



# **The Impact of Pharmacogenomics on the Pharmaceutical Industry**

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August 7, 2008

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## Executive Summary

Pharmacogenomics is the study of genetic variation in humans to realize more effective and safe approaches to drug therapy. The specificity of matching the drug compound to an individual is more generally known as “personalized medicine”. Identification of relevant genetic markers would help to predict an individual’s predisposition to a given condition, thereby reducing trial-and-error dosing and adverse drug responses, ranked between fourth- and sixth-leading cause of death in United States. Although the social benefits of pharmacogenomics are promising, many challenges remain, and the technology must not compromise health safety and not exacerbate health disparities across ethnic or socio-economic lines. The emergence of pharmacogenomics will drive fundamental changes in drug development and marketing, government regulatory processes, and the health care systems.

By limiting the use of pharmacogenomic drugs to specific sub-populations, the profitable breadth of the pharmaceutical companies’ approach may decrease. However, the smaller market size may be offset by the reduced development time and the increased likelihood of regulatory approval. Improving a drug’s efficacy and safety by eliminating those groups of patients who would not respond favorably to the treatment would increase the overall efficiency of the drug therapy. For physicians, knowledge of the patients’ predicted responses would allow them to prescribe tailored drug treatments prior to the administration. For patients, a greater confidence in their assigned drug therapy would lead to higher compliance rates and, thus, a more productive health care system.

As individualized therapy is gaining importance in medicine, the many challenges and concerns must be addressed. Currently, the greatest hurdle to the realization of personalized medicine is the lack of consistency and validity in direct-to-consumer genetic tests. Passing Senate Bill 736, the Laboratory Test Improvement Act, would provide greater oversight for the Food and Drug Administration on genetic test standardization and administration. The current health care infrastructure is another issue that must be mitigated by integrating genetic information with current clinical records. Senate bill 976, called the Genomics and Personalized Medicine Act, proposes to integrate the various government agencies to improve health care practice by incorporating genetic information.

Passing the Genetic Information Nondiscrimination Act of 2008 is a significant step toward advancing personalized medicine by prohibiting discrimination in employment and insurance based on genetic information. Regulatory and government agencies will have to step in to level the social and distributive justice implications of pharmacogenomics.

From the pharmaceutical companies’ standpoint, the development of pharmacogenomic drugs will be evaluated based on expected return on investment, time saved, and market size. The industry may re-configure their entire approach to drug development and marketing to provide individualized treatment, as has happened with the introduction of BiDil, Herceptin, and

Abacavir. In the end, however, the consumer will be the judge of the state of pharmacogenomics: is there sufficient incentive to take a costly diagnostic test that may prohibit the issuance of the desired drug, or do the benefits of reduced misdiagnoses and side effects warrant enough interest? Until then, sufficient government regulation must be implemented to advance from the current reality of personalized medicine to the expected payoffs in the overall health care efficiency.

### Key Findings

- Pharmacogenomics has greatest potential in oncology therapies, which have a significant genetic base and current relevance.
- Pharmacogenomics will have immediate relevance for Mendelian-based diseases for which degree of risk is discrete and identifiable.
- Genetic tests as diagnostics will be most pertinent in all-or-nothing benefit.
- Smaller biotechnology firms are likely to lead in the pharmacogenomics-based products because of their ability to incorporate new technologies and absorb risk.
- Larger pharmaceutical companies may be more inclined to produce those drugs that are for a common disease or for a large sub-group. Biotech firms may tend to develop “orphan” drugs for less common diseases or for a smaller population.
- New uses for current drugs, particularly for those identified as commercial failures or for those that have significant side effects, may be created by combining a genetic diagnostic test to the drug in order to provide a more effective and safe treatment.

## 1.0 Introduction

Personalized medicine has been gaining momentum in actuating the science and in requiring more regulatory oversight. In the general public, genomic information teamed with medicine is becoming more prevalent and putative, from news<sup>1,2</sup> to popular media. With the completion of the Human Genome Project in 2003, the growing knowledge and application of genetics allows it to be integrated into practicing medicine. The science has pushed for the government control in order to maintain the momentum and progress. The potential of pharmacogenomics is to increase the efficaciousness of drug therapy, thereby reducing the number of injuries or deaths resulting from incorrect or ineffective prescriptions. However, lagging regulatory control, minimal public understanding, and the lack of integrated systems prevent the technology from moving forward. Yet, much has been learned from the discourse on the pharmacogenomic-based drugs like BiDil and Herceptin and from blockbuster failures like Vioxx that have provided critical evidence for the relevance of personalized medicine.

This paper will explore the uses and implications of pharmacogenomics on the pharmaceutical industry. First, the genetic difference between individuals will be explained as the main basis of pharmacogenomics. Then, the short- and long-term benefits of pharmacogenomics will pave way for a discussion on the current state of genetic testing. The next section will provide a background on the pharmaceutical industry structure and its tendency to change with the incorporation of pharmacogenomics. A case study of BiDil, a pharmacogenomic-type drug released in 2005, followed by a policy analysis and recommendations will identify what actions must be taken to fully realize the pharmacogenomic promise.

### 1.1 The basis of pharmacogenomics

The first pharmacogenomic-type drug was for treatment of alkaptonuria, a metabolic disorder. Studies in 1902 suggested a genetic basis as the underlying cause.<sup>3</sup> During World War II, hemolysis as a result of antimalarial treatment was found to be more prevalent in African-American soldiers, leading to the identification of a specific enzyme as the genetic variable.<sup>4</sup>

Humans share 99.9% of genetic sequence in a genome, allowing for pharmacogenomics to exploit the 0.1% difference between individuals. Pharmacogenetics is the focus of genetic variation in genes, contributing to the concept of “many genomes, one drug,” implying patient variability to attain the desired product. Pharmacogenomics, conversely, is based on the concept of varying the drug compounds to select for the specific genome, leading to “many drugs, one

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<sup>1</sup> Mincer, Jilian, “Genetic Testing Guidance,” *Wall Street Journal*, July 13, 2008

<sup>2</sup> Pollack, Andrew, “A Special Drug Just for You, At the End of a Long Pipeline,” *The New York Times*, November 5, 2005

<sup>3</sup> Personalized Medicine and the Practice of Medicine in the 21<sup>st</sup> Century; Amalia M. Issa; *McGill Journal of Medicine*; 2007

<sup>4</sup> Pharmacogenomics: Social, Ethical and Clinical Dimensions, Edited by Mark A. Rothstein, Wiley-Liss Publication, Hoboken, NJ, 2003.

genome”.<sup>5</sup> Both tailor to an individual’s drug metabolism and drug response to diminish side effects<sup>6</sup> but the concept of pharmacogenomics is broader in its application to the pharmaceutical industry as a tool for compound selectivity.<sup>7</sup> This method of selectivity yields a very specific patient treatment, known more generally as “personalized medicine”.

Genetic variation can be used to determine drug metabolism, drug targets, and drug distribution differences. Drug effectiveness varies from individual to individual because of the body’s response to a drug. Once the drug is absorbed, it must be distributed to the correct source to undergo metabolism, whereupon most of the drug’s active ingredient is harnessed, and then the remainder is excreted. Pharmacokinetics is the study of the effect of the concentration of the drug on its rate of uptake, and pharmacodynamics is the study of the influence of the targets and receptor binding on the drug. Once at the receptor site, the drug is able to target the necessary downstream routes, but the level of effect is dependent on its concentration.<sup>6,8</sup>

### 1.2 Short-term benefits

Of the 3 billion prescriptions per year, an estimated 3 million are incorrect or ineffective<sup>6</sup>, resulting in over 100,000 deaths per year from adverse drug responses (ADRs) in United States<sup>9,10,11</sup>, ranking this between the fourth- and the sixth-leading cause of death.<sup>6</sup> Because drugs are currently prescribed to curb an ailing condition, a drug could be assigned to anyone with such a predisposition without knowledge of expected response. Indeed, a blockbuster drug – a commercially successful drug for the overall population – is only efficacious in 40-60% of the general population.<sup>11</sup> To eliminate trial-and-error of dosing or the presumption of the drug’s capacity, a drug based on genetic makeup of an individual or population could predict the expected response. An application of pharmacogenomics is its ability to classify older drugs based on genetic predisposition to lower the risk of ADRs.<sup>6</sup> As such, personalized drug therapy could prove valuable in diminishing time, money, and lives lost because of a complementary drug and genetic profile.

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<sup>5</sup> Lindpaintner, Klaus, “The role of pharmacogenomics in drug discovery and therapeutics,” in Pharmacogenomics: The Search for Individualized Therapies, Edited by Julio Licinio and Ma-Li Wong, Wiley-VCH, 2002.

<sup>6</sup> Report of the Secretary’s Advisory Committee on Genetics, Health, and Society: Realizing the Potential of Pharmacogenomics: Opportunities and Challenges

<sup>7</sup> Vail, Jane “Pharmacogenomics: The end of trail-and-error medicine?” *International Journal of Pharmaceutical Compounding*, 2007, 11(1), 59-65.

<sup>8</sup> Merck Manual, <http://www.merck.com/mmpe/sec20/ch304/ch304a.html>, Observed July 3, 2008

<sup>9</sup> NCBI, A Science Primer; [www.ncbi.nlm.nih.gov/about/primer/pharm.html](http://www.ncbi.nlm.nih.gov/about/primer/pharm.html); Observed June 14, 2008

<sup>10</sup> Peterson-Iyer, Karen, “Pharmacogenomics, Ethics, and Public Policy,” *Kennedy Institute of Ethics Journal*, Vol. 18, No. 1, 2008, Johns Hopkins University Press; PROJECT MUSE

<sup>11</sup> “Personalized Medicine: The Emerging Pharmacogenomics Revolution”, *PricewaterhouseCoopers*, Global Technology Centre, Health Research Institute, Feb. 2005

The pharmacogenomics principle would assist scientists in identifying the precise drug action in the body. This would in turn result in a safer, more efficacious response, leading to a more manageable method of prescription by physicians.<sup>9</sup>

From the safety and economical standpoint, pharmacogenomics is predicted to benefit the consumer by 1) the indirect aversion of those drugs not specific to the consumer, reducing the number of side effect incidents, and 2) by the direct translation of smaller drug cost due to the pharmaceutical company's limited clinical trial sizes. In targeting a specific population, only those candidates viable for the drug therapy would participate in clinical trials, eliminating the population statistics necessary in traditional drug trials. Although this corresponds to decreased clinical trial costs, the cost of smaller clinical trials may be offset by the marginal profits due to a smaller prescribed population. Further discussion of the economics of the pharmaceutical company's decision to venture into this field are discussed in a later section.

### 1.3 Long-term benefits

An anticipated product of pharmacogenomics is a more effective health care system. By integrating a patient's clinical history with genetic predispositions, a physician would be more likely to provide accurate recommendations. With confidence in the health care system, a patient's behavior toward health may improve. Because of the high number of ineffective prescriptions today, one-half of all patients discontinue their medications for treatment of chronic conditions after one year.<sup>12</sup> With a more responsive drug therapy based on the principle of pharmacogenomics, patients may see the outcome as beneficial, making them less inclined to stop the necessary treatments. Such high compliance rates may be attributed to physicians' ability to prescribe accurate medication, in turn, reducing the concomitant costs of the non-responder groups. Using the combined genetic and clinical data, health care efficiency can be improved by the reduction in ADRs and by the increased speed in finding appropriate treatments, translating to lowered health risks and costs.<sup>6</sup>

Pharmacogenomics has the potential to reduce disparities by providing drug access to those individuals who were previously not specifically targeted. This would allow underserved communities greater access to more safe and effective drug therapies.<sup>6</sup> However, pharmacogenomics may have the opposite effect of exacerbating disparities if the novelty of pharmacogenomic drugs implies higher costs, making them inaccessible to the population targeted. Moreover, the pharmaceutical companies may choose to mitigate the profit risk in pursuing a limited market by selecting a common disease or by focusing on a profitable subgroup of a population. Thus, this disparities imbalance must be carefully evaluated in economic and social benefit terms.

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<sup>12</sup> Teutsch, Steven M. and Marc L. Berger, "Misaligned Incentives in America's Health: Who's Minding the Store?" *Annals of Family Medicine*, 2005; editorial

## 1.4 Implications of genetic testing

A genetic test can predict future outcomes to certain diseases. Such a test enables one to identify high-risk markers to take preventive action. A genetic test with a pharmacogenetic drug determines if one is sufficiently qualified to take the drug therapy. This combinatory therapy would aid in determining the dosing strategy, maximizing effectiveness, and reducing side effects.<sup>13</sup>

The first type of genetic test would identify individual's drug uptake – from absorption, to distribution, to metabolism, to excretion. The second type of test would focus on matching individuals to certain drug compounds to increase effectiveness. Finally, genetic testing would identify those individuals with higher risk for certain conditions.<sup>13</sup>

Genetic testing allows an individual to access predictive information regarding one's health and predisposition to certain diseases or conditions. By obtaining a specific portion of the genetic code known to encode a given predisposition, individuals can assess their likelihood of contracting a particular disease or condition. Because the response to such information may either provide incentive or disincentive for behavior change – even when the outcome is independent of the environment, some are concerned of the method of administration.<sup>14</sup>

The results relayed to the individual may inadvertently over-emphasize the risk of one's predisposition by not appropriately contextualizing the individual's risk in the general population, leading to an exaggerated interpretation and response. The response of an individual to a test depends on his health background and motivation. Highly-motivated people are more likely to obtain these genetic tests willfully in the first place. If an individual receives high-risk results where none were expected, he may dismiss those findings. Contrary, if one expects certain results based on family's history and does not receive corroborating data from the genetic tests, then the individual may either be relieved, but more likely, to disbelieve the results.<sup>14</sup>

Few regulations are imposed on genetic test companies that provide results directly to consumers.<sup>13, 15</sup> Laboratories administer genetic tests using equipment developed by them rather than by health care professionals.<sup>13</sup> If a laboratory develops its own test and reagents, then the Food and Drug Administration (FDA) does not have to approve the product.<sup>15</sup> The Clinical Laboratory Improvement Amendments (CLIA) of 1988 is imposed to ensure the laboratory complies to relevant standards, but does not evaluate the specific test.<sup>15</sup> Furthermore, in part due to competition, these companies set their own standards for the panel of tests, analysis of results, and the methodology of testing. As such, there is no known consensus between genes scanned at one company compared to those scanned at another.<sup>14</sup> However, some states like New York and

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<sup>13</sup> Melzer, Raven, Ling, Detmer, and Zimmern, "Pharmacogenetics: policy needs for personal prescribing," *Journal of Health Services Research & Policy*, Vol. 10, No.1, January 2005.

<sup>14</sup> DNAPolicy.org, Genetic Perspectives on Policy Seminar, 2008

<sup>15</sup> Erickson, Britt E. "Barriers to Genetic-Based Medicine," *Chemical and Engineering News*, July 7, 2008.

California have a stricter control over the federal regulations to ensure the tests are valid.<sup>15</sup> Because the tests may impact an individual's response toward his or her health, consistent, valid, and reliable testing procedures must be mandated by the government.<sup>15</sup> In particular, the FDA and the Centers for Medicare & Medicaid Services (CMS), part of the Department of Health & Human Services, must impose stricter regulation on the quality of genetic tests.<sup>15</sup>

In conjunction with drug therapy, a reliable, consistent, and valid genetic test is necessary to establish what constraints are necessary to administer the corresponding drug. The pharmaceutical companies must establish the limits of the level of risk for indication of drug treatment. A high risk, based on a threshold average risk, may mandate certainty of the treatment. However, the risk may in turn raise the implication of dosing. Should a high-risk individual receive different dosing requirements than one with lower risk? If so, then the dosing trial-and-error that was originally thought to be eliminated using the pharmacogenomic principle is again a concern. The amount of evidence needed to determine dosage is unclear.

One example where the level of proof was clearly indicated is Roche's Abacavir drug for the treatment of HIV. It was found that 4-8% of the population taking this medicine suffered side effects including fever, rashes, and lethargy. A particular human leucocyte antigen was found to be a predictor for these Abacavir symptoms. A genetic test was then included to exclude those individuals who would be predisposed to the hypersensitive reactions and assign them to alternative antiretroviral treatments.<sup>16</sup> This type of genetic test, where the risk is a discrete presence, is easily categorized and most beneficial to reducing the adverse drug response.

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<sup>16</sup> Highleyman, Liz, "HLA B\*5701 Genetic Test Predicts Abacavir Hypersensitivity in Black as well as White HIV Patients," *HIVandHepatitis.com*, May 2, 2008.

## 2.0 Impact on the Pharmaceutical Industry

The traditional blockbuster business model streamlines its production pipeline to generate a few billion-dollar products per year.<sup>17</sup> By focusing on a few revenue-leading products, the pharmaceutical companies are compelled to develop drugs for the general population, especially those drugs for long-term use. The following figure shows the standard development process and timeline.

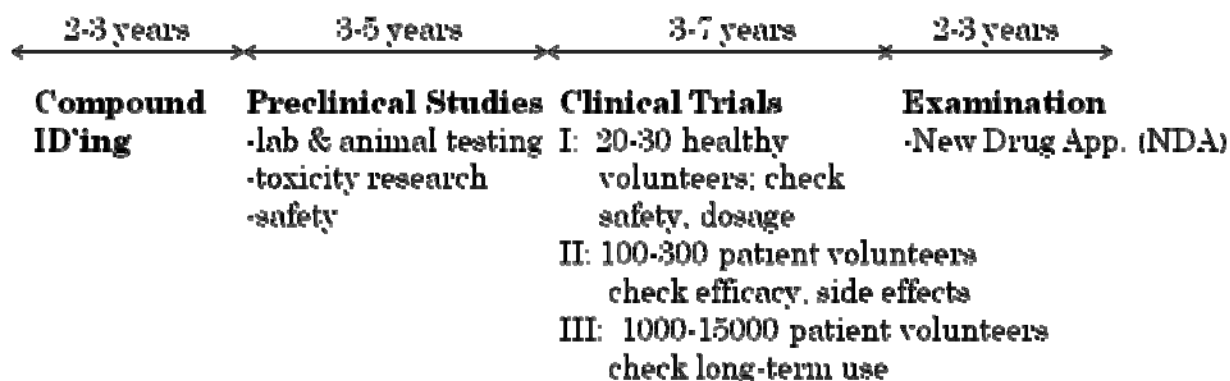


Figure 1. Traditional drug development process and timeline.<sup>18</sup>

About 10,000 initial compounds are slowly funneled through the process of drug discovery and development in order to achieve the one final robust compound which will become the patented active ingredient in the drug.<sup>18</sup> With developing technology, such as the use of high-throughput screening and microarrays, a candidate drug can be more quickly isolated and identified for potential development. The preclinical stage is the rate-limiting step in the overall process, as toxicity and safety must be carefully analyzed in test tubes and animals to allow only those candidates safe enough to be introduced into humans. If this step is coupled with a gene expression profile of various animal tissues correlated to the drug response, toxicity could be more efficiently predicted. Moreover, the probability of the compound making it to the market is increased if a thorough genetic-based profile is initiated early in the process.

As the drug development process proceeds into the clinical trial stages, the cost increases because of the larger sample sizes, the need for more specific data, and because of the participation of humans. In Phase I trials, dosage and safety is determined in healthy volunteers. This step determines pharmacokinetics and pharmacodynamics in humans. In Phase II clinical trials, a selective group of volunteers, excluding the elderly, the young, and those with other diseases, are used to determine the efficacy of the drug. By incorporating pharmacogenetics, a

<sup>17</sup> "Personalized Medicine: The Emerging Pharmacogenomics Revolution", *PricewaterhouseCoopers*, Global Technology Centre, Health Research Institute, Feb. 2005

<sup>18</sup> Furness, Mike L., "Genomics Applications that facilitate the understanding of drug action and toxicity," in *Pharmacogenomics: The Search for Individualized Therapies*, Ed. By Julio Licinio and Ma-Li Wong, Wiley-VCH, 2002.

relationship between efficacy and/or safety and biomarkers may reveal critical data. This data can be used to reduce the population group to the potential responders or to alter the compound's effective ingredient. Genetic information collection and storage, in compliance with good laboratory practice (GLP), would be essential in identifying these biomarkers. This added information would be vital in providing a comprehensive categorization of adverse events for when the drug is released on the market.

The phase III clinical trial is the largest and most comprehensive. Fortunately, by applying pharmacogenomics, the initial size may be quickly reduced once the non-responders are eliminated.<sup>4</sup> The clinical trials will determine those patients – about 1 in 100 – who experience common adverse events using a genetic basis and use that information to prevent the predisposed patients from taking this drug. For rare adverse events – about 1 in 1000 – the overall clinical trial is not sufficiently large to identify with certainty these pre-disposed individuals. Therefore, once the drug has been released into the market, the patients experiencing the severe side effects will be identified to determine the genetic basis for the reaction. In this case, a specific methodology for post-marketing surveillance will have to be implemented by the Office of Postmarketing Drug Risk Assessment (OPDRA) in FDA's Center for Drug Evaluation and Research.<sup>4</sup> For instance, a network for physicians may be set up to report the rate of adverse events in order to quickly evaluate the genetic basis and then pass the information to other physicians for comparison, evaluation, and patient identification.<sup>4</sup> For this to work, the patients must consent to using their genetic information in the future at the time of prescribing. The benefit, however, would be termination of the drug therapy for consumers with predisposition for the adverse events, and thus, a more effective therapy for the remaining patients.

Knowledge of the patient base may reduce the number of drug withdrawals from the market. The cost of product removal is estimated between \$1-1.5 billion in lost research funding.<sup>4</sup> This includes the costs of those who suffered side effects and the costs of those who benefitted from the drug but must now terminate the prescription. A more comprehensive estimate for the annual cost of drug-related problems was \$177.4 billion in 2001.<sup>4</sup> With the aid of pharmacogenomics, the drug's effectiveness could be predicted by matching the active ingredient with the correct target. In this case, the compound's success may be increased, reducing the costs and potential losses.

With the drug development cost reaching over \$1.7 billion in 2003<sup>19</sup>, the pharmaceutical companies are under increasing pressure to yield greater productivity. As research and development (R&D) costs have increased to \$30 billion/year, the FDA has approved fewer new drugs.<sup>4</sup> This is in part due to the cost of failed compounds that must be terminated, which is estimated at about 70% of the overall R&D cost.<sup>18</sup> Another reason is accounted by the fact that less than half of the drugs approved between 1998 and 2002 were considered new molecular

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<sup>19</sup> Mullin, Rick, "Drug Development Costs About \$1.7 billion," *Chemical & Engineering News*, December 15, 2003, Vol. 81, No. 50, p. 8

entities.<sup>17</sup> Some companies package two patented active ingredients to result in one new active ingredient, reducing the costs of discovery. Other companies have ventured into new fields of drug discovery, opening niches, such as anti-obesity drugs.<sup>17</sup> Still others opt to rescue drugs from commercial or clinical failures by re-focusing the compound for a particular patient group.<sup>4</sup>

Costs can be mitigated by decreasing the ten-year development time, decreasing the costs by focusing on smaller populations, or by introducing more products into the pipeline to increase the chance of discovering viable candidates. Increasing the pipeline size would not necessarily increase the outcome as more resources might be poured into the initial stages of drug development; this is indicated by the statistic that only 9% of viable candidates reaching the preclinical stage are ever filed for a New Drug Application (NDA) with the FDA.<sup>17</sup> Even so, a viable commercialized drug does not translate directly to a market success – only 3 out of 10 drugs on the market exceed their return on investment<sup>17</sup>, and only 1 out of 10 to reach the market are deemed a commercial success, as defined by sales exceeding \$500 million/year.<sup>4</sup> Moreover, drug development takes a costly ten years, allowing for marginal profit-exclusivity after filing with the FDA. Competition from generic marketing and similar “me-too” drugs further limit the potential profits.<sup>17</sup>

Decreasing the development time would allow less time for competitors to encroach on the market exclusivity and would provide longer time on the market before the patent expiration. Accelerated development is at the core of pharmacogenomics in its inherent population-constraint, allowing pharmaceutical companies to reduce clinical trial costs. Whereas a blockbuster drug must prove effectiveness in the majority of the population and few side effects in the remaining population, a pharmacogenomic drug would limit the clinical studies to those who would already be predisposed to benefit.

Another advantage of pharmacogenomics is its immediate identification of suitability indicated by biomarkers, and hence, the elimination of those candidates that would not be viable in the given population group. By determining early on the potential drug pool for commercialization – based on pharmacoeconomics, safety, efficacy, toxicity, expected market base, difficulty of production – pharmacogenomics has the promise to cut costs.

Instead of the traditional randomized clinical trials, stratifying the clinical trials to a certain group reduces clinical size and response variation, yielding a more expected outcome when prescribing drugs. The group size would be continually diminished with continuing clinical trials, so as to eliminate those individuals prone to adverse side effects and retain those with greatest benefit. The methodology of dosing can be pinpointed with the continuing timeline of drug testing. Consequently, the drug compound would be streamlined for the specific group in order to optimize the benefit. In so doing, the trial sizes diminish, reducing the time for regulatory reviews.<sup>17</sup> Overall, the drug development timeline is predicted to be narrowed down to 3-5 years.<sup>17</sup> And for every 1-2 years cut from the development process, the savings are estimated to be about 20%.<sup>18</sup>

However, a smaller trial size may over-simplify the drug's reaction in the body and may not produce a comprehensive analysis on the variation of drug-drug interaction between individuals.<sup>13</sup> Further, marketing to a smaller population size may contribute to "off-label-use," which is the use of the drug beyond its originally intended group.<sup>13</sup> In opposition to original purpose, off-labeling may introduce more adverse-drug response incidents. To ensure safety, health care practitioners must carefully comply with the drug's label.<sup>13</sup> Additionally, a follow-up clinical trial once the drug is on the market would indicate what groups may also benefit from this treatment and what other responses are observed in a larger, long-term study.

### 2.1 Pharmaeconomics for drug development

Currently, the development of personalized drug therapy may not be economically viable for pharmaceutical companies who are used to the "one-for-all" approach to producing blockbuster drugs. Unlike the \$1 billion blockbuster products, pharmacogenomic drugs are expected to yield \$350-500 million in sales<sup>17</sup>, which may prohibit the large pharmaceutical companies from pursuing pharmacogenomic drug development.

Considering the average cost of a new drug to be over \$1 billion<sup>19</sup>, the pharmaeconomic principle aids in maximizing the return on investment by finding an economic relationship between customers, insurers, and clinicians in order to produce those drugs that are in societal demand.<sup>20</sup> The traditional role of pharmaeconomics has been to evaluate the products in Phase III based on expected costs and revenues. By considering the product pipeline early in development, resources could be allocated accordingly so as not to continue those products with little promise in latter clinical trials and moving forward only those with greatest potential. Earlier decisions regarding a compound's potential could translate to more robust clinical trial designs based on a more fitted timeline.<sup>20</sup> The utility of pharmacogenomics, hence, is most significant in its use in earlier stages of drug development in order to accurately identify potential candidates using biomarkers.

Another alternative is to issue a genetic test along with the drug therapy in order to provide a more effective treatment at the time of marketing. This method, relying on explicit knowledge of who would benefit and who would be prone to side effects, would be based on data gathered in clinical trials. The issuance of a genetic test along with the drug is a critical economical issue that must be resolved prior to launch. Matching the genetic test to the drug may increase costs and furthermore divide the population into responders and non-responders, thereby, reducing the potential profit. A pharmaceutical company may stand to benefit if such a test would complement the drug therapy, and by exclusion of the test, other competitors may fill in the gap. Depending on the solitary cost of the competitors' genetic test, a pharmaceutical company may opt to include the test in combination with the drug based on this optimal value. From the

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<sup>20</sup> Miller, Paul, "Role of Pharmaeconomic Analysis in R&D Decision Making: When, Where, How?," *Pharmaeconomics*, 2005; 23(1): 1-12.

perspective of a patient, the decision to correspond drug therapy with genetic advice may prove to be worthwhile if they are willing to expend the initial cost of the test even if the drug may not be suit their genetic profile. A cost-effectiveness analysis - based on consumer behavior, drug cost, insurance coverage, and the added value of the genetic test – provides a method for determining when the combination would be most economically viable to the pharmaceutical company.<sup>21</sup>

It is expected that the pharmacogenomic model would first explore the addition of a genetic test to a drug currently on the market, particularly for a generic.<sup>13,17</sup> This would diminish costs for producing a novel drug and benefit the company by patenting an existing drug for its more focused application. To consumers, the adverse drug symptoms present in that drug would be reduced and the efficiency per drug would be increased.

### 2.2 Re-configuring the pharmaceutical business model

Pharmacogenomics is predicted to be an integral part of mainstream medicine within the decade.<sup>17</sup> The biotechnology companies, using the genomics data, are expected to lead in the shaping of pharmacogenomics.<sup>17</sup> Because of their ability to incorporate technologies and risk in developing non-blockbuster drugs, these companies have an incentive to take up the greater portion of the pharmacogenomics research. Smaller biotechnology firms focus on a niche market or on a single compound development, adding resources as the drug moves along the development path. In this approach, the smaller firms are not encroaching on the market base of the larger firms. Large pharmaceutical companies, having greater capacity for latter clinical trials, tend to partner with the smaller biotechnology companies to outsource the research and to strategizing the point at which the research is handed off to the larger company for clinical testing and marketing.<sup>17</sup>

Smaller firms would be more driven to cut costs by way of reducing preliminary risk in mis-identifying the population base, and hence, reducing downstream cost in clinical trials. By an efficient means of determining biomarkers, the smaller companies do not further the expenditure on continuing a drug with lowered efficacy.<sup>17</sup> Indeed, pharmacogenomics is expected to save up to 45% of clinical drug development costs through the use of biomarkers. Additionally, the smaller pharmaceutical companies may create niche markets by pursuing limited populations. It is particularly note-worthy that the smaller biotechnology firms may also create niche markets by developing “orphan” drugs for rare diseases.<sup>4</sup> In contrast, the large pharmaceutical companies may be more likely to focus on common diseases or large subgroup populations in order to continue the high revenues from the blockbuster days of drug development.<sup>4</sup>

In pursuing pharmacogenomics, smaller companies may be able to address a greater portion of the drug development process because of the predicted shorter time-length and smaller costs due

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<sup>21</sup> Vernon, John A., Scott J. Johnson, W. Keener HUGHEN, and Antonio Trujillo, “Economic and Development Considerations for Pharmacogenomic Technology,” *Pharmaeconomics*, 2006; 24(4); 335-343.

to the incorporation of pharmacogenomics. In contradiction to the above analysis, this may decrease collaboration between the larger and smaller firms. However, because of a larger company's expertise in commercializing and marketing their products, the more likely scenario would be partnering at the latter stage of development.<sup>17</sup>

Pharmaceutical companies consider pharmacogenomics as an added value to their traditional drug development in eliminating un-viable candidates early in the process.<sup>22</sup> Pharmaceutical companies may be more hesitant in incorporating pharmacogenomics at the latter part of the drug development process, which would perhaps reduce the market size and identify side effects that would have otherwise remained unknown. Integrating pharmacogenomics into the earlier stages of development may have lower risk in the beginning stages of pharmacogenomic realization because of the ability to absorb new techniques at this stage of production to eliminate those compounds that would fail in the long-term.<sup>22</sup>

Although the pharmaceutical business model is one of the most lucrative, its sustainability is questionable when incorporating the pharmacogenomic business plan. First, pharmacogenomics may only apply to drug therapies with clear biomarkers with all-or-nothing benefit. Biomarkers that only distinguish a degree of risk would pose greater trouble for physicians and payers. Moreover, the pharmacogenomic-based drugs may not be able to compete with current drugs – albeit less effective – that are considered safe and inexpensive.<sup>17</sup> An added diagnostic test may only increase the cost and consumer invalidation. Smaller market size would decrease the cost distribution, leading to greater drug cost per consumer. However, that assumption may be offset by early development cost-cutting resulting from the same principle of smaller market size.

Using pharmacogenomics to find new uses for drugs is a promising alternative. This method would revive past commercial or biological failures by prescribing the drug to a specific population.<sup>23</sup> A diagnostic test added to an existing drug may provide more efficacious results, garnering a new patent and a social benefit, perhaps justifying greater cost to the consumer for these results. Some larger firms are developing diagnostic tests, investing in the possibility that these tests may become mandated prior to certain drug treatments. As such, the companies would enjoy un-shared markets.

An additional means of re-shaping the way drug therapies are conducted is to identify an early diagnosis for a long-term condition and to follow up with long-term treatment. This method would retain those patients from an earlier set-point, monitoring their prognosis. Genetic tests may replace other, more expensive therapies – such as MRI or PET scans.<sup>17</sup>

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<sup>22</sup> Nunally, Allen C., Scott A. Brown and Gary Cohen, "Intellectual Property and Commercial Aspects of Pharmacogenomics," in *Pharmacogenomics: Social, Ethical, and Clinical Dimensions*, Edited by Mark A. Rothstein, Wiley-Liss Publication, Hoboken, NJ, 2003.

<sup>23</sup> Faiz Kermani (2007, October). "The future is pharmacogenomic," *Pharmaceutical Technology Europe*, 19(10), 17-18.

### 2.3 BiDil case study

Unlike traditional pharmacogenomic drugs, BiDil, approved in June 2005 by the FDA, is based on the phenotypic diagnostic of race and is the first drug to target a single racial-ethnic group of self-described African Americans at risk for heart failure. Although BiDil has significant evidence for its effectiveness, specifically for its greater effect for the self-identified black patients than for other populations, the controversy has raised ethical and regulatory questions.<sup>24</sup> In focusing on a subpopulation, BiDil conforms to the principle of personalized medicine without providing a complementary genetic test.<sup>25</sup>

BiDil is a combination of the vasodilator drugs isosorbide dinitrate and hydralazine hydrochloride, which are independently indicated for treatment of angina and hypertension, respectively.<sup>25</sup> In combination, however, the drug has capacity to treat heart failure.<sup>25</sup> In order to gain FDA's approval and patent control until 2020 as an entirely new drug with individually patented active ingredients, NitroMed, the maker of BiDil, indicated the drug to be race-specific.<sup>24</sup>

To support the commercial basis of the drug, the African American Heart Failure Trial (A-HeFT) enrolled 1,015 subjects<sup>26</sup>, which indicated that heart failure in black patients was significantly higher than for other Americans – about twice the mortality rate.<sup>26</sup> In other studies, the statistic is relevant only in the age group 45-64 year olds, accounting for only 6% of the overall mortality rate.<sup>24</sup> Other sources corroborate the basis for NitroMed's ethnic target, indicating that heart failure in black persons is significantly different than in the general American population.<sup>25</sup> Behavioral and cultural attributes, such as high prevalence of individuals with diabetes and hypertension and disparities in equitable health care, have been cited to contribute to the disproportionate statistic.<sup>24</sup> Biological basis, largely the justification for rejuvenating the BiDil drug components, indicates a lower nitric oxide bioavailability – which corresponds to decreased blood flow due to arterial constriction – in African American patients.<sup>24</sup> By selling to less than 10% of the total American population suffering from heart failure, NitroMed was able to carve out a niche market whether to found its commercial basis or help solve some of the health disparity issues.<sup>27</sup>

Although the selection of the study group for the drug's basis is criticized, the A-HeFT trials showed that BiDil did indeed prove to be effective by reducing the mortality rate by 43% and the

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<sup>24</sup> Kahn, Jonathan, "Race, Pharmacogenomics, and Marketing: Putting BiDil in Context," *The American Journal of Bioethics*, 6(5): W1-W5, 2006.

<sup>25</sup> Issa, Amalia M., L. Todd Weiss, Waqas Tufail, Kathryn A. Philips, and Stephanie L. Van Bebber, "Innovation in Personalized Medicine: BiDil as a case study for integrating clinical and policy developments," *Personalized Medicine*, 3(4): 421-427, 2006, Issa, 2006

<sup>26</sup> Jordan, Sara R. "Race, Medicine, and Social Justice: Pharmacogenomics, Diversity, and the Case of BiDil," *Review of Policy Research*, Vol. 25, No. 1, 2008.

<sup>27</sup> Sefuin, B., B. Hardy, PA Singer, and AS Daar, "BiDil: Recontextualizing the race debate," *The Pharmacogenomics Journal*, Jan 15, 2008, 8, 169-173.

first hospitalization rate by 33%.<sup>26</sup> Furthermore, A-HeFT is considered a landmark case for its focus on minority recruitment.<sup>27</sup>

As BiDil is lauded for its minority recruitment, the method by which the subjects were selected raises concerns. The scientific basis and definition for race can be construed to replace genetic characteristic without the added genetic component of DNA testing.<sup>27</sup> This phenotypic relationship is hardly justified, considering that – if only 1 percent of the human race is genetically different from one another – less than 0.015 percent of the human race variation is due to race.<sup>26</sup> Subjectively, the definition of race itself is dependent on social context, but if the subjects self-reported their race as a supplement to their geographical ancestry or a genomic qualifier, the clinical trials would have been more adequately standardized.<sup>27</sup>

The transition of personalized medicine to individual genomic or biomarker characteristics for the prescription of a drug will first pass through the cheaper route of population categorizations. In the meantime, the narrow racial focus should be examined to determine if other groups fit the profile benefit of BiDil and other such therapies. Regulatory agencies could establish a Phase IV trial to expand the original clinical trial studies of these pharmacogenomic drugs to determine if similar benefits exist for a larger population.<sup>27</sup> Currently, NitroMed is voluntarily producing follow-up genetic studies.<sup>27</sup>

In the context of BiDil, the following are important outcomes and recommendations:

- Regulatory mandate to initiate follow-up studies (Phase IV Clinical Trial) to determine the scope of the drug potential in other populations.
- Standardization of self-identified racial groups. Determine the extent of sufficient justification of one's racial or ethnic background in order to be included in the clinical studies and for later prescriptions.
- Assessment of the disparities in population-targeting: biological or social basis? Is the level of significance found for the higher-risk of heart failure in black individuals due to a genetic basis or health care inequity? If the latter, does that indicate sufficient proof for drug development?
- The evidence necessary to determine level of significance in the results: by limiting the size of the clinical trials, is the statistical value diminished by also limiting such factors as drug-drug interaction or variation within the group?
- Analysis of the population that subscribed to the race-specific drug: was there “off-labeling” prescription to those individuals who did not fit the diagnostic profile of race but had the given risk of heart failure?

### **3.0 Policy Analysis**

With the passage of the Genetic Information Non-discrimination Act, discrimination based on genetic information is prohibited in places of employment and in insurance coverage. This mandate allows for personalized medicine to forge ahead. Prior to full realization, however, the following are areas of further legislative need.

#### **3.1 Genetic test standardization**

Without genetic test standardization, the practice of assessing one's genetic profile is questionable and unreliable. Until this method has greater regulation, the public will be wary of any genetic information, particularly because of its direct impact on the individual's health. The Laboratory Test Improvement Act (S. 736) proposes to increase FDA oversight on direct-to-consumer genetic tests. As of now, laboratory developed tests are not regulated by the FDA to ensure that the tests deliver what is promised. Those tests that involve reagents from various laboratories are monitored by FDA, but a test entirely developed within the laboratory does not have the same regulation. Only CLIA mandate is followed to ensure the general laboratory complies with the given regulations. Therefore, the bill would ensure greater FDA regulation so as to standardize the tests by categorizing them as a prescription test.

The bill should also be expanded to determine the method by which the test is administered. Does a licensed genetic consultant deliver the test in an appropriate manner so as not to elicit a negative response from the patient? Is there sufficient treatment for the genetic predisposition that one is tested? More stringent guidelines for the development and administration of tests would ensure public safety.

#### **3.2 Integration of clinical and genomic data**

One objective of Genomics and Personalized Medicines Act (S. 976) calls for integration of clinical and genomic data. This would provide a more efficient delivery of an appropriate treatment. The bill must also identify issues in the method by which the data would be stored and transferred between providers to ensure privacy and security.

#### **3.3 Incentive for coupling diagnostic and drug treatment**

The pharmaceutical industry may not have sufficient incentive to complement a diagnostic genetic test with drug therapy. Such a test may limit the marketable population and may increase costs for development. S. 976 identifies the National Academy of Science to investigate what would motivate a complementary method to encourage a more efficacious and safe drug treatment. A diagnostic test may be appended to an existing drug, to a failed drug in order to restore it and the profits, or to a new drug entirely. These categories have various inherent incentives that must be investigated and appropriately defined to encourage the pharmaceutical industry's cooperation.

### 3.4 Mitigate ethical concerns

The prioritization and selection for the drugs to be developed must be scrutinized to ensure distributive equity. The pharmaceutical industry is anticipated to be segmented based on the size of the company's, which is loosely translated to the company's initiatives. Larger pharmaceutical companies are predicted to pursue those drugs that are for a common disease in order to retain much of the general population or to target a significant sub-population. In this way, the blockbuster business model is maintained to yield profits on the order of \$1 billion.

In regards to distribute justice, what incentives must be present in order to encourage pharmaceutical companies to target a disease that has high genetic prevalence in impoverished communities compared to profitable markets? This gap is expected to be filled in by smaller biotechnology companies. These firms are predicted to pursue the rare-disease market to gain security in entering the pharmaceutical market, without encroaching on the larger market shares. This would mitigate risk from the large pharmaceutical companies' competition. Consequently, the industry is expected to be demarcated based on the market and risk into large and small pharmaceutical companies' initiatives. This presents significant ethical concerns in regards to how the drugs will be selected, prioritized, and marketed. Which population group is expected to gain from the pharmacogenomic outcome: those that have access to insurance, those in the prevalent disease group, or those in the higher-income groups?

The pharmacogenomic technology is first expected to be released to the developed markets because of their ability to galvanize the necessary research and to provide the profitable market groups.<sup>28</sup> The Institutional Review Board must be called upon to investigate potential injustices that may result in exacerbation of disparities. A full discussion on these topics can be found in Appendix A.

### 3.5 Mandate Phase IV clinical trials

In order to ensure that the limited target-base is correctly identified in the earlier clinical trials, a post-marketing study by the pharmaceutical companies would ascertain the benefit to the patient base and perhaps extend it beyond the originally-intended group. Further, the post-marketing study would identify drug-drug interaction, impact in those with concomitant disease, and severe adverse events within the larger group being marketed to. Other factors to consider in this study are the off-labeling use and the physicians' tendency to prescribe this treatment to the given population. Public perception of the population-limiting drug would be critical in identifying the marketing strategy post-consumer release.

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<sup>28</sup> McLeod, Howard L. and Margaret M. Ameyaw, "Ethnicity and Pharmacogenomics," in Pharmacogenomics: The Search for Individualized Therapies. Editors Julio Licinio and Ma-Li Wong. Wiley-VCH, 2002.

### **3.6 Encourage cooperation within the pharmaceutical industry**

In order to ensure that public's interests are met in regards to the types of drugs produced, incentives to promote cooperation between the larger and smaller pharmaceutical companies would be essential. A large pharmaceutical company would be interested in producing a pharmacogenomic drug that has similarities to a blockbuster drug in its ability to be generalized for a large sub-group. In contrast, a smaller biotechnology firm may have greater motivation to pursue a niche market by developing drugs for "orphan" diseases, those not represented by a large population. A small biotech firm may then strategize with the larger firm to market the drug. By combining the efforts of the two businesses, a more equitable approach to drug development would be created. Cooperation may be inherently plausible between the businesses, but perhaps a more open approach to encouraging this may have to be analyzed by such organizations as the National Academy of Sciences. This would also ensure that one segment of the pharmaceutical industry does not dominate in securing its market profits.

## 4.0 Recommendations

Personalized medicine has much potential in matching drug treatment to the individual, thereby reducing side effects and ineffective prescriptions. In fact, pharmacogenomics, rather than rooted in profit gains, is expected to lead to positive health outcomes, such as more personal health care. The challenges, however, hinder the full realization of pharmacogenomics. Without rigor genetic test compliance, lack of public understanding, and many ethical concerns, pharmacogenomics cannot yield effective products.

Pharmacogenomics has greatest potential in treating cancer, as it is an individualized disease that is heavily genetic-based. Additionally, the utility of pharmacogenomics is greatest in cancer treatments because of the limited time available to correctly diagnose and predict the patient's response without confusing the treatment symptoms or progress with the disease. Generally, the most immediate impact of pharmacogenomics would be its application to a single- or limited-number gene-based disease that is environmentally-independent. Further, the principle of pharmacogenomics promises more efficient development of drugs, which may translate to lowered costs and faster, more personalized outcomes. Although there has been significant progress in personalized medicine such as with the introduction of the successful Herceptin treatment, the pace of pharmacogenomics will follow the pace of regulation establishment. The following is a list of recommendations in order to progress the state of pharmacogenomics. Until then, we must differentiate between expected payoffs and current state of perception by encouraging awareness and education on and between the sciences of genomics, medicine, and drug development for the benefit of the public.

### Recommendations to American Institute of Chemical Engineers

- Analyze the impact the predicted re-structuring of the pharmaceutical industry will have on the needs of chemical engineers in the advent of pharmacogenomics. Is a change in hiring of chemical engineers expected? Will a chemical engineer with a greater background in biology and genetics be preferred?
- Arrange a conference with various leaders in the pharmaceutical and biotech industry, the regulatory bodies (ie, FDA), and government research agencies (ie, NIH) to analyze the emerging trends in the predicted shift of the pharmaceutical business plan.

### Recommendations to regulatory bodies

- Enact laws requiring the FDA to standardize direct-to-consumer genetic tests in the following fashion
  - for the test reagents and makeup: ensure that the validity between tests is not compromised

- for how the test is administered: consumer information relayed in an effective and appropriate manner by trained clinicians
- for the level of evidence (risk) necessary to justify a specific drug treatment: what constraints indicate proof for the given disease to begin the corresponding treatment?
- based on ethical boundaries: provide only those tests for a which treatment is known and available.
- Provide incentives, in patent exclusivity or faster review-turnaround, for the industry to pursue those pharmacogenomic drugs that would benefit a large population with a critical disease.
- Ensure distributive justice by encouraging the industry to pursue under-served communities and to promote cooperation with the health care systems in order to diminish the health system inequities.
- Encourage other regulatory bodies, such as ASTM or NIST, to provide guidance in regards to genetic testing materials to ensure reliability.

### Recommendations to the industry

- Train and promote the pharmacogenomic concept to physicians. How receptive are the practitioners to incorporating genetic tests into the treatments for their patients? What is preventing them, if anything, from accepting this more individualized approach to therapy? Ensure that the physicians are aware of the specifications of the pharmacogenomic treatment: who is it tailored for, and who else may benefit without the improper off-labeling use? Proper training and effective information may differentiate the drug from becoming a commercial failure or a success.
- Voluntarily submit to a Phase IV Clinical Trial for pharmacogenomic drugs to investigate other patient groups who may significantly be impacted by the treatment. Also, determine what long-term effects there are on the initial sub-group and what is the variation in that group (ie, what percent of that limited population experiences side effects and how does that value compare with the side effects from an average blockbuster drug?).
- Perform a cost-benefit analysis for bridging diagnostic test with drug therapy. Is it better to outsource the genetic test or to incorporate into the treatment during drug development?

## **About WISE**

Founded in 1980 through the collaborative efforts of several professional engineering societies, the Washington Internships for Students of Engineering has become one of the premier Washington internship programs. Its goal is to groom future leaders of the engineering profession who are aware of and can contribute to the important intersections of technology and public policy. Please see <http://www.wise-intern.org> for more information.

## **About the author**

Viktoriya Buchko has received B.S. in Chemical Engineering with a focus on biotechnology from Georgia Institute of Technology in 2008 and will receive M.S. in Chemical Engineering in 2009.

## **Acknowledgments**

Viktoriya Buchko would like to acknowledge individuals and organizations that have helped with this research. Particularly, she would like to thank the American Institute of Chemical Engineers for its commitment to the WISE program. For their mentorship and encouragement, she would like to thank Dr. King, Mr. Stone, and Dr. Burka. For providing scientific guidance, she would like to thank Dr. Steen and Mr. Buydos from the Library of Congress. For coordinating the program, she would like to thank Melissa Carl and Erica Wissolik. And for constant support throughout this process, she would like to thank the fellow WISE interns.

## Appendix A. Mitigating Ethical Concerns

The full realization of personalized medicine is hindered by the lack of understanding of the implications of integrating the genetic component to drug therapy. The novelty of genetic information raises concern for the privacy, validity, and relevance of the diagnostic tests. The inherent stipulation of a limiting market in personalized medicine feeds the concern of the exacerbation of health disparity.

### Implications of genetic tests

With little uniformity among genetic test companies, the test procedures and results may not be accurate or valid. Even when the results are correct, proper care must be taken in relaying this information to the customer. Some tests should not be administered for those diseases for which there are currently no cures. Data regarding behavioral response to these tests may be critical in establishing guidelines for those willing to be tested.

**Policy Action:** Enact the FDA to have more stringent regulation on direct-to-consumer genetic tests. Enact the International Review Board ethics committee to determine the means by which the tests are administered complies with ethical standards.

### Privacy and ownership of genetic information

Genetic privacy and ownership are forefront concerns in the advent of personalized medicine. Genetic tests will become an integral component in clinical trials, and even more ubiquitous as a test for drug/treatment correspondence. Today, over 1200 genetic tests are available<sup>14</sup> offered by about 30 direct-to-consumer genetic test companies<sup>15</sup>, with SNP genetic tests priced between \$1000-\$2500 for a preliminary test and \$250 for follow-up tests<sup>29,30</sup> and a full genomic sequence approximated at \$350,000.<sup>29</sup>

On May 21, 2008, President Bush signed the Genetic Information Nondiscrimination Act to prohibit discrimination in health insurance and employment. This law prevents health insurance companies and employers to filter its constituents by their predisposition to health concerns. By providing protection and constraints on genetic use, people may be more likely to participate in genetic diagnostic tests and research, allowing the biomedical sciences to move forward.

However, some opponents of the legislation argue that the bill is airily crafted, open to loopholes and future litigations. The details of consent and ownership transfer are not defined. For instance, what happens to the data collected from clinical trials? It may be directed to future

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<sup>29</sup> Feero, W. Gregory, Alan E. Guttmacher, and Francis S. Collins, "The Genome Gets Personal – Almost," *American Medical Association*, 2008

<sup>30</sup> Mullin, Rick, "Personalized Medicine: Armed with the decoded human genome, drug researchers and clinicians are working to close the gap between patient and therapy," *Chemical & Engineering News*, Feb 11, 2008, Vol. 86, No. 6: 17-27.

clinical trial research aligned with the individual's predispositions.<sup>15</sup> Uncertainty in the GINA bill must be reduced.

**Policy Action:** Determine the loopholes in the GINA act as they pertain to biobanks, consent forms, and privacy issues to ensure full protection from employment and insurance discrimination.

### Race Identification

With some drugs marketed to specific sub-populations without a precursor diagnostic test, the pharmacogenomic principle may conflate biological race with social categories of race.<sup>31</sup> Since less than 0.01% of the genetic variation between individuals is attributed to race, the basis for these drugs may not be sufficient to rely only on social categorization of race. Still, the method for identification of individuals fitting the given pharmacogenomic profile would have to be corroborated with a follow-up genetic test or with an ancestry mapping.<sup>27</sup> Although self-identification may provide a crude basis for appealing to health disparities – as in the BiDiI study – the pharmacogenomic effect may not be understood in anyone other than those voluntarily submitting to the trials based on their self-categorizing.<sup>27,31</sup> Additionally, race categorization is tenuous if not similarly defined globally. Thus, a smaller niche market would have to balance the principle that race is relevant versus that marketing opportunity is driving the cause.<sup>31</sup>

The classification of race is largely influenced by federal agencies' incentives and guidelines.<sup>31</sup> In order to diminish the impact in conflating race with biological evidence, more specific guidelines must be implemented in order to not favor one group over another and yet to provide sufficient incentive to pursue drug development for specific diseases to address health disparities. If coupled with a genetic test analysis, drug therapy may only then be viable with a preponderance of evidence for limiting it to a specific population.

**Policy Action:** Enact the FDA to stipulate precise definition for race and ethnic identification for use as the base for population targeting.

### Prioritization and selection of drug development

One of the ethical consequences of pharmacogenomics is the selection and prioritization of drug development. If only a certain population is to benefit, then certain regulations must be established to determine how this population is determined and for what disease. One possible criteria for development is classification of disease: if the disease is predominately genetic-based, as opposed to environmentally-influenced, then those drugs would have the most immediate impact for the development and understanding of future pharmacogenomic drugs. As such, Mendelian diseases like type 1 diabetes may have more current relevance than those like alcoholism. Furthermore, pharmacogenomics may have greatest potential at this time in treating

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<sup>31</sup> Kahn, Jonathan, "Genes, Race, and Population: Avoiding a Collision of Categories," *American Journal of Public Health*, Nov. 2006, Vol. 96, No. 11

one-gene diseases rather than multi-gene diseases. Therefore, certain diseases may have a better outcome and promise for the science of pharmacogenomics.<sup>32</sup>

Pharmaceutical companies may come under harsh scrutiny if thought to select drugs for profit-gain rather than for public need. Therefore, a government protocol must be in place to outline the prioritization of development of drugs based on prevalence of disease. Incentives may enforce these prioritization measures - whether a longer patent-life or certain tax exemptions.

However, development of drugs for less common diseases would have to be incorporated into the drug portfolio development too. Legislation could provide incentive to pursue these drug therapy candidates so as not to alienate a portion of society. This could be achieved by enacting the Health and Human Services, or such a federal agency, to provide grants, by strategically pricing these drugs, or by ensuring longer exclusivity rights.<sup>10</sup>

**Policy Action:** Involve the Institutional Review Board to determine the basis for patient-selection groups and ensure distributive justice.

### Health care concerns

To be of relevance, pharmacogenomics must be studied not just in its drug development, but also in its administration and incorporation into the health care industry. Majority of government biomedical research is not funded for translational research – research for ways to improve the health care system by taking up this technology. Pharmaceutical companies measure their success by profits rather than by health indices, otherwise, they may not generate much profit. Profit drives technology, based on free market, not on social welfare. Therefore, more funding must be budgeted for allowing health care systems to influence drug development in order to balance the process for social welfare. More funding would also be necessary to quickly assess the impact of new technology and its implications, as related to pharmacogenomics.<sup>12</sup>

**Policy Action:** Provide incentives to the pharmaceutical companies producing the pharmacogenomic-based drugs to research downstream effects on health care and physicians' acceptance.

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<sup>32</sup> Merikangas, Kathleen Ries, Risen, Neil, "Genomic Priorities and Public Health," *Science*, Vol. 302, Issue 5645, Oct. 24, 2003. Editorial.

## Appendix B. Pharmacogenomic-type Treatments

Drug: Herceptin produced by Genentech and Roche and FDA-approved in 1998

Purpose: To treat breast cancer

Implications: Breast cancer is characterized by extra copies of the ERBB2 gene that causes uncontrolled tumor growth in 25% of the population. Herceptin treatment first provides the genetic test to identify responders.

Drug: Abacavir produced by Roche

Purpose: To treat HIV

Implications: To eliminate the population (4-8%) that has greater predisposition for severe side effect. Using this drug therapy, a genetic test is given to identify the particular antigen to predict the symptoms. This type of genetic test provides a discrete measure of whether one is predisposed to the severe side effects or not.

Genetic Test: Identification of BRCA1 and BRCA2

Purpose: To identify genes that increase likelihood of breast and ovarian cancer

Implications: Use genetic tests to determine if individual is predisposed to breast cancer and determine the follow-up for treatment.

Drug: Gleevec produced by Novartis

Purpose: To treat cancers, such as chronic myelogenous leukemia and gastrointestinal stromal tumors

Implications: The development was based on inhibiting a specific enzyme that would then inhibit cell proliferation. Unlike traditional methods of drug discovery, this drug is based on knowledge of specific enzymatic activities, which was then fit to the predisposed population.

Drug: Warfarin

Purpose: To prevent blood clots

Implications: By working to reduce clotting, Warfarin results in a higher risk for bleeding in other parts of the body. Pharmacogenomics has identified the enzymes responsible for increasing the rate of adverse events, allowing physicians to modify the dosing.

Drug: 6-mercaptopurine (6-MP)

Purpose: Treat acute lymphoblastic leukemia

Implications: High percent of children are treated effectively, yet a few died from the treatment due to the presence of a defect in the thiopurine methyltransferase enzyme. Pharmacogenomics suggests testing for the enzyme in order to adjust dosing and reduce toxicity.

## Appendix C. Legislative Action

### S. 358, H. R. 493

Title: Genetic Information Non-discrimination Act (GINA)

Status: Passed into law (05/21/2008)

Purpose: To prohibit discrimination in employment and insurance based on genetic information.

Concerns: Details on biobanking and storage of data are not explicit. What happens if consumer consents to a genetic test for a clinical study – could those results be retrieved for later research on the same genetic basis? How will genetic information transfer if coverage plan is altered?

### S. 976

Title: Genomics and Personalized Medicines Act

Status: Referred to Committee on Health, Education, Labor, and Pensions (03/23/2007)

Purpose: To accelerate genomics research and initiatives by improving the methods for disease diagnosis and increasing the safety of drugs. To integrate clinical and genomic data for improved prescription accuracy. Identifies the National Academy of Sciences to analyze the incentives for combination of diagnostic test and drug therapy.

### H.R. 6498

Title: Genomics and Personalized Medicines Act

Status: Referred to House Ways and Means (07/15/2008)

Purpose: To accelerate genomics research and initiatives by improving the methods for disease diagnosis and increasing the safety of drugs. To encourage cooperation within federal agencies by establishing the Interagency Working Group within the Department of Human Health and Services. Genomics and genetics research is suggested to focus on population reception and perception of genetic testing, to encourage provider acceptance of pharmacogenomic-based therapies, to understand disease based on genetic prevalence in a population, etc.

Concerns: The encouragement to prioritize focus on “studies of diseases and health conditions with substantial public health impact” may segment the population into common and rare diseases, which may compromise health equity.

### S.736

Title: Laboratory Test Improvement Act

Status: Referred to Committee on Health, Education, Labor, and Pensions (03/01/2007)

Purpose: To have greater regulatory oversight on direct-to-consumer genetic tests.

Enacts the Federal Food, Drug, and Cosmetic Act to indicate the direct-to-consumer test to be considered as a prescription test. To increase the validity of such tests.

Concerns: The guidance on the method for administration of the test to consumers is not outlined. Does not limit which tests can or cannot be provided based on the presence of a follow-up treatment to a given predisposition.