



PHARMACOGENOMICS: THE FUTURE OF HEALTHCARE

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Introduction

By any objective criteria, the United States healthcare system is broken. Drug companies face pressures and threats to their business model and practices, providers are perceived as puppets of either the drug industry or the managed care industry, payers find it nearly impossible to balance patient concerns of low quality care with shareholder concerns of higher profits, regulatory agencies are blamed for unsafe drugs, and patients are fed up with high prices and inadequate care.

One solution that could potentially address many of these problems is to move toward a pharmacogenomics model of healthcare, where scientists use their knowledge of individual genetic variations to create safer and more effective therapies. This vision of a new era in personalized medicine has existed for many years, but the pressures facing the healthcare system make this solution increasingly attractive as an alternative to the existing “blockbuster” model. Moreover, recent advances in genetics and diagnostics have finally made the technology viable for the first time.

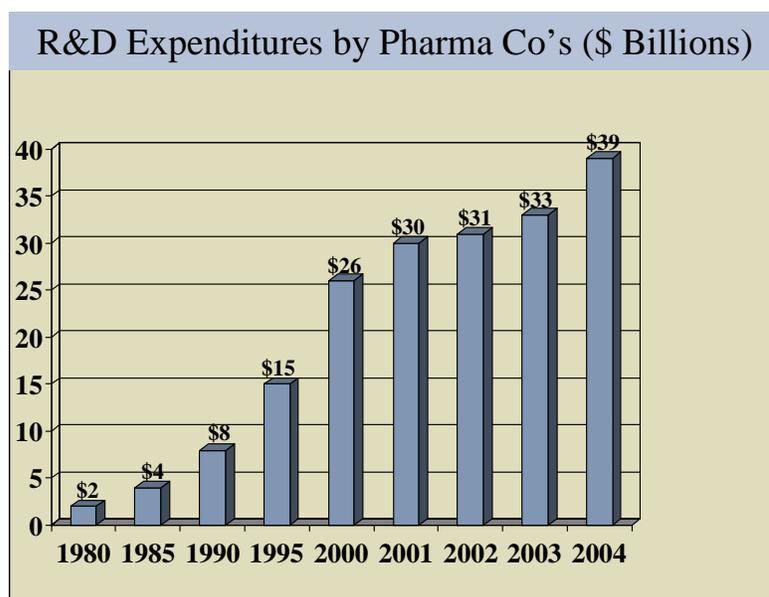
This paper will attempt to answer several related questions. First, what is pharmacogenomics? There are many articles written on the topic, but very few define it in the same way. Second, what does the pharmacogenomics model have to offer each of the key players in the healthcare system? These groups include the drug industry, payers, providers, patients, and the regulatory agencies. Third, what challenges remain for pharmacogenomics to become a viable part of our healthcare system? From research collaboration to patient education to economic incentives, there are numerous structural impediments to the new model. Finally, what companies are taking the initial steps towards realizing the promise of pharmacogenomics? Genentech and an Icelandic company called deCODE offer two examples of how this technology could alter the future of the pharmaceutical industry.

The Impetus for Change

The pharmaceutical industry has seen incredible growth since 1980. This is due primarily to the industry's strategy to focus efforts towards developing "blockbuster" drugs – those with the potential to generate over \$1 billion in sales. This strategy has become so pervasive within the industry that in the last decade, 80 percent of growth from the 10 biggest pharmaceutical companies came from blockbuster drugs.¹

However, recent trends indicate that this model may no longer ensure high growth rates for the pharmaceutical industry. One study by Bain Consulting indicates that the average cost of discovering, developing and launching a new drug in June 2004 was \$1.7 billion – a 55% increase over the average cost from 1995 to 2000.² This enormous increase is highlighted by the fact that R&D expenses have risen from only \$2 billion in 1980 to \$39 billion in 2004 [see Figure 1].³

Figure 1: R&D Expenditures, 1980-2004



Source: PhRMA Press Release, *R&D Investment by Pharmaceutical Companies Tops \$38 Billion in 2004* February 18, 2005

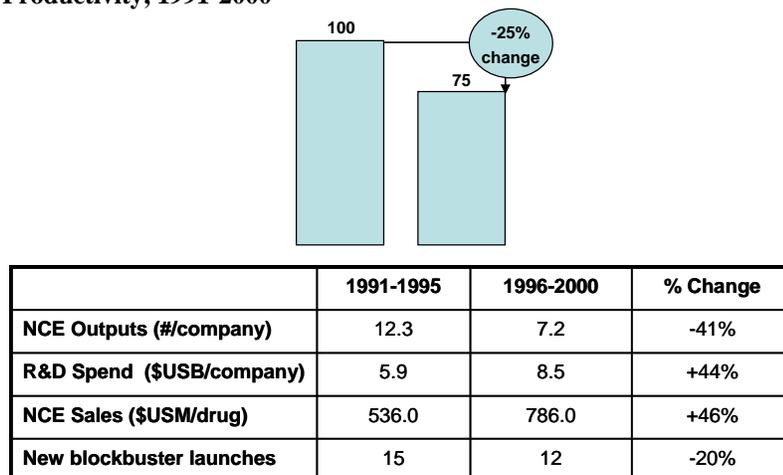
¹ Simon Frantz, *2004 approvals: the demise of the blockbuster?*, Drug Discovery, February 2005, Vol. 4, pp. 93-4.

² Ann M. Thayer, *Blockbuster Model Breaking Down*, Modern Drug Discovery, June 2004, pp. 23-4.

³ Frantz, pp. 93-4.

Surprisingly, these increases in R&D expenses have not led to a corresponding increase in the number and efficacy of new drug compounds. In fact, R&D productivity for the pharmaceutical industry has declined considerably [see Figure 2].

Figure 2: R&D Productivity, 1991-2000



- 1 R&D productivity metric, indexed to industry 1991-1995
 - 2 Total number of NCEs over 5 years for an average company in the industry
 - 3 Total R&D spend in US\$B over 5 years for an average company in the industry
 - 4 Sales for 4 years after launch for an average drug, all year 2000 dollars(millions)
 - 5 Change from 1991-95 period to 1996-2000 period
 - 6 Includes only drugs launched in that 5-year period which went on to peak sales of >\$1 billion
- Source: McKinsey analysis; PBJ Publications Pharmaprojects; FDA/CDER; Company reports; Analyst reports, IMS Health

Comparing 1995-2000 with 1991-1995, the number of New Molecular Entities (NMEs) submitted for approval dropped by nearly 50 percent, to about 40, and the number of New Chemical Entities (NCEs) produced per company declined by 41 percent. Moreover, the number of approvals for New Molecular Entities (NMEs) has steadily declined reaching a low of 17 in 2002⁴. A Data Monitor report from June 2002 indicates that there are only 18 potential blockbuster drugs worth an estimated \$24 billion in sales by 2008 currently in the pipelines of major pharmaceutical companies. Meanwhile, there is no guarantee those drugs will be effective

⁴ David Filmore et. al., *Pipeline Challenges*, Modern Drug Discovery, October 2004, pp. 28-34.

for all patients. One top geneticist at a major drug firm estimates that 90 percent of prescription drugs work on only 30 to 50 percent of the patients who take them.⁵

At the same time, according to management consulting firm A.T. Kearney, there are approximately \$30 billion worth of blockbuster drugs coming off patent between 2004 and 2007.⁶ As past evidence has shown, sales of drugs coming off patent tend to drop precipitously. Add to this the increased government and consumer pressures on drug prices coupled with increased regulatory scrutiny and it is clear that the future of the blockbuster model appears bleak. Indeed, the average compound annual growth rate for large pharmaceutical companies between 2003 and 2008 is forecasted to be 8.4 percent – a respectable number but a far cry from the historical 12-15 percent growth rates of yesteryear.⁷

As a result of all these factors many analysts believe that the current blockbuster model—the “the one drug to fit all, or nearly all” approach—will be unsustainable in the near future and that a new model is necessary for future scientific and monetary growth. Many experts believe the convergence of recent developments in genomics and molecular pharmacology will pave the way for a more personalized medicine approach where genetic data will be used to match the right drug to the right patient at the right dosage. This new utopian model of pharmacogenomics has the potential to revolutionize human health, but the challenges it poses to all players in the health care system threaten to delay or even prevent its emergence.

A Utopian Model for Personalized Medicine

Before one can truly appreciate the vision of the future, some scientific groundwork must be laid and terms defined. To begin with, any two randomly-chosen human beings will only

⁵ Bernadette Tansey, ‘*Personalized Medicine*’ Can Help Patient and Drug Firms, SF Gate, May 17, 2004.

⁶ Frantz, pp. 93-4.

⁷ Ibid.

have a 0.1% difference in their genotype; yet this small variation is enough to explain the vast differences in phenotypes between those people. Similarly, this subtle genetic difference also has a significant influence in how two different individuals might respond to the same drug.

The recent completion of the Human Genome Project has shed new light on the source of these individual genetic variations and their effects. The most common variations are the substitution of a single nucleotide for another at a given location in the genetic sequence. These are known as *single nucleotide polymorphisms (SNPs)*. Combinations of linked SNPs that travel together are known as *haplotypes* which are useful genetic markers for indicating potential drug responses of patients.

Individual polymorphisms can account for the vast differences in drug efficacy, specifically how one drug can be highly therapeutic for one individual and ineffective or even toxic to another. In general, drug responses can be linked to variations in three types of genes: (1) drug-metabolizing enzyme genes, (2) drug-action pathway genes, and (3) disease-related or disease-pathway genes.⁸ Variations in these genes lead to differences in how well an individual absorbs, metabolizes, and excretes a particular drug compound. Furthermore, variations in patient drug target cells can affect the ability of a properly-metabolized drug molecule to perform its job correctly. Recent scientific discoveries have already isolated many of the SNPs that lead to differences in drug-metabolizing enzymes, but a lot of uncertainty remains as to what polymorphisms lead to variances in patient drug target cells.

The idea that inherited differences in DNA, RNA, and protein makeup can directly influence how different individuals react to and metabolize drug compounds (a.k.a.

⁸ Michael M. Shi, Michael R. Bleavins, and Felix A. De La Iglesia, *Pharmacogenic Application in Drug Development and Clinical Trials*, Drug Metabolism and Disposition, Vol. 29, No. 4, Part 2.

“pharmacogenetics”) has been around for over half a century.⁹ Accordingly, *pharmacogenomics* is a broader concept that combines the recent advances in DNA sequencing, genotyping, and expression profiling with pharmacogenetics to provide a more rational way for drugs to be discovered, developed, and delivered.¹⁰ In scientific parlance, both terms tend to be used interchangeably. The subtle difference is that pharmacogenetics is used to identify how individuals will react to a particular therapy - “one drug across many genomes.”¹¹ This concept can be applied to existing drugs and patients to reduce Adverse Drug Reactions (ADRs). On the other hand, pharmacogenomics is more relevant to the earlier stages of drug development and its impact will be felt over the long term. With a greater understanding of individual genetic variations and their influence on the drug metabolic and activity pathways, scientists can design *new* chemical entities to optimize therapeutic effects (or “many drugs across one genome”).¹² The ultimate goal of this “new” science is to take the knowledge of an individual’s DNA sequence and use it to provide more efficacious and safer therapy. By taking drugs to which they are genetically-predisposed to respond favorably, patients will experience fewer ADRs and better results.

Pharmacogenomics can lead to the discovery of better drugs targeted at specific population sub-groups, as well as drugs that will work on all sub-groups. This involves understanding the mechanism-of-action of drugs on cells as revealed by gene expression patterns.¹³ At the developmental level, this model will improve the safety and efficacy of new

⁹ Jai Shah, *Concept and Putative Application of Pharmacogenetics and Pharmacogenomics*, Health Law Review, Spring 2004, Vol 12, p. i2.

¹⁰ Richard Weinshilboum and Liewei Wang, *Pharmacogenomics: Bench to Bedside*, Nature Reviews Drug Discovery, Sept. 2004, Vol. 3, pp. 739-47.

¹¹ Shah, p. i2.

¹² Ibid.

¹³ *Personalized Medicine Based on Pharmacogenomics, Pharmacogenetics and Pharmacoproteomic; Research and Markets announce the addition of ‘Personalized Medicine – Scientific and Commerical Aspects’ to their offering*, Oct 8, 2004.

drugs. In clinical trials, patients will be stratified according to genotype/phenotype data to ensure the drugs are tested only against patients exhibiting a particular genetic polymorphism for which the drug was designed. Patients will be protected from toxicity while allowing otherwise effective, and potentially life-saving, drugs to be approved for use in patients who are at low risk of toxicity. This will result in smaller, cheaper, faster clinical trials with much more suitable data enabling faster approval rates by regulatory agencies.

Pharmacogenomics will also prevent effective drugs from being abandoned in clinical trials because they were used on the “wrong patient.” In fact, the industry may see a wave of “Lazarus drugs” – drugs which had been previously ‘killed’ for failing clinical trials, but that are now ‘resurrected’ due to improved clinical trial designs that include the proper patient populations. Moreover, the safety and efficacy of previously-licensed drugs will increase as well. Pre-prescription genetic tests can be run to determine an individual’s tolerance and ability to respond positively to a certain drug. Genetic tests will be effective in reducing ADRs especially in new treatments and in existing treatments with narrow therapeutic indexes.¹⁴

The changes in business models and health policy that would result from the implementation of a personalized medicine standard are large and the effects and concerns vary for different players. Pharmaceutical companies would benefit from smaller, faster, and cheaper clinical trials, but would not be excited at the prospect of potentially reducing the market for their existing licensed drugs. Similarly, payers may not want to absorb the cost of conducting expensive pre-prescription testing. For their part, patients need to weigh the benefits and risks associated with revealing private genetic information in order to receive potentially better health

¹⁴ M & Lewis G. Pirmohamed, *Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality.*, Open University Press, Maidenhead, 2004, pp. 279-96.

care. There are many other benefits and concerns for these and other groups—how those are weighed will determine the extent and degree of the future application of this model.

The Challenges Ahead

For pharmacogenomics to work in practice, both additional research and structural change are critical. First, continuing studies need to be performed to determine which gene networks govern drug responses. The Human Genome Project identified over 5,000 potential drug targets to date, but only 450 have been validated.¹⁵ The ongoing International HapMap Project, a partnership of scientists and funding agencies from Canada, China, Japan, Nigeria, the United Kingdom and the United States, was created to develop a public resource that will help researchers find genes associated with human disease and response to pharmaceuticals. Second, pharmacists and physicians need to be able to properly interpret genetic data to allow for optimal prescription of drugs and dosages. Future research should yield more genotype-phenotype correlations that would make this process easier for providers. Third, patients need to be educated on the potential benefits of pharmacogenomics so they would be willing to divulge genetic information for health-related studies. As reassurance, legal protections will need to be in place in order to protect against the misuse of genetic information. Finally, economic incentives are necessary to motivate pharmaceutical and biotech companies to undertake this expensive research at the risk of potentially reducing their target markets. The most obvious incentive would be the promise of faster approval times due to unequivocal genetic data to support clinical trial data. This will benefit both the pharmaceutical companies and the regulatory agencies.

¹⁵ Ronald M. Norton, *Clinical pharmacogenetics: Applications in Pharmaceutical R&D*, Drug Discovery Today 6 (2001), p. 180.

Given the extent to which these changes will alter the existing healthcare landscape, each of the major players in the healthcare industry are likely to have reservations. The following section examines these constituencies individually and assesses the pros and cons of the pharmacogenomics model from their unique vantage point.

The Drug Industry

Given the increased costs associated with bringing new drugs to market, pharmaceutical companies are eager to explore alternative, cost effective methods of developing new products. Pharmacogenomics may be the answer to their problems, but there are many obstacles to consider before any company is willing to invest significant time and money to develop a pharmacogenomics-based model.

The most obvious dilemma faced by drug companies wishing to adopt a pharmacogenomics model is the fact that prescribing drugs according to genotype will reduce the overall market for their drugs. This represents a complete break with the existing “blockbuster” model employed by the industry. As more variations in drug response are discovered, drugs will be segmented into smaller and smaller sub-groups, reducing the current revenue stream and profits that can be re-invested in R&D, thereby compounding the drug discovery problems the industry is currently facing.¹⁶ Instead of looking for one or two “blockbusters,” drug companies will have to settle on six to ten moderately-successful drugs to compensate for the overall loss in revenue. Unless new drugs offset that reduction, pharmacogenomics-based medicine could increase market fragmentation, reduce profits, and perhaps even alter investment patterns and the scope of industry-funded research.¹⁶

¹⁶ John A. Robertson, Baruch Brody, Allen Buchanan, Jeffrey Kahn, and Elizabeth McPherson, *Pharmacogenetic Challenges for the Health Care System*, Health Affairs – Volume 21, Number 4, pp. 4-13.

However, even with a reduced total patient population for a drug, there are benefits to targeting a sub-segment of the population by genetically screening for drug efficacy. As Dr. William Evans, chairman of the pharmaceutical sciences department at St. Jude's Children's Research Hospital pointed out recently, “pharmaceutical companies may develop a drug that only 10 per cent of the market can use, but 100 per cent of that 10 per cent will use it.”¹⁷ Moreover, targeting patients more precisely could enable drug companies to get drugs to market more quickly as they continue to gain a better understanding of the genetics of drug responsiveness, thus reducing the risk and length of time required in late-stage clinical trials, by far the costliest aspect of the drug development cycle. In addition, by decreasing the total amount of time spent in clinical trials, drug companies will be able to maximize the revenue incurred under patent protection. Of course, these costs savings may be offset or reduced by the increased costs related to data collection, aggregation, and storage necessary to conduct pharmacogenomics-based clinical trials (i.e., each patient’s genetic profile must be obtained, analyzed, etc.).

By reducing ADRs to drugs, genetic screening could prove to be a powerful marketing tool for drug companies, differentiating their product from other “me too” drugs. Although the legal and ethical issues concerning direct-to-consumer marketing for drugs is currently being debated, advertising a drug’s reduced ADRs would be very powerful for reaching consumers. However, by providing drug companies with a better means of differentiating their product from competing products, pharmacogenetics could also increase the number of “me too” drugs being developed by providing drug companies with defensible, measurable benefits that a slightly-

¹⁷ Robert Sneddon, *Pharmacogenetics Workshop: Background Paper*, The Wellcome Trust, November 1999.

modified product will have on a patient sub-segment with a different genetic make-up.¹⁸

Another benefit to drug companies is the potential to reduce the size and/or costs of post-launch marketing surveillance studies. Since these post-launch trials track the long-term effects drugs have on increased patient populations, smaller trials may be needed due to the improved labeling garnered from the early pharmacogenomics-based clinical trials.

In some cases, genetic screening might increase the total amount of drugs sold. For example, if genetic screening helps physicians determine the safety and efficacy risks involved, they may be more willing to prescribe a “riskier” drug that they might otherwise not have prescribed. Physicians will also feel less constrained by liability issues with better testing to ensure safety and efficacy. In addition, with the understanding that sub-sets of patients can be targeted, if a particular sub-segment of the population has an adverse reaction during a clinical trial, the entire trial may not be scrapped if the genetic make-up of that sub-segment can be identified through testing. This will result in a more ongoing, working relationship with the FDA and other regulators as drugs are segmented to specific targets – this will enable more drugs to come to market than ever before.

There are many challenges related to pharmacogenomics that face drug companies as well. Although opportunity for “Lazarus” drugs will likely increase, it remains to be seen how viable it will be for most companies to try and “revive” drugs that previously failed clinical trials due to the enormous investment that it would require with limited long-term revenue prospects. Since intellectual property claims are filed before regulatory approval, there will likely be limited patent life remaining on the original drug, compounded by the additional time involved from further testing required before the drug would be approved.¹⁸ One solution would be for

¹⁸ Jai Shah, *Economic and regulatory considerations in pharmacogenomics for drug licensing and healthcare*, Nature Biotechnology 21 (2003), pp. 747-53.

legislation to extend patent life for drugs that are tested in this manner to create an incentive for pharma companies.

An additional challenge faced by drug companies is the difficulty in conducting clinical trials that prove that individualized drug therapy based on genetics actually improves outcomes. Clinical trials trying to prove this could be complicated by several factors: (1) multiple genes may influence patient response to the drug, (2) interaction with other drugs given simultaneously may occur, and (3) the seriousness or rate of progression of the disease as well as diet and activities such as smoking might affect treatment outcomes.¹⁹ Due to these concerns, there is little willingness to incorporate pharmacogenomics into clinical trials despite the enthusiasm researchers have for advancing biomedical technology and exploring the human genome.

Additionally, with pharmacogenomics-based drug portfolios, drug company profits may rise simply due to reduced sales and marketing expenses required. With smaller target patient populations, the ‘armies’ of sales reps that are currently infiltrating our physician’s offices may no longer be needed. The savings from cutting the sales force alone (estimated at approximately \$170,000 per sales rep), would provide a significant boost to Big Pharma’s profits.

As more data is collected on the genetics of drug responsiveness, additional opportunities in drug development will be created to meet unmet medical needs. An improved understanding of patient responsiveness could result in more efficient clinical trials, providing companies with additional years of revenue under a drug’s patent.²⁰ Some drug companies are currently gathering genotypic information from subjects involved in late-stage clinical trials to have a better understanding of the factors affecting safety and efficacy. This genotypic information

¹⁹ William E. Evans and Mary V. Relling, *Pharmacogenomics Could Replace ‘Trial-and-Error’ with Science from the Human Genome to Optimize Drug Therapy*, *Nature*, May 27, 2004.

²⁰ Phillips et al., *Potential Role of Pharmacogenomics*, p. 2276.

could also help to reduce legal liability by allowing for more detailed and accurate labeling on drugs, including drug contraindications, warnings, and precautions.¹⁶

Physicians and Health Care Providers

A key linchpin to the adoption of pharmacogenetics is physicians. As a key decision-maker in the care of patients, physician endorsement of this new model of health care is essential for it to be effective. One major hurdle to overcome with physicians involves their current lack of genetic knowledge. Today, physicians receive a minimal amount of education and training on the recent developments within the field of genetics. If genetic testing is to become more commonplace, the medical community must answer two questions concerning their patients: (1) when should a genetic screen take place, and (2) how should the results of the genetic test be interpreted? Inherent in these questions are several other considerations. For example, should a physician disregard the results of the genetic test if it provides contradictory results to other, more traditional types of tests?¹⁶

Introducing genetic screening could simultaneously increase and reduce the legal liability for providers. Physicians will be more confident in prescribing certain medications that have additional genetic data on efficacy and safety. However, if a patient has an adverse reaction to a medication and the physician prescribed the drug without first conducting a genetic screen, the physician could be found to be negligent.

In addition, if pharmacogenetics becomes part of the healthcare system, the current responsibilities of healthcare professionals could change, thus changing liabilities as well. Will people continue to go to their physicians to receive genetic testing or will their PCP refer them to a geneticist to perform and interpret the test? The change will also affect the pharmacology

business as well. Physicians might be responsible for determining if a genetic test is required, analyzing the results of the test, and prescribing the indicated drug. However, pharmacists could be responsible for determining dosage amount and drug sub-type given the results of the genetic test. This shift in responsibilities could thus increase the responsibility and liability of the pharmacist, while reducing the liability to the physician.¹⁸

Most important, however, is the challenge physicians will face incorporating genetic testing into their everyday practice of medicine. With pharmacogenomics, the typical ‘trial-and-error’ practice of dispensing medicine by physicians will be replaced with a standard procedure that includes genetic testing followed by a prescription tailored to each individual. In addition, physicians will no longer have to begin treatments using a precautionary “average dose” as they do now, since genetic testing will enable them to determine whether their patient requires a stronger or weaker dose.

Patients

Another major obstacle to the success of pharmacogenomics is gaining the ‘buy-in’ of patients themselves. One hurdle that must be overcome is the negative connotations that the field of “genetics” has with the general public. A great deal of patient education will be required before people feel comfortable undergoing genetic screening, particularly for non-life threatening diseases, where patients feel less urgency in getting the most effective medication. Some patients might choose potential side effects from a medication rather than have their genetic make-up documented. Significant effort will be needed to convince patients that genetic screening is in their best interest and that the results of the tests will be kept strictly confidential. One method to combat the negative perception by patients is to advertise the fact that many

existing practices currently employ genetic screening, such as family history of heart disease and blood type. However, it would only take one instance of a person's genetic make-up being used for discriminatory purposes to generate a major public backlash.

Even if patients are willing to undergo genetic screening, there are potential issues involved if a patient's genetic make-up causes them to be denied medication. It may be difficult for a physician to explain to a patient that the medications currently available will be ineffective for them due to their genetic make-up. Many patients would rather opt for the medication and take their chances with ADRs, thus reducing many of the cost benefits involved in genetic screening.

The fact that an individual's race and ethnicity may be linked to their genotype could also be disconcerting to some individuals. In recent years, science has made it abundantly clear that distinct differences do in fact exist between people of different race and ethnic backgrounds. For example, it has been known for many years that the ability of people to oxidize ethyl alcohol is dependent on person's genetic makeup. Individuals within the Asian population commonly have the ADH2 or ADH3 types of alcohol dehydrogenase (ADH) enzymes which convert alcohol to acetaldehyde more rapidly than normal. This increases the production and build-up of acetaldehyde in their bodies and makes many Asians who drink excessively uncomfortable and ill.²¹

Similarly, there is evidence that certain ethnic groups respond differently to medications. In fact, clinical trials underway by the pharmaceutical company, NitroMed, may soon lead to the approval of the first drug specifically for a single ethnic group. The drug, known as BiDil, is aimed at treating heart failure specifically in African-American patients. BiDil failed to achieve

²¹ R. Lorraine Collins and Lily D. McNair, *Minority Women and Alcohol Use*, Alcohol Research and Health, Winter 2002.

statistical significance many years ago when it was tested in clinical trials with a more diverse patient population, but when it was recently retested in clinical trials with only African-Americans, the results were so effective that the clinical trial was halted earlier than expected because physicians felt it would be unethical to continue giving some patients a placebo since those getting the drug were living significantly longer.²² This approach has ignited controversy on the relevance of race to medicine and may slow down the adoption of pharmacogenomics if the issue is not addressed to the satisfaction of critics.

Lastly, pharmacogenomics may actually raise the cost of individual prescriptions for patients. Although long-term healthcare costs would probably decrease for patients since their chances of taking ineffective or harmful drugs would be reduced, many patients may rebel against paying the higher prices today. However, one may argue that genetic testing would most likely be a one-time expense and well worth it at that. Once a patient (or payer) pays for a genetic test, the patient then can use these results for the rest of their life for all future diagnoses and prescriptions.

Payers

A key success factor in the adoption of pharmacogenomics is the support of the managed care industry. Similar to the many issues facing pharmaceutical companies, health insurers must consider many obstacles. The primary concern to insurers is the high costs involved in genetic screening. However, if genetic screening increases the efficacy and safety of covered drugs, the costs avoided thru misdiagnosis could more than offset the increased costs of screening.²³ If this scenario is accurate, it is likely that insurance companies will encourage physicians to use

²² Andrew Pollack, *Drug Approved for Heart Failure in Black Patients*, The New York Times, July 20, 2004.

²³ D.L. Veenstra, M.K. Higashi, and K.A. Phillips, *Assessing the Cost-Effectiveness of Pharmacogenomicism*, AAPS PharmSci, September 14, 2000, www.pharmsci.org/scientificjournals/pharmsci/journal/29.html.

genetic tests when indicated, similar to how they currently encourage doctors to prescribe generic drugs.

A major ethical issue facing insurers is whether they should be allowed to base insurance coverage on a patient's genetic-screening test.²⁴ If insurance companies attempt to institute a pre-screening requirement to determine coverage, the tests will have to be nearly 100% reliable, something will likely be extremely difficult and costly to develop for each drug. Without a reliable, consistent test, physicians may still prescribe a drug and patients may still demand it, regardless of the results of genetic screening. Health insurers will have to develop a robust set of policies and procedures to deal with these types of contingencies if genetic screening is employed.¹⁶

Pharmacogenetics could place another ethical dilemma on the payer industry with the fact that patients with a specific genotype found to have a smaller chance of appropriate therapies could be at risk of being denied future coverage. An interesting scenario could develop where a patient with a low probability of manifesting a disease but a poor predicted response to existing treatment might be denied coverage over somebody with a likely chance of manifesting the disease but a strong predictive positive response to treatment. Although this scenario makes sense from an economic perspective, it will be very difficult for the public to accept genetic screening if these types of scenarios become commonplace.¹⁸

Another ethical issue relating to potential inequalities of insuring people based on genetic makeup is whether insurance companies will be allowed to determine reimbursement based on the cost effectiveness of an individual drug vs. a group of drugs. There is potential for large price differentials in drugs affecting the same type of disease, similar to today's tiered-pricing for branded drugs vs. generic drugs. A patient could be denied coverage because they may have a

²⁴ S.L. Burton et al., *The Ethics of Pharmaceutical Benefit Management*, Health Affairs, Sep/Oct 2001, pp. 150–63.

“high maintenance” genotype - a genotype that makes the patient only respond to the most expensive drugs. It is likely insurers will have to provide the same coverage on medicines that affect a therapy group to avoid this type of discrimination.¹⁸

Regulators and Policy-Makers

The last cog in the healthcare machine is the principal regulatory body, the Food and Drug Administration (FDA). If the FDA does not embrace pharmacogenomics and provide incentives to drug companies to develop pharmacogenomics-based treatments and to run pharmacogenetics-based clinical trials, the vision will never be realized. An important decision in the regulatory process will be how the drug label conveys genotypic information about drug response (i.e., whether the need to have a pharmacogenetics test to determine whether a patient has a particular drug-response genotype should be listed as a contraindication, a warning, or a precaution to prescribing a drug.¹⁸ As mentioned above, the inclusion or exclusion of certain groups of people could raise major issues in the healthcare system, policy and in public perceptions. Accordingly, the FDA may soon have to decide whether or not to approve drugs based on race or ethnicity when clinical trials clearly show drug responsiveness is correlated to these groups.

In addition, current legislation may have to be re-written to accommodate the new pharmacogenomics model. For example, the current Orphan Drug laws provide incentives to drug companies wishing to pursue indications in patient populations of less than 200,000. With pharmacogenomics, many diseases may be subdivided into smaller patient subgroups – many of which are likely to fall below this 200,000 patient population threshold. Therefore, regulators

and policy-makers may soon have to redesign the current Orphan Drug laws to incorporate the effects pharmacogenetics will have on the treatment of patients.

The FDA also has responsibility for regulating genetic tests to ensure validity and utility. To date, researchers have been able to avoid FDA scrutiny by describing their tests as “clinical services.” Genetic testing “kits” are considered medical diagnostics, which require more testing by the FDA.¹⁶ As mentioned previously, the accuracy of these tests are critical to the acceptance of pharmacogenomics and thus, will need to be more regulated than they previously have been.

Most importantly, pharmacogenomics will place an incredible strain on existing resources of regulatory agencies due to the increase in the number of new drugs entering clinical trials, increased demand and scrutiny required to genetic tests, and the legal and ethical issues raised by pharmacogenomics. International regulatory agencies that have traditionally worked more autonomously will have to join efforts to help with the additional burden. In the near future, it is likely the UK's Medicines and Healthcare Products Regulatory Agency, the European Agency for the Evaluation of Medicinal Products, Japan's Pharmaceutical Affairs Bureau and the Food and Drug Administration will join forces, particularly around newer regulation concerning pharmacogenomics¹⁸.

Overall, incorporating pharmacogenomics into prescribing decisions represents a major change for the health care industry. Until it is clear that health insurance companies will not discriminate against patients at high genetic risk for adverse health events, physicians will be reluctant to incorporate genetic information into the medical record and patients will resist taking genetic tests. And until regulators offer incentives for developing pharmacogenetics-based medicines (faster approvals, extended patents, etc.), drug companies will not be eager to adopt this new model.

Taking the First Steps

In order to achieve the goals that pharmacogenomics promises to bring, several steps need to be taken. Patients and physicians must be educated, insurance companies must be prepared to reimburse diagnostics, regulatory bodies must assuage concerns over discrimination and other ethical dilemmas, and, most importantly, drug companies have to start reorganizing themselves to develop personalized medicines. With the risks of failure so great in being the first-mover, it is understandable that most pharmaceutical companies are hesitant to make this leap until the rest of industry adopts the model. This ‘catch-22’ situation can only be rectified if one or two drug developers are willing to bet that the interplay of diagnostics and drug design will yield across-the-board gains for patients, insurance companies, and pharmaceutical companies. With their equally innovative approaches, the two companies highlighted here offer a glimpse into the promise of pharmacogenomics.

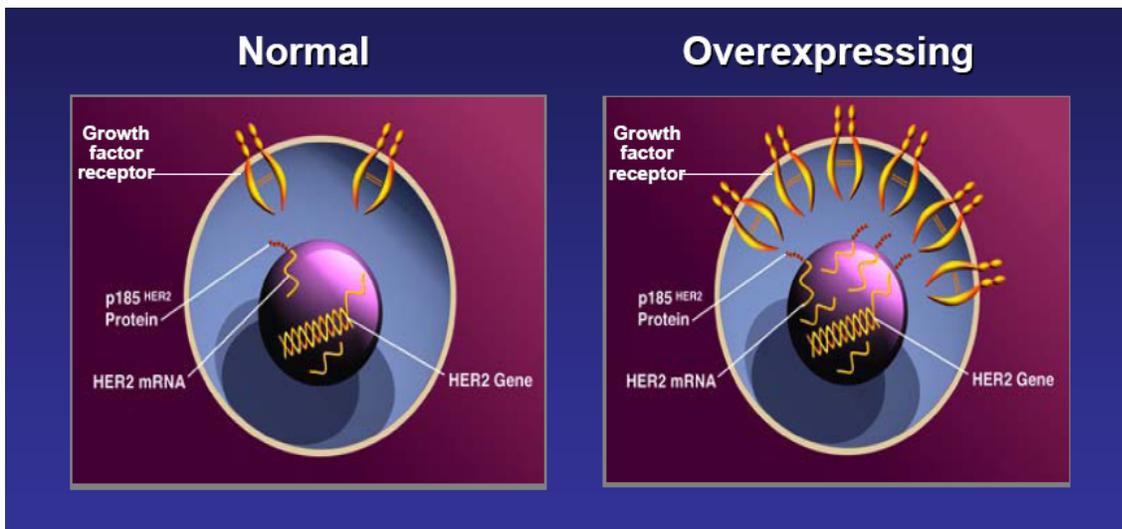
Genentech and HER-2

One of the first drugs to demonstrate the potential of diagnostics in drug design was Genentech’s breast cancer drug, Herceptin. The story behind how scientists at the South San Francisco biotech company discovered the HER-2 gene and developed a therapeutic antibody for its over-expression illustrates how testing patient populations can lead to extraordinary results.

At the most basic level, cancer begins when the DNA of a normal cell changes, or “mutates,” making normal cells grow uncontrollably. Signal transduction, the “conversation” between two cells, involves a molecular messenger (called a ligand) from the sender and a receptor protein on the surface of the cell receiving the signal. Accordingly, overexpression of this receptor protein can cause cells to divide, multiply, and grow more rapidly than normal. In

oncology, one of the most important signaling networks is a group of receptors belonging to the HER family (for “human epidural growth factor”). Overexpression of the HER-2 gene in particular is positively correlated with an aggressive form of breast cancer that occurs in approximately 25% of all breast tumors. This overexpression is the result of a genetic alteration that generates multiple copies of a gene that encodes a growth receptor. The excessive number of growth receptors enlarge the growth signals stimulating the cell, thus accelerating cell division and tumor growth [see Figure 3].

Figure 3: HER-2 Protein Overexpression



Source: Genentech

Genentech developed a therapeutic antibody called Herceptin that specifically targets and blocks the HER-2 gene, making the cancerous cells normal again. More importantly, Herceptin was the first cancer remedy that came with a reliable test to identify the women it was likely to help, the 25% whose tumors had abnormally high level of the HER-2 receptor protein. Indeed, if the breast cancer patient’s tumor is HER-2 negative, the antibody is unlikely to be effective.

The diagnostic test for HER-2 enabled Genentech to streamline the Phase III trials, using only patients who overexpressed HER-2. For example, a trial with 469 women took less than 20

months to yield a 50% increase in survival time. With patients randomly selected from the general population of breast cancer patients, this would typically have required a 10-year trial with approximately 2,200 women. Genentech was thus able to demonstrate strong survival benefits with a clinical trial that was smaller, faster, and cheaper than usual.

Despite pharmaceutical industry concerns over the profitability of more targeted therapies, Herceptin has not disappointed. The company's 2004 revenues of \$483.2 million were not equal to that of a \$1 billion blockbuster, but Herceptin represents a core component of Genentech's growing cancer franchise.²⁵ Moreover, the decrease in duration of clinical trials will afford the biotech firm a larger window of opportunity to maximize revenues while Herceptin enjoys patent protection. The knowledge Genentech gained about cancer growth pathways also aided the company in designing an experimental drug, Omnitarg, that could potentially help patients that lack excess HER-2 receptors.

Herceptin thus illustrates how companies targeting specific patient populations can profitably develop efficacious drugs, save time in clinical trials, and spur new research. Of course, the HER-2 test is not a true pharmacogenomic test, because it measures protein expression in a tumor rather than the underlying genetic makeup of the patient. That said, Genentech's approach to personalized medicine demonstrates the potential of genetic screening as a powerful tool and potential differentiator from "me too" drugs.

deCODE Genetics

An even more powerful case study in the potential of pharmacogenomics to identify new therapies is provided by deCODE Genetics. Based in its founder's native Iceland, deCODE's approach is to combine molecular biology with population genomics. The company achieved

²⁵ Genentech Press Release, January 10, 2005.

this convergence by investing heavily in a proprietary informatics system to leverage its most valuable asset—the world’s first “phenotype database,” a collection of the health records of all 280,000 Icelanders. By systematically mining this data, deCODE hopes to (1) identify the specific genes behind certain diseases, and (2) develop patient-tailored therapies and diagnostics, as well as new broadly-acting drugs, depending on how common the genes turn out to be in other populations. For example, deCODE analyzed a limited number of key markers spread out along the chromosomes of heart attack victims and used them to identify chunks of chromosomes that were more highly shared than other chunks. The results include a heart attack medication in clinical trials and a drug for peripheral artery disease nearing the end of the development pipeline.

While a barren island nestled just below the Arctic Circle might seem an unlikely place for a leading biotech company, the truth is that Iceland offers deCODE several unique advantages for its population-based medical research. To begin with, the nation has excellent medical record keeping and a high-quality, universal healthcare system. The results include a national hospital registry includes all Icelanders who had heart attacks before the age of 75 between 1981 and 2000. The Icelandic population also possesses a general openness to medical research. More than 110,000 Icelanders have given their DNA to deCODE, giving the biotech company enough data to tackle not only heart disease but 50 different ailments, including asthma, diabetes, and cancer.²⁶ deCODE also benefits from another unique Icelandic resource—an extensive collection of publicly-available genealogical records. With censuses dating back to the 1700s and ancestry charts detailing relations back to the island’s settlement by Vikings in the ninth century, deCODE can more easily identify related patients with particular diseases. Related individuals share longer stretches of DNA, so choosing clusters of such Icelanders

²⁶ Corie Lok, *Translating Iceland’s Genes into Medicine*, Technology Review, September 2004, p. 62.

allows deCODE to use only 1,000 markers to find a suspect chromosome region, making the approach much more cost effective. The same search with unrelated patients' DNA would require more than a million such markers. Finally, the entire process of isolating disease genes is made simpler by the homogenous genetics of an insular island nation.

The aforementioned heart disease example illustrates both the benefits of deCODE's drug development process and the potential of such research to produce 'Lazarus drugs.' As background, cardiologists believe that when plaques—fatty deposits in arterial walls—get inflamed, they are more likely to break away, form clots, and cause heart attacks. Icelanders with a specific variant of the chromosome-13 inflammation gene have double the normal risk of heart attack, so deCODE theorized that blocking the protein encoded by the gene might keep the plaques from getting inflamed. As luck would have it, pharmaceutical companies developed drugs to inhibit this very protein during the 1980s, believing it to be involved in asthma. deCODE was thus able to license a compound from Bayer that had already made it to the last stage of human trials before the German drug-maker shelved it due to ineffectiveness in treating asthma. Since deCODE did not have to make a new drug from scratch, it was able to save five to seven years of work.²⁷ Moreover, deCODE's information-rich clinical trial (IRCT) methodology means the Phase III trial for the prevention of heart attacks will require only a fraction of the number of participants needed for a traditional phase III trial.

Despite the enormous potential it has to develop successful diagnostic tools and drug treatments, deCODE faces several business challenges and ethical concerns. First and foremost, treating genetic risk factors is no panacea. Numerous lifestyle and environmental factors may be closely intertwined with genetic factors, limiting the efficacy of such treatments in certain patient populations. Moreover, many geneticists wonder if deCODE's research findings in Icelanders,

²⁷ Lok, p. 64.

and the drugs based on those findings, will be relevant to other populations. deCODE contends that pinpointing the protein or pathway that has malfunctioned in a particular disease is what really matters, but replicating their findings in other populations will be critical. On the moral side of the debate, there are still public concerns over the security of personal medical information in deCODE's database, particularly in light of the potential for abuse of such information. Kari Stefansson, CEO and founder of deCODE, responds to such criticism by observing that the only groups likely to abuse such data are insurance companies, and that regulation is the most appropriate response.²⁸ Finally, critics argue that deCODE's private control over Iceland's genetic data will prevent other researchers from taking advantage of an invaluable tool. Despite the fact that deCODE conceived, created, and paid for the database, many scientists in Iceland and abroad are enraged that the nation's genetic heritage should be the property of a single company. Such challenges could limit the firm's competitive advantage going forward, but it is clear that deCODE's approach holds enormous potential for the future of drug development.

Conclusion

Pharmacogenomics offers a viable alternative to the current blockbuster model of drug development within the pharmaceutical industry. By targeting specific patient populations with tailored drugs that offer greater efficacy and fewer side effects, the healthcare system could potentially address the diverse needs of its many participants. Several structural impediments stand in the way, including research shortcomings, privacy concerns, physician practices, and regulatory hurdles, but the way forward promises a more tailored approach to healthcare that draws on our individual genetic variations.

²⁸ *Population, Inc.* [interview with Kari Stefansson], *Technology Review*, April 2001, p. 55.