, its pitfalls, and analyzes how pharmacogenomics can help it.

### **1. The FDA Process**

The Food and Drug Administration (FDA) new drug approval process comprises a complex web of regulations. This section is not an exhaustive explanation of the New Drug Application (NDA) approval process, but merely purports to examine the basic structure of the three Phases which make

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<sup>37</sup> See Frazer et al., *supra* note 30.

<sup>38</sup> Barbara J. Evans et al., *Creating Incentives for Genomic Research to Improve Targeting of Therapies*, 10 NATURE MED. 1289, 1289 (2004).

up the process. Current estimates place this process at around a decade to complete<sup>39</sup> with only about a 0.005% success rate<sup>40</sup> at an astronomical cost of \$0.8 to \$1.7 billion per approved drug.<sup>41</sup>

The FDA's main purpose is to ensure that drugs are "safe and effective."<sup>42</sup> The FDA accomplishes this goal through three Phases of clinical testing prior to market approval. It is important to bear in mind that in spite of all that is currently known about individuals' differing responses to pharmaceuticals, pharmacogenomics plays little to no role in the FDA process.

Prior to filing an NDA, a drug sponsor<sup>43</sup> must compile all relevant information about the drug observed through laboratory<sup>44</sup> and animal testing<sup>45</sup> and submit an Investigational New Drug (IND) Application.<sup>46</sup> An IND Application must contain all information currently available to the sponsor,<sup>47</sup> the general investigational plan,<sup>48</sup> and protocols of human testing.<sup>49</sup>

Approval of an IND Application allows the drug sponsor to proceed to Phase I of clinical testing. The FDA's central purpose in Phase I is to determine the safety of new drugs.<sup>50</sup> An IND's effects in humans are identified through use in patients or healthy volunteers.<sup>51</sup> Subjects are closely observed<sup>52</sup>

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<sup>39</sup> Lesko & Woodcock, *supra* note 15, at 764.

<sup>40</sup> Teresa Kelton, *Pharmacogenomics: The Re-Discovery of the Concept of Tailored Drug Therapy and Personalized Medicine*, 19 HEALTH L. 1, 6 (2007).

<sup>41</sup> TUFTS CTR. FOR THE STUDY OF DRUG DEV., TUFTS UNIV., BACKGROUND: HOW NEW DRUGS MOVE THROUGH THE DEVELOPMENT AND APPROVAL PROCESS 1, (2001), [http://csdd.tufts.edu/files/uploads/how\\_new\\_drugs\\_move.pdf](http://csdd.tufts.edu/files/uploads/how_new_drugs_move.pdf).

<sup>42</sup> 21 U.S.C. § 321(v)(1) (2006).

<sup>43</sup> 21 C.F.R. § 312.3(b) (2009). ("Sponsor means any person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization.")

<sup>44</sup> U.S. Food & Drug Admin., *The Beginnings: Laboratory and Animal Studies*, FROM TEST TUBE TO PATIENT: PROTECTING AMERICA'S HEALTH THROUGH HUMAN DRUGS, Dec. 2005, at 12, 12, *available at* <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143475.htm>.

<sup>45</sup> *Id.* at 13 ("[I]n animal testing, scientists measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body.")

<sup>46</sup> 21 C.F.R. § 312.20(a) (2009).

<sup>47</sup> *Id.* at § 312.23; *see also id.* at § 312.22(b).

<sup>48</sup> *Id.* at § 312.22(c); *see also id.* at § 312.23(a)(3)(iv)(5).

<sup>49</sup> *Id.* at § 312.22(c); *see also id.* at § 312.23(a)(6).

<sup>50</sup> *Id.* at § 312.22(a).

<sup>51</sup> *Id.* at § 312.21(a)(1).

<sup>52</sup> *Id.*

and study sizes are usually limited in size—generally between twenty to eighty subjects.<sup>53</sup> The key data needed from Phase I testing includes identifying the new drug’s metabolism, side effects, and pharmacologic action at increasing dosage levels.<sup>54</sup>

If Phase I testing produces data sufficient to show a drug’s relative safety, the drug can advance to Phase II.<sup>55</sup> Phase II evaluates a new drug’s effectiveness for its intended purpose.<sup>56</sup> In Phase II, researchers typically conduct experiments in a controlled population setting, with more participants than Phase I—generally several hundred subjects.<sup>57</sup> This Phase also studies the short-term side effects and risks of the new drug.<sup>58</sup>

After satisfying the safety and effectiveness standards of Phase I and II, new drugs enter Phase III testing.<sup>59</sup> Phase III testing is used to gather safety and efficacy information on a much larger scale. Generally several thousand participants are used to gather further drug information.<sup>60</sup> The FDA uses the information from all three phases to identify a drug’s risks and benefits and to gather information to provide to physicians on the drug label.<sup>61</sup>

## 2. Pharmaceutical Failures

One of the biggest problems with pharmaceutical development, including the FDA’s NDA process, is its lack of genetic input. The above described NDA process requires no pharmacogenomic input, even though each human being is different.<sup>62</sup> It should be noted, however,

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<sup>53</sup> *Id.*

<sup>54</sup> *Id.*

<sup>55</sup> *Id.*

<sup>56</sup> *Id.* at § 312.21(b).

<sup>57</sup> *Id.*

<sup>58</sup> *Id.*

<sup>59</sup> *Id.* at § 312.21(c).

<sup>60</sup> *Id.*

<sup>61</sup> *Id.*

<sup>62</sup> See Frazer et al., *supra* note 30 (stating that there are 3.1 million SNPs).

that the FDA is currently *encouraging* pharmacogenomic data submissions by drug sponsors,<sup>63</sup> with several drug companies actually submitting pharmacogenomic data.<sup>64</sup> To facilitate submissions, the FDA stated that the data will not be used in regulatory decision making.<sup>65</sup> Also, the FDA is encouraging the development of pharmacogenomic tests for use in optimizing pharmaceutical therapies.<sup>66</sup>

In spite of the FDA's admirable attempts to promote use of pharmacogenomic data, approved pharmaceuticals take a large physical toll on American society through adverse drug reactions (ADRs). Although estimates are fifteen years old, a meta-analysis of ADR studies of hospitalized patients revealed staggering health statistics.<sup>67</sup> Researchers observed that ADRs led to approximately two million hospitalizations yearly.<sup>68</sup> Also, of those two million hospitalizations, more than 100,000 individuals suffered fatal ADRs.<sup>69</sup> At the time of the study, this large number of fatalities placed ADRs in the top six leading causes of death,<sup>70</sup> a shocking statistic when considering physicians administer pharmaceuticals to aid in alleviation of symptoms and disease recovery.

Also, ADRs exact a financial toll on Americans. Regardless of the serious side effects and safety issues associated with ADRs, pharmaceuticals exhibit a relatively poor track record for efficacy. In spite of the lengthy and expensive Phases of FDA approval (and likely because of the lack of pharmacogenomic input in to the process), only about 60% of prescriptions produce their

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<sup>63</sup> CTR. FOR DRUG EVALUATION & RESEARCH ET AL., U.S. FOOD & DRUG. ADMIN., GUIDANCE FOR INDUSTRY: PHARMACOGENOMIC DATA SUBMISSIONS 3-4 (2005), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf>.

<sup>64</sup> See Shashi Amur et al., *Integration and Use of Biomarkers in Drug Development, Regulation, and Clinical Practice: A US Regulatory Perspective*, 2 BIOMARKERS MED. 305, 305, 306 box.1 (2008).

<sup>65</sup> *Id.* at 305.b

<sup>66</sup> See CTR. FOR DEVICES AND RADIOLOGICAL HEALTH ET AL., U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF: PHARMACOGENETIC TESTS AND GENETIC TESTS FOR HERITABLE MARKERS 3 (2007), <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071075.pdf>.

<sup>67</sup> See Lazarou et al., *supra* note 11.

<sup>68</sup> *Id.* at 1202.

<sup>69</sup> *Id.* at 1204.

<sup>70</sup> *Id.* .

desired outcome.<sup>71</sup> In 2007 Americans spent \$227.5 billion on pharmaceuticals.<sup>72</sup> The math reveals that Americans wasted \$90 billion on pharmaceuticals in 2007.<sup>73</sup> These numbers become even more staggering when one considers the relative efficacy of certain types of drugs. Some cancer drugs (often some of the most expensive pharmaceuticals) have efficacy rates of as low as 5%, and many of those drugs prolong life by a matter of months, not years.<sup>74</sup> Other drugs' efficacy rates vary from 80% for a Cox2 inhibitor to 30% for Alzheimer's drugs.<sup>75</sup>

In conclusion, the health and financial costs arising from ADRs is astonishing. Admittedly, some of these costs may arise because of human error or other non-genetic factors. However, genetic input in to the drug discovery and approval process could ameliorate some of these huge tolls on the health care system.

### 3. Pharmacogenomics to the Rescue?

Pharmaceutical companies invest eight to ten years and about a billion dollars to obtain FDA approval on a drug. Americans waste billions on non-efficacious drugs. Two million Americans will be sent to the hospital and 100,000 of them will die as a result of an ADR. Something has to be changed to improve these shocking statistics. Pharmacogenomics is one way the FDA and drug companies can improve drug safety and efficacy. This section details pharmacogenomics' potential for alleviating some of these shortfalls. Admittedly, there likely exist non-genetic factors playing a role in all of this; they cannot be alleviated by pharmacogenomics. After the genetic component is addressed, however, the non-genetic factors can be analyzed in the future.

So, how can pharmacogenomics help? First, prior to filing an IND application (even before the

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<sup>71</sup> Peakman & Arlington, *supra* note 9, at 36.

<sup>72</sup> CTRS. FOR MEDICARE & MEDICAID SERV., U.S. DEP'T. OF HEALTH AND HUMAN SERVS., *supra* note 10.

<sup>73</sup> *See id.* and Peakman & Arlington, *supra* note 9. This number was obtained by multiplying the percent of ineffective prescriptions written (40%) by the amount spent by Americans on prescription care (\$227.5 billion).

<sup>74</sup> Manish Agrawal & Ezekiel J. Emanuel, *Ethics of Phase I Oncology Studies*, 290 JAMA 1075, 10757 (2003).

<sup>75</sup> Manasco & Arledge, *supra* note 14, at 86 tbl.5.1.

clinical testing), drug companies can target or avoid certain molecules in the body. If it is known that a new pharmaceutical's primary mode of action involves a protein with an associated large amount of variability in the gene (either through copy number variation, SNPs or any other variability), it may be wise to cautiously develop (or even avoid) that product.

If a drug sponsor goes ahead with the expensive process, pharmacogenomic data will be helpful. During the early safety studies of Phase 1, pharmacogenetic data can be collected. Responders who suffer side effects, pending their informed consent, could receive genetic tests to determine their genotype at several loci and data can be compared among the adverse responders to determine if a genetic component to the ADR exists.

Phase 2 can be used to create a larger scale genetic database of those who respond adversely to the drug. Given Phase 2's large study participant numbers, positive and negative responses can be correlated with a genotype, which would be obtained from all study participants' DNA tests, which is already happening.<sup>76</sup> This larger group would allow researchers to categorize different genotypes, and perhaps save lives and money later on. And, given this use of Phase 2, Phase 3 could then be a more targeted group, people of a certain genotype that respond well to the drug and are minimally harmed by its administration. This would likely drastically reduce non-efficacious and unsafe prescription drug use.

No good plan lacks drawbacks, and there are drawbacks here. First, this plan would create pharmaceuticals with a more targeted population. Although this would be good for the patients, this would be detrimental to the drug sponsors. This could drastically reduce the intended market and in turn, drastically limit the amount of money that could be recouped on their investment.<sup>77</sup> Along the

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<sup>76</sup> See Amur, *supra* note 63, at 306.

<sup>77</sup> But see Joseph Cook et al., *The Future Risks, Costs, and Rewards of Drug Development: The Economics of Pharmacogenomics*, 27 PHARMACOECONOMICS 355, 355 (2009) (detailing how pharmacogenomic strategies can still yield huge profits for drug makers).

same lines, this method of testing, although it would use a reduced Phase 3 population, would likely be much more expensive because of the genetic tests required. This could also reduce the incentive to develop the drug. Finally, it would require the American population to be genotyped for the appropriate gene before being given a drug.<sup>78</sup> This could have serious implications in several fields of medicine, privacy, insurance, and health law, but above all, it would also be very expensive. Thus, the FDA's use of pharmacogenomic data to make market approval decisions would greatly benefit the population, but it would come at a significant cost.

As a final note, the FDA and physicians already use some pharmacogenomic data to determine who receives which pharmaceuticals. The FDA recently approved a genetic test for two genes, *CYP2C9* and *VKORC1* to determine whether or not the anti-coagulant, Warfarin, should be prescribed.<sup>79</sup> Also, Herceptin, the first drug approved using pharmacogenomic data, also requires a genetic test before use because it will be effective only for those over expressing *HER2*, which is only 30% of women with breast cancer.<sup>80</sup> It is becoming clearer to the FDA, pharmaceutical companies, and physicians that pharmacogenomic data should be used in both the premarket approval process as well as the doctor-patient relationship.

## II. Legal Issues

Although it is clear from the prior discussion that the use of pharmacogenomics in drug development would potentially significantly reduce costs to the system, there are also equally

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<sup>78</sup> It should be noted that the FDA encourages the development of drugs with diagnostic tests to *personalize* medical treatments. See U.S. FOOD & DRUG ADMIN., Drug-Diagnostic Co-Development Concept Paper 1-2 (Apr.2005) (unpublished draft), available at <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM116689.pdf>.

<sup>79</sup> Tong Yin & Toshiyuki Miyata, *Warfarin Dose and the Pharmacogenomics of CYP2C9 and VKORC1 — Rationale and Perspectives*, 120 THROMBOSIS RESEARCH 1, 1 (2006); Letter from Jean M. Cooper, Dir., Div. of Chemistry & Toxicology, Food & Drug Admin., U.S. Dep't of Health & Human Servs., to Deborah Kloos, Dir., Quality Sys. (Apr. 28, 2008), available at [http://www.accessdata.fda.gov/cdrh\\_docs/pdf7/K071867.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf7/K071867.pdf). This is the approval notice for the *CYP2C9* and *VKORC1* genetic tests. It should be noted that these tests were largely approved because the FDA changed the warfarin label to include pharmacogenomic data.

<sup>80</sup> Kelton, *supra* note 39, at 5.

significant burdens. In addition to the difficulty in actually developing drugs in this manner, there are a host of potential legal issues. Legal liability and pharmacogenomics will eventually cross paths. This could have a huge impact in shaping how industry and health-care professionals respond to pharmacogenomics advancements. The legal impacts on the different segments of the pharmaceutical industry, including manufacturers and health-care professionals are discussed below.

#### **A. Pharmaceutical Manufacturer's Potential Liability**

If pharmacogenomics becomes integrated in American health care, pharmaceutical manufacturers may face at least two different forms of products liability, but defenses will still exist.

##### **1. Design Defects**

In a design defect case, a plaintiff alleges a product manufacturer defectively designed the product, and that *defect* caused the plaintiff's injuries. Generally, a product's manufacturer will be held to a *strict liability* standard in tort for a design defect.<sup>81</sup> This standard of liability, based on a cost-benefit analysis revealing that the manufacturer is the cheapest-cost avoider and is in the best economic position to avoid potential harms, is widely accepted for *most* products' manufacturers, except for pharmaceutical manufacturers.

Prescription drug design defects hold a special recognition in tort law. The Restatement (Second) of Torts recognizes pharmaceuticals as "unavoidably unsafe" products.<sup>82</sup> This classification as a special group of products stems from the Restatement's authors' recognition that pharmaceuticals, even with proper testing and labeling can never be completely safe.<sup>83</sup> The authors recognize that risks are inherent with the great benefits accompanying drugs. Because the benefits outweighed the risks, and the fact that dangerous pharmaceuticals only come to consumers via a

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<sup>81</sup> RESTATEMENT (SECOND) OF TORTS § 402A (1965); DAVID G. OWEN, PRODUCTS LIABILITY LAW 482 (2005).

<sup>82</sup> RESTATEMENT (SECOND) OF TORTS § 402A cmt. k (1965).

<sup>83</sup> *Id.*

physician's prescription, the authors stated that drug manufactures should *not* be held to a strict liability standard.<sup>84</sup> Under this standard, if a drug's benefits exceed the risks, liability will not be imposed.

This relatively generous liability standard is now even more favorable for pharmaceutical manufacturers. Under the Restatement (Third) of Torts: Products Liability, the standard is now:

A prescription drug . . . is not reasonably safe due to defective design if the foreseeable risks of harm posed by the drug . . . are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health-care providers, knowing of such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for *any class of patients*. (Emphasis added)<sup>85</sup>

This standard creates a giant loophole for pharmaceutical manufacturers. If a pharmaceutical would have benefits that exceed the risks for "any class of patients," then no liability would be imposed upon the manufacturer for defective design.<sup>86</sup> Of course, the pharmaceutical company must supply physicians with adequate information and warnings so that the prescribing doctor can assess the foreseeable risks and therapeutics. Liability for omissions of warnings, however, does not fall under design defects liability.

Incorporation of pharmacogenomics into the American health-care system would change little in the manner in which pharmaceutical manufacturers view design-defects liability. Given the already lax pharmaceutical products liability standard and the now *very* relaxed Restatement view on prescription drugs, manufacturers have little about which they should worry. Even with pharmacogenomics data acquired during the FDA's pre-market approval process showing that a given drug poses problems for individuals with a certain genotype, as long as the drug's benefits

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<sup>84</sup> *Id.*

<sup>85</sup> RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6(c) (1998) (emphasis added).

<sup>86</sup> A great example of this is thalidomide. In the late 1990s, the drug that caused so many birth defects in Europe in the 1960s was approved by the FDA to treat leprosy. Thalidomide manufacturers face no liability under the Restatement view for design defects because of the benefit to lepers. See Letter from Murry M. Lumpkin, Deputy Ctr. Dir., Ctr. for Drug Evaluation & Research, to Steve Thomas, Celgene Corp. (July 16, 1998), *available at* [http://www.accessdata.fda.gov/drugsatfda\\_docs/appletter/1998/207851tr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/207851tr.pdf).

exceed the risks for *any class of patients* (i.e., those who lack the problem genotype), no design defect liability will be imposed. This creates a very easy standard that any pharmaceutical receiving FDA approval should meet. It should be noted, however, in spite of the Restatement's powerful view, that it is only persuasive authority. Given this, at least one court refused to adopt the pro-drug manufacturer view of § 6(c) and viewed the Restatement (Second) of Torts § 402A as an affirmative defense the manufacturer must prove.<sup>87</sup> Even though at least one state disagrees with the Restatement (Third) of Torts' approach to pharmaceutical design-defect liability, the amount of deference paid to drug makers for their designs means that, even with the use of pharmacogenomics, manufacturers face little liability for design defects.

On top of this lax standard, pharmaceuticals companies could likely use a *state of the art* defense. This defense limits what courts can consider in determining what actions are reasonable in light of the state of science and technology in existence at the time a decision to market the drug was made.<sup>88</sup> In light of this defense, if a drug manufacturer could prove that if /when they collected pharmacogenomic data, they could not intelligently discern the impact or relationship of the adverse drug reactions to a certain genotype; they may not be held liable. All of this would depend on the technology itself and scientists' ability to easily discern between one or two genetic differences which give rise to these adverse events, however, science may not quite be far enough along yet.

## 2. Failure to Warn

Unlike the fuzzy bounds of design-defects liability, drug manufacturers' *failure to warn* liability is much more transparent and strongly impacted by pharmacogenomics. In fact, failure to warn

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<sup>87</sup> *Freeman v. Hoffman-La Roche, Inc.*, 618 N.W.2d 827, 834-40 (Neb. 2000).

<sup>88</sup> Thomas Parker Redick, *Twenty-first Century Toxicogenomics Meets Twentieth Century Mass Tort Precedent: Is There a Duty to Warn of a Hypothetical Harm to an "Eggshell" Gene?*, 42 WASHBURN L.J. 547, 567 (2003).

claims predominate suits against drug-makers.<sup>89</sup> Scholars find the Restatement (Third) of Tort's standard for failure to warn less controversial than its design defects standard.<sup>90</sup> The failure to warn standard is:

A prescription drug or medical device is not reasonably safe due to inadequate instructions or warnings if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to:

(1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings; or

(2) the patient when the manufacturer knows or has reason to know that health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings.<sup>91</sup>

This standard is framed in negligence terms. Although manufacturers will not face a strict liability standard, they do have to follow reasonable precautions and warn of foreseeable risks.

Pharmacogenomics changes the failure to warn standard. Because the failure to warn standard is phrased in terms of reasonableness and foreseeability, changing the status quo shifts what is reasonable and foreseeable. If pharmacogenomic information becomes a standardized aspect of the pre-market approval process, it would likely no longer be considered *reasonable* to fail to include a genotype warning, if one was needed. It would not be reasonable because the pharmacogenomic data obtained during the three Phases of FDA testing would clearly disclose to which genotypes this particular drug poses a *foreseeable risk*. Also, the further advanced pharmacogenomics becomes, the less reasonable it becomes to fail to include pharmacogenomics-related warnings on package inserts and the less reasonable it becomes to fail to test for specific genotype interactions. In fact, currently, more than 121 package inserts contain pharmacogenomics data.<sup>92</sup> Although, a drug's label is carefully a negotiated document between the drug's sponsor and the FDA, the FDA has the final

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<sup>89</sup> RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6 cmt. d (1998).

<sup>90</sup> OWEN, *supra* note 80, at 617.

<sup>91</sup> RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6(d) (1998).

<sup>92</sup> Felix W. Frueh et al., *Pharmacogenomic Biomarker Information in Drug Labels Approved by the United States Food and Drug Administration: Prevalence of Related Drug Use*, 28 PHARMACOTHERAPY 992, 995 fig.2 (2008).

decision as to what should be included on the label. If the sponsor submitted pharmacogenomic data and the FDA decided it should not be included, it should not be the sponsor's liability.

Like design defects liability, pharmaceutical manufacturers also have defenses to failure to warn liability. Two defenses could be used to rebut a failure to warn claim: (1) a state of the art defense; and (2) the "learned intermediary defense." Also, prior to 2009, a drug manufacturer may have tried to assert that the FDA pre-market approval process preempted state tort litigation, however, after *Wyeth v. Levine*, that argument is no longer feasible.<sup>93</sup>

#### **a. State of the Art Defense**

Unlike the implications for use of the state of the art defense in an action alleging design defect, in a case alleging failure to warn, this defense would limit courts' consideration of drug makers' decisions not to warn in light of the technology available to manufacturers *at the time of drug approval*.<sup>94</sup> The rationale behind this defense is that courts are reluctant to hold drug makers liable for warnings unforeseeable to them at the time of the products' launch.<sup>95</sup> This rationale is commensurate with failure to warn liability—a manufacturer is not liable where they fail to warn of an unforeseeable risk.

With the advent of the pharmacogenomic age, however, lack of reliance on pharmacogenomic data becomes less reasonable with each advance in the technology. The FDA, however, has the final decision over drug labels' content. This could impact the manner in which courts view liability. Currently, given the state of pharmacogenomic technology, the state of the art defense to a pharmacogenomic claim may have teeth, given that so few drugs contain pharmacogenomic warnings. In the future, however, as technology progresses, drug companies will not be able to rely

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<sup>93</sup> *Wyeth v. Levine*, 129 S. Ct. 1187, 1196-97 (2009).

<sup>94</sup> Redick, *supra* note 87.

<sup>95</sup> *Id.*

on this defense to rebut a failure to warn claim because the state of the technology will be advanced enough to understand what risks are foreseeable.

### **b. The Learned Intermediary Doctrine**

The *Learned Intermediary Doctrine* is the strongest defense a drug manufacturer has against a failure to warn claim. This doctrine states that the duty to warn of foreseeable risks flows directly to medical professionals, not to patients. Although, when this duty is breached, patients may sue. The rationale behind this rule is that medical professionals responsible for providing prescriptions are the only parties who have the necessary knowledge, skill, and judgment to weigh the risks and benefits of prescribing a drug to a patient.<sup>96</sup> Thus, as long as a drug manufacturer warns medical professionals of the foreseeable risks, their duty to warn is fulfilled. In light of the information above, assuming a pharmaceutical company invests in obtaining and deciphers pharmacogenomic data during its clinical trials, by passing along this information to prescribing physicians, the company *possibly* creates an air-tight defense. Although this defense is still firmly entrenched in pharmaceutical liability cases, two landmark cases out of New Jersey and West Virginia created some doubts about this defense.

A growing trend in advertising led to the Supreme Court of New Jersey's decision to limit the Learned Intermediary Doctrine. In 1999, the FDA published a final guidance in the Federal Register expanding the ability of drug manufacturers to advertise directly to consumers.<sup>97</sup> Since 1999, drug manufacturers spent \$2.5 billion on direct to consumer (DTC) advertising.<sup>98</sup> Given this DTC advertising atmosphere, the Supreme Court of New Jersey declined to extend the Learned Intermediary Doctrine to cases where the drug in question was directly advertised to the consumer.<sup>99</sup>

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<sup>96</sup> *Larkin v. Pfizer, Inc.*, 153 S.W.3d 758, 763-64 (Ky. 2004).

<sup>97</sup> Guidance for Industry on Consumer-Directed Broadcast Advertisements; Availability, 64 Fed. Reg. 43197 (Aug. 9, 1999).

<sup>98</sup> THE LANCET, *Europe on the Brink of Direct-to-Consumer Drug Advertising*, 359 THE LANCET 1709, 1709 (2002).

<sup>99</sup> *Perez v. Wyeth Labs, Inc.*, 734 A.2d 1245, 1255-56 (N.J. 1999).

The court reasoned that the Learned Intermediary Doctrine is based on an out-dated version of health care; one that no longer exists.<sup>100</sup> The Doctrine was based on a time when doctors met with patients in their offices to discuss the risks and benefits of a particular drug.<sup>101</sup> The court stated that drugs are now mass-marketed in all forms of media and those portraits do not adequately disclose the risks so that a consumer can make an informed decision, given the great changes in the American health-care system.<sup>102</sup>

With *Perez* as a backdrop, the Supreme Court of West Virginia expanded the move away from the Learned Intermediary Doctrine. Using rationale similar to *Perez*, the Supreme Court of West Virginia refused to adopt the Learned Intermediary Doctrine for *any* failure to warn case, not just limited to DTC advertising cases.<sup>103</sup> This holding shocked pharmaceutical companies and scholars alike,<sup>104</sup> and, in the future, could create serious trouble for drug makers.

In spite of these developments, to date, these are the only two state Supreme Courts to limit the Learned Intermediary Doctrine, although there are known exceptions for mass immunizations<sup>105</sup> and birth control pills.<sup>106</sup> Without further adoption by other states, the Learned Intermediary Doctrine will still be a solid defense for drug makers against failure to warn claims.

### 3. Cassidy v. SmithKline Beecham

To date, only one pharmacogenomic-related suit has been filed against a manufacturer, *Cassidy v. SmithKline Beecham*.<sup>107</sup> In *Cassidy*, the plaintiffs alleged SmithKline's LYMERix vaccine caused a chronic autoimmune reaction for individuals with a certain genotype carried by 30% of the population.

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<sup>100</sup> *Id.*

<sup>101</sup> *Id.*

<sup>102</sup> *Id.* at 1252-53.

<sup>103</sup> *State ex rel. Johnson & Johnson v. Karl*, 647 S.E.2d 899, 910 (2007).

<sup>104</sup> See Jerica L. Peters, *State v. Karl: An Unreasonable Rejection of the Learned Intermediary Doctrine*, 48 JURIMETRICS J. 285, 285 (2008).

<sup>105</sup> See, e.g., *Petty v. United States*, 740 F.2d 1428, 1440 (8th Cir. 1984).

<sup>106</sup> See e.g., *MacDonald v. Ortho Pharm. Corp.*, 475 N.E.2d 65, 74 (Mass. 1985).

<sup>107</sup> *Cassidy v. Smithkline Beecham*, No. 99-10423, 2003 WL 2216528 at \*1 (Pa. Com. Pl. July 1, 2003).

The plaintiffs further alleged SmithKline knew of this genotype-specific reaction, but failed to provide a warning to physicians or consumers. In 2002, the plaintiffs settled out of court for an undisclosed sum that included attorneys' fees and court costs.<sup>108</sup> Later, citing poor sales, SmithKline pulled LYMErix from the market.<sup>109</sup> Although this case settled and no other published opinions exist, similar lawsuits likely will likely be on the horizon.

In conclusion, as a result of pharmacogenomics hopefully playing a more prominent role in drug development, pharmaceutical companies may face more liability due to either design defects or failure to warn claims. These claims may be rebutted by defenses such as *state of the art* or the *Learned Intermediary Doctrine*, but as detailed earlier, those defenses may not necessarily apply. And finally, even though the initial pharmacogenomic law suit ended in a settlement, there is no guaranty that future suits are not around the corner.

### **B. Physician's Possible Liability**

The increased validation, acceptance, and use of pharmacogenomics in clinical practice could result in a difficult time for physicians. As previously discussed, even though pharmaceutical companies face potential liability for design defects and failure to warn claims, the Learned Intermediary Doctrine and state of the art defense provide more than adequate protection from suits. Unfortunately for physicians, much of the potential liability falls to them. After all, if a pharmaceutical company discovers pharmacogenomically relevant information during the FDA-approval process and discloses that information in the drug insert, with a few noted exceptions, the requirements of the Learned Intermediary Doctrine are satisfied, and the liability passes to the physician. This section details the two major forms of liability physicians could face: medical malpractice and lack of informed consent.

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<sup>108</sup> See *id.* at \*2-\*3.

<sup>109</sup> *Sole Lyme Vaccine Is Pulled Off Market*, N.Y. TIMES, Feb. 28, 2002, at C5.

## 1. Medical Malpractice

Pharmacogenomics will alter the way physicians practice medicine. As physicians incorporate pharmacogenomic techniques in their practice, patients will likely suffer fewer ADRs.

Pharmacogenomics' incorporation into medicine, however, will likely be accompanied by (if not spurred on by) medical malpractice suits based on a number of claims.

### a. Legal Standards of Medical Malpractice

Medical malpractice claims are negligence-based,<sup>110</sup> meaning these claims include a duty owed by the physician to their patient, a breach of that duty, causation, and damages.<sup>111</sup> The physician-patient duty, however, differs from most other common law duties because of its professional nature. Generally, physicians are expected to provide professional services that meet the standard of care of other physicians in the same field.<sup>112</sup> The "standard of care" is the standard by which courts judge physicians' services. The standard means that physicians will provide services in accord with other members of their profession in terms of skill, knowledge, and care.<sup>113</sup>

If a patient suffers an adverse drug reaction or ineffective treatment, and real physical, emotional, and financial damages exist, the major hurdle is establishing a standard of care that the prescribing physician breached. Generally, a plaintiff establishes a standard of care via medical experts, in the same field as the defendant physician, testifying as to whether a particular procedure is medically acceptable.<sup>114</sup> Currently, a potential plaintiff could face difficulty establishing a standard of care that would give rise to liability for failure to administer a pharmacogenomic test because so few physicians (13% based on the AMA study)<sup>115</sup> rely on this technology. It is important to note,

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<sup>110</sup> DAN B. DOBBS, *THE LAW OF TORTS* 631 (2000).

<sup>111</sup> *Id.*

<sup>112</sup> RESTATEMENT (SECOND) OF TORTS § 299A (1965).

<sup>113</sup> DOBBS, *supra* note 109 at 632.

<sup>114</sup> DOBBS, *supra* note 109, at 633-34.

<sup>115</sup> Melissa Healy, *Doctors Untrained to Utilize Genetic Testing*, L.A. TIMES, Oct. 24, 2009, at A19.

however, that the AMA study did not distinguish between specialties. Certain drugs, like herceptin, require genetic testing prior to administration. So, medical specialties dispensing drugs like herceptin would likely have more experience using this technology. Thus, their standards of care would differ from others.

Although increased future incorporation of pharmacogenomics into the health care system will no doubt ease the burden on patients to establish a standard of care including pharmacogenomics, other avenues currently exist where a plaintiff could circumvent the fact that pharmacogenomics is today not widely used. The Restatement (Second) of Torts states “[i]n determining whether conduct is negligent, the customs of the community, or of others under like circumstances, are factors to be taken into account, but are not controlling where a reasonable man [or woman] would follow them.”<sup>116</sup> Perhaps, when a pharmacogenomic warning is prominently included on a drug label, and a physician still does not order pharmacogenomics testing which in turn leads to a plaintiff’s injury, the physician could face liability under this standard. It could be argued that medical custom, stemming from physicians’ limited background in genetics, dictates that physicians do not need to employ pharmacogenomics’ tests. If a reasonable person, given the prominence of a pharmacogenomic warning, however, would have ordered the test, medical custom may not dictate the outcome. Additionally, although not directly about pharmacogenomics warnings, some courts have held that when a physician prescribes a drug without heeding the warnings present in the drug insert, the insert itself can be treated as evidence of the standard of care.<sup>117</sup>

Finally, at least on court has applied a reasonable person objective standard in a medical malpractice setting. In *Helling v. Carey*, even though air puff tests to detect early glaucoma were not in routine use by ophthalmologists, when imposing liability for a breach of the standard of care, the

<sup>116</sup> RESTATEMENT (SECOND) OF TORTS § 295A (1965).

<sup>117</sup> See *Bowman v. Songer*, 820 P.2d 1110, 1114 (Colo. 1991); *Craft v. Peebles*, 893 P.2d 138, 151 (Haw. 1995); *Thompson v. Carter*, 518 So.2d 609,613 (Miss. 1987).

court stated “irrespective of its disregard by the standards of the ophthalmology profession, it is the duty of the courts to say what is required to protect patients”<sup>118</sup> Using this rationale, pharmacogenomics testing could save thousands of lives, and courts should impose liability for physicians who fail use available tests.

### **b. Potential Claims**

Physicians could face a host of medical malpractice claims from patients. First, physicians could face liability for failure to test patients for problem genotypes that could lead to adverse drug interactions. In 2008, 121 drug labels contained pharmacogenomic data and warnings.<sup>119</sup> A recent study by the American Medical Association (AMA), however, revealed that only 13% of the more than 10,000 physicians surveyed had ever prescribed a pharmacogenomic test.<sup>120</sup> Because of the Learned Intermediary Doctrine, drug companies are passing liability to physicians, but doctors are not properly responding. Physicians are not adhering to warnings present in pharmaceutical labels and by failing to act, they expose themselves to liability and their patients to potential ADRs or ineffective treatments leading to economic waste. Although no physician has faced liability to date for failing to test based on a pharmacogenomics theory, courts recognize a physicians’ duty recommend genetic testing generally<sup>121</sup> which could easily be extended to the pharmacogenomic context, especially when warnings are provided in the drug label.

Even those few physicians who do request pharmacogenomic testing in accord with drug label warnings may still expose themselves to liability. Now, the FDA regulates drugs, among other things. The agency does not regulate the practice of medicine. The FDA cannot order a physician to

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<sup>118</sup> *Helling v. Carey*, 519 P.2d 981, 983 (Wash. 1974) (en banc), *superseded by statute*, WASH. REV. CODE ANN. § 4,24,290 (West 2010)..

<sup>119</sup> See Frueh et al., *supra* note 91.

<sup>120</sup> See Healey, *supra* note 114.

<sup>121</sup> See *Molloy v. Meier*, 679 N.W.2d 711, 719 (Minn. 2004); *Geler v. Akawie*, 818 A.2d 402, 413 (N.J. Super. Ct. App. Div. 2003) (citing *Berman v. Allan*, 404 A.2d 8, 14 (N.J. 1979); *Paretta v. Med. Office for Human Reprod.* 760 N.Y.S.2d 639, 747 (N.Y. Sup. Ct. 2003); *Becker v. Schwartz*, 386 N.E.2d 807, 808-09, 813 (N.Y. 1978).

order a test; however, by providing a pharmacogenomic warning, it could at least alert the physician to some serious consequences. Physicians who do order genetic tests must still interpret the results and decide which drug should be prescribed, in light of the patient's genotype. The interpretation of the genetic tests could further give rise to liability. Physicians could misinterpret the genetic test's results and still prescribe a dangerous or ineffective pharmaceutical. Additionally, the physician could fail to properly counsel the patient when discussing the results. Simply revealing the genetic information without any context could affect the patients psyche. These forms of medical malpractice liability stem from the generally poor background physicians have when it comes to genetics. The above-discussed AMA study also revealed that only 10% of physicians possessed the requisite knowledge to use genetic testing.<sup>122</sup> Thus, even when physicians read the drugs labels, and perform the genetic tests, a correct decision about which drug should be prescribed is not a guarantee.<sup>123</sup>

One final potential claim could be for failing to warn patients' relatives of the implications of the pharmacogenomic testing. Pharmacogenomic traits by their nature are heritable and there is no guarantee that a patient and their off-spring, or other genetic relative, will share physicians. Depending on the jurisdiction, even when a physician orders a pharmacogenomic test, properly interprets that test, and prescribes the correct drug in the correct dose, the doctor could still face liability if a close relative is not warned, even if it means going outside the doctor-patient relationship. Florida<sup>124</sup> and New Jersey<sup>125</sup> courts recognize a physician's duty to inform a patient that they should warn close relatives of a harmful genotype the patient possess, with New Jersey

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<sup>122</sup> Healey, *supra* note 114.

<sup>123</sup> It should be noted that there are serious questions whether doctors pay attention to labels at all. See J. A. W. Wildsmith, Letter to the Editor, *Doctors Must Read Drug Labels, Not Whinge About Them*, 324 BMJ 170, 170 (2002) (describing how doctors need to read labels to discern between different pharmaceuticals, but fail to do so).

<sup>124</sup> *Pate v. Threlkel*, 661 So.2d 278, 279, 282 (Fla. 1995).

<sup>125</sup> *Safer v. Estate of Pack*, 677 A.2d 1188, 1192 (N.J. Super. Ct. App. Div. 1996) (quoting *Schroeder v. Perkel*, 432 A.2d 834, 839 (N.J. 1981)).

indicating that warning the patient may not be enough – warnings may have to be given to patient’s relatives directly by the physician.<sup>126</sup>

Overall, physicians could face several forms of liability. These medical malpractice claims could stem from a failure to require proper pharmacogenomic testing or a failure to correctly interpret a pharmacogenomic test. Liability also could stem from a failure to properly counsel patients when physicians share test results with patients or even, in some jurisdictions, failure to share this genetic information with patients’ at-risk relatives. Now that sources of liability have been discussed, the legal mechanisms of medical malpractice will be analyzed.

## 2. Lack of Informed Consent

In addition to medical malpractice claims, injured patients could sue under a theory of informed consent. Informed consent claims stem from the principles of autonomy and self-determination in deciding which medical procedures a patient may wish to undergo.<sup>127</sup> To establish informed consent liability an injured patient must establish that their physician failed to disclose all pertinent information, including risks, benefits, and alternatives, and the patient must also prove by a preponderance of the evidence that if the patient would have received all necessary information about the procedure, they would have chosen a different avenue of treatment.<sup>128</sup>

Patients’ lack of informed consent claims would be similar to those described in the medical malpractice section. Basically, the injured patient would allege that, if given the proper information about a prescription drug’s potential pharmacogenomic warnings, the patient would have asked for a genetic test to determine whether they would be injured by the drug, or would have avoided the

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<sup>126</sup> *Id.* at 1192-93 (citing *Pate*, *supra* note 123, at 282).

<sup>127</sup> Richard A. Heinemann, *Pushing the Limits of Informed Consent: Johnson v. Kookemor and Physician-Specific Disclosure*, 1997 WIS. L. REV. 1079, 1081-82 (1997) (quoting *Schlonedorff v. Soc’y of N.Y. Hosp.*, 105 N.E. 92, 93 (N.Y. 1914), *abrogated by Bing v. Thunig*, 143 N.E.2d 3 (N.Y. 1957).

<sup>128</sup> DOBBS, *supra* note 109, at 654.

potential ADRs altogether by asking for a different treatment regimen.

Depending on the jurisdiction, proving an informed consent claim could be easier than proving a medical malpractice claim. A majority of the states apply the “reasonable practitioner standard.”<sup>129</sup> This standard is analogous to the medical malpractice standard in that it a plaintiff must establish what a reasonable physician would disclose to their patient and then prove that their own physician did not disclose that information and that the patient was harmed by this lack of disclosure.<sup>130</sup> Plaintiffs in jurisdictions applying this standard face the same difficulties discussed in the medical malpractice section – currently, pharmacogenomics is not widely used and it would be hard to show that a reasonable practitioner would disclose (or would be even be able to adequately explain) pharmacogenomic information.

A minority of states apply a different, more patient-oriented, informed consent standard. In lieu of a plaintiff establishing what a “reasonable practitioner” would disclose, these minority states require a plaintiff to establish what “reasonable patient” would need to know to make an informed decision.<sup>131</sup> The policy rationale behind this shift is that it furthers patient autonomy and minimizes physician paternalism, effectively empowering patients to determine their own medical future.<sup>132</sup> One court noted “the test for determining whether a particular peril must be divulged is its materiality to the patient's decision: all risks potentially affecting the decision must be unmasked.”<sup>133</sup>

It should be noted that this is an objective standard, not a subjective one. A plaintiff could not simply testify that he or she would have wanted to know about pharmacogenomic warnings; the plaintiff must establish was a reasonable patient in their position would want to know about the risks,

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<sup>129</sup> Peter H. Schuck, *Rethinking Informed Consent*, 103 YALE L.J. 899, 916 (1994).

<sup>130</sup> *Id.*

<sup>131</sup> Heinemann, *supra* note 126, at 1082-83.

<sup>132</sup> *Id.*

<sup>133</sup> *Canterbury v. Spence*, 464 F.2d 772, 786-87 (D.C. Cir. 1972) (citing Jon R. Waltz & Thomas W. Scheuneman, *Informed Consent to Therapy*, 64 NW. U. L. REV., 628, 639-41 (1970)).

benefits, and alternatives of a course of treatment.<sup>134</sup> The plaintiff would still be required to prove that material pharmacogenomic information was present and that something could be done about it. If no test was commercially available and the plaintiff could not have determined his genotype, then the information could not have been materially relevant. Of course, the advancement of pharmacogenomics will bring increases in both the number and power of genetic tests, increasing the need for informed consent and cooperative decision-making between physicians and patients.

Overall, in the near future, physicians will begin to face suits stemming from pharmacogenomics-related claims, be it for failure to provide genetic tests or failure to properly interpret those tests. This places physicians on the front lines of liability and may force doctors into a position of learning about these techniques and incorporating them in to their practice. Although the transition may be difficult at first, pharmacogenomics' increased use will benefit doctors and their patients by reducing the numbers of those harmed by drugs.

### C. Pharmacists

Pharmacists also face potential liability stemming from pharmacogenomics' increased incorporation in to the health care system. Traditionally, pharmacists' sole duty to customers was to accurately fill legally written prescriptions based on a negligence standard;<sup>135</sup> no other duty existed.<sup>136</sup> Pharmacists' lack of duties to patients stemmed from three policy rationales: (1) physicians and nurse practitioners are the true professionals, and the learned intermediary doctrine's placement of warning duties on them; (2) prescribers' judgment should not be questioned; and (3) it

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<sup>134</sup> See Heinemann, *supra* note 126, at 1083.

<sup>135</sup> Steven W. Huang, *The Omnibus Reconciliation Act of 1990: Redefining Pharmacists' Legal Responsibilities*, 24 AM. J.L. & MED. 417, 422-23 (1998).

<sup>136</sup> David B. Brushwood, *The Challenges of Pharmacogenomics for Pharmacy Education, Practice, and Regulation*, in PHARMACOGENOMICS: SOCIAL, ETHICAL, AND CLINICAL DIMENSIONS 219-220 (Mark A. Rothstein ed., 2003).

would likely confuse patients to share warning information.<sup>137</sup> Pharmacogenomic-related claims against pharmacists will likely arise out of a failure to provide adequate warnings about pharmaceuticals and a plaintiffs' injury connected to that lack of warning. Accordingly, this section will largely focus on pharmacists' duty to warn.

Within the last two decades, cracks are beginning to appear in pharmacists' general immunity from a duty to warn, reflecting changes in both common law and legislative attitudes toward the profession.

### **1. Common Law Changes in Pharmacists' Immunity from Duty to Warn Suits**

The traditional "no duty" rule discussed above is slowly beginning to crack. Courts are recognizing pharmacists' increased role in the health care system and their increased educational background by imposing upon them a standard of care, skill, and intelligence which ordinarily categorizes the profession.<sup>138</sup> Some courts now treat pharmacists as they do other professionals, like physicians – their conduct in negligence suits is judged on a "reasonable professional" standard.<sup>139</sup>

Several jurisdictions around the country have adopted this "reasonable pharmacist" standard. Arizona was one of the first states to recognize a duty to warn for pharmacists. In *Lasley v. Sharke's Country Club Pharmacy*, Lasley became addicted to medications prescribed to him over the course of ten years.<sup>140</sup> Lasley sued his pharmacist for failure to provide a warning of the drugs' addictive nature.<sup>141</sup> The pharmacist countered that its only duty was to accurately provide Lasley with his drugs because he had a legal prescription.<sup>142</sup> The Arizona Court of Appeals rejected the pharmacists' argument stating that the pharmacist had a "duty to act as a prudent and reasonable pharmacist,"

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<sup>137</sup> OWEN, *supra* note 80, at 619.

<sup>138</sup> *Dooley v. Everett*, 805 S.W.2d 380, 386 (Tenn. Ct. App. 1990).

<sup>139</sup> Michele L. Hornish, *Just What the Doctor Ordered – Or Was It?: Missouri Pharmacists' Duty of Care in the 21st Century*, 65 MO. L. REV. 1075, 1085 (2000).

<sup>140</sup> *Lasley v. Sharke's Country Club Pharmacy*, 880 P.2d 1129, 1131 (Ariz. Ct. App. 1994).

<sup>141</sup> *Id.*

<sup>142</sup> *Id.*

which included warning of the drugs addictive properties.<sup>143</sup> Other courts have likewise adopted similar “reasonable pharmacist” standards on the basis of pharmacists’ increased role as professionals and increased knowledge stemming from more rigorous schooling.<sup>144</sup>

Also, relevant to this discussion is a pharmacist’s duty to warn after the pharmacist acquires information about the patient. Several courts have recognized this duty to warn, which can be present in jurisdictions lacking the “reasonable pharmacist” standard. The Illinois Supreme Court recognized this duty in *Happel v. Wal-Mart Stores*.<sup>145</sup> In *Happel*, a Wal-Mart pharmacy, in an effort to minimize customer ADRs, collected data about patient allergies and stored it in their computer.<sup>146</sup> The court held that when a pharmacist knows of a customer’s allergies and a drug is contraindicated for those allergies, the pharmacist has a duty to warn the customer of the potential consequences.<sup>147</sup> Other jurisdictions also recognize this duty.<sup>148</sup>

Courts’ increased imposition of duties upon the pharmacy profession show that greater responsibilities will be heaped on the pharmacists because the more-professional role they have taken in the health care system in combination with the fact that they are medicine’s “safety net.” This view is further emphasized by the legislative attitudes toward the pharmacy profession.

## 2. Omnibus Budget Reconciliation Act of 1990 (OBRA)<sup>149</sup>

Congress enacted OBRA in 1990 to control the cost of providing Medicaid payments for prescription drugs.<sup>150</sup> One of the major policies behind OBRA was to enable pharmacists to better

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<sup>143</sup> *Id.* at 1132.

<sup>144</sup> *See, e.g., Horner v. Spalitto*, 1 S.W. 3d 519, 522 (Mo. Ct. App. 1999); *Heredia v. Johnson*, 827 F. Supp. 1522 (D. Nev. 1993); *Hooks SuperX, Inc. v. McLaughlin*, 642 N.E.2d 514, 519 (Ind. Ct. App. 1994); *Hand v. Krakowski*, 453 N.Y.S.2d 121, 122-23 (N.Y. App. Div. 1982).

<sup>145</sup> *Happel v. Wal-Mart Stores, Inc.*, 766 N.E. 2d 1118, 1123-25 (Ill. 2002).

<sup>146</sup> *Id.* at 1120-21.

<sup>147</sup> *Id.* at 187-89.

<sup>148</sup> *See, e.g., Hand*, 453 N.Y.S.2d at 123.; *Brienze v. Casserly*, 2003 WL 23018810, at \*2 (Mass. Super. Ct. 2003).

<sup>149</sup> Omnibus Budget Reconciliation Act of 1990, Pub. L. No. 101-508, 104 Stat. 1388 (1990).

<sup>150</sup> Huang, *supra* note 134, at 433.

counsel Medicaid customers by providing more information about their prescription drugs.<sup>151</sup>

Importantly, although OBRA's programs were intended to serve Medicaid customers, nearly all states have extended OBRA's requirements to cover all prescriptions filled.<sup>152</sup>

For this discussion, OBRA's most relevant provision is the requirement that pharmacists offer to counsel their customers.<sup>153</sup> During these counseling sessions, "[a] reasonable effort must be made by the pharmacist to obtain, record, and maintain . . . the following information . . . (bb) Individual history where significant, including disease state or states, known allergies and drug reactions, and a comprehensive list of medications . . . ."<sup>154</sup> This could be construed as a codified duty on the part of pharmacists. By combining this statutory requirement with jurisdictional requirements that recognize a duty to warn when advanced knowledge is imparted upon pharmacists,<sup>155</sup> one easily arrives at a powerful duty with which pharmacists must comply.

Although each state possesses the power to regulate its pharmacists, OBRA sets a powerful tone that pharmacists are to legally be treated as medical professionals with their own standards and duties.

Together, common law and legislative mandates create an environment where pharmacogenomics-related claims could flourish. The common theme amongst these imposed duties is information. Courts have not, and likely will not, impose a duty to warn customers about potential ADRs due to pharmacogenomic data unless the pharmacist knows the results of a pharmacogenomic test. In light of this, pharmacists will not soon face pharmacogenomic liability for two reasons: (1) so few pharmacogenomic tests exist; and (2) the lack of interconnectedness between physicians and

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<sup>151</sup> Jill Casson Owen, *The Pharmacist's Duty to Warn: Lasley v. Shrake's Country Club Pharmacy*, 37 ARIZ. L. REV. 677, 689 (1995).

<sup>152</sup> *Id.* at 690.

<sup>153</sup> 42 U.S.C. § 1396r-8(g)(2)(A)(ii) (2006).

<sup>154</sup> *Id.* at § 1396r-8(g)(2)(A)(ii)(II).

<sup>155</sup> *See supra* § II.C.1

pharmacists (the lack of electronic, interconnected medical records). Without knowledge of risk passing from the physician, who herself, as discussed above, is unlikely to know the risks, to the pharmacist, no grounds for imposing a duty to warn currently exist.<sup>156</sup>

Future advancements in pharmacogenomic technology and interconnected, electronic medical records could lead to greater liability for pharmacists. With the ever-closer \$1000 genome<sup>157</sup> and increasing numbers of pharmacogenomics-related genetic tests, the technology will soon be present where each person, if interested, could know their pharmacogenomic profile. Once this information is known, all that will be needed to complete the puzzle for pharmacist's duty to warn will be the advent of interconnected medical records. As recently as when President Barak Obama signed the American Recovery and Reinvestment Act of 2009, has the federal government pushed a policy of interconnected medical records.<sup>158</sup> The Recovery Act included \$1.5 billion for improving health information technology systems. Additionally, Congress enacted the HITECH Act to further promote health information technology and set new standards for electronic medical records.<sup>159</sup> Combined, these two pieces of legislation support the idea medical records moving toward an interconnected web of information that will (hopefully) be accessible by physicians and pharmacists. Between advances in pharmacogenomic technology and relevant information at pharmacists' computer terminals, pharmacists will be presented with great amounts of pharmacogenomic information. This information will provide pharmacists with a knowledge for which courts will hold them responsible. Although physicians should catch potential ADRs before prescribing a drug, this interconnected pharmacogenomic information will provide pharmacists with the knowledge to

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<sup>156</sup> It should be noted that by simply implementing pharmacogenomics in the doctor's office and a corresponding fine-tuning of prescription strengths to suit a patient's genotype, liability could also arise. The increasing complexity of drug dose could lead to a growth of simple negligence claims arising because pharmacists may be inundated with varying doses with which they cannot adequately fill.

<sup>157</sup> See John Markoff, *I.B.M. Pursues \$1000 Genome Sequencing*, N.Y. TIMES, Oct. 6, 2009, at D2.

<sup>158</sup> American Recovery and Reinvestment Act of 2009, Pub. L. No. 111-5, 123 Stat. 115.

<sup>159</sup> HITECH Act, Pub. L. No. 111-5, 123 Stat. 226 (2009).

provide warnings to all of their customers.

Overall, courts and legislatures willingness to break from pharmacists' "no duty" rule combined with pharmacogenomics and interconnected medical records increased role in the health care system will give rise to liability for pharmacists. Until then, pharmacists can only begin to prepare for the information age to grasp them.

### **III. Conclusion**

In conclusion, science has taken step to incorporate pharmacogenomics in to our health care system and how that incorporation can potentially stop 100,000 deaths per year. In light of the demonstrated need for pharmacogenomics in medicine, three different parties must brace for the legal issues that come with its adoption: (1) drug manufacturers, (2) physicians, and (3) pharmacists. Each of these three parties faces unique forms of liability and must adjust their practices accordingly so that pharmacogenomics may more easily be integrated and save lives.