Using Whole Genome-Wide Genetic Information for Making Choices in Drug Therapy Use

By Ginny Taliadouros

Master's Thesis June 2010
Student #: 3076989

Supervisor: Dr. Edwin Cuppen

Abstract

It is no secret that the genomic era is upon us. Through the wealth of data generated by the Human Genome Project, in conjunction with parallel advances in genomics, proteomics, bioinformatics and biotechnology, the personal genome has become readily accessible. It is currently being applied in pharmacogenomics, which utilizes the personal genome as a means to detect biological markers associated with drug outcomes in order to direct drug therapy.

This paper addresses current applications of pharmacogenomics, including the anticipated benefits, its promise and the tools used for uncovering genetic markers and molecular diagnostics. Also, technological advances, genome-wide association studies, as well as limitations and potential ethical ramifications are further discussed.

Table of Contents

Introduction

The science fiction movie “Gattaca” (Niccol, 1997) portrays the trials and tribulations of a genetically inadequate man who seeks out his dream of going on a space mission. As one of the last naturally born humans, he lives in a world where fetuses are genetically engineered, and eliminated of any nullifications that could hinder potential future possibilities. Gattaca is set in what would be the not-too-distant future with the premise that humans are no longer discriminated by their age, sex, race or religion but instead by their genetic imperfections. A daily DNA analysis replaces identification cards and becomes the accepted norm for the employees at Gattaca allowing for constant surveillance of one’s personal genome. Although Gattaca is just a movie, it renders the idea of exposing the personal genome, allowing it to become more readily accessible and pertinent to various facets of peoples’ lives.

At present, application of the personal genome is still a relatively “new” idea. It is only within the last decade that a paradigm shift is occurring in which biomedical research is advancing to focus on applying the personal genome as a means for directing therapy (Buchanan et al., 2009). Essentially a new era in biomedical research is emerging, the genome era. By searching through massive quantities of genomic data, researchers are in pursuit for the sequences and genetic markers that will bring about new, individualized therapeutics. This has also brought with it, vast technological improvements including high throughput technologies that enable researchers to study the simultaneous expression of thousands of genes and test thousands of discrete genetic variations (i.e. single-nucleotide polymorphisms (SNPs), structural variants (SVs) and copy number variants (CNVs)) in one sample. Also, combining different research areas – genomics, proteomics and bioinformatics – delivers a global approach to research and invaluable insight into the personal genome and its applications.

Current applications of biomedical research are starting to make their way into the clinic. Medical professionals in accordance with pharmaceutical companies are beginning to change the way they approach diagnoses and treatment of patients. More specifically this is the field known as pharmacogenomics where the personal genome is examined and the results are used to direct personalized therapeutics. The most current applications of pharmacogenomics, including molecular diagnostics, technological advances, genome-wide association studies, as well as any limitations and potential ethical ramifications are further discussed.

Rise of the Personal Genome

With a world wide effort, billions of dollars and some controversy, the completion of the Human Genome Project (HGP) in 2003 (International Human Genome Sequencing, 2004) marked the beginning of a new approach towards biomedical research. In conjunction with parallel advances in bioinformatics and biotechnology, the HGP has generated a wealth of data bringing with it new perspectives in research and medicine. Systematically a large domain of important biological knowledge has been uncovered and this has opened the door into looking at whole genomes, and revealing the relationship between human genetic variation and biological outcomes such as physiology and disease. The HGP has further led to the development of a variety of human genome spin-off projects such as the Human Microbiome Project (Turnbaugh et al., 2007), the Human Variome Project (Ring et al., 2006), the Human Cytome Project (Valet and Tarnok, 2004) and the Personal Genome Project (Church, 2005). Although all these projects contribute important information to biomedical research, the latter is of particular interest as it aims to establish a database to include information on individual genomes, medical histories, along with RNA, proteomic, metabolic and MRI information from each project participant in order to make the personal genome accessible for research and to ultimately advance personalized medicine.

This personalized approach to medicine is considerably different than today's conventional modalities of therapy. Currently, most western countries do not take the personal genome into account; conventional medical practice adheres to the masses as a consequence of overall cost-benefit ratios (Leeder and Spielberg, 2009). In particular, primary focus on how medicine is directed is based on the different categories of stakeholders, which include patients/consumers, healthcare providers, pharmaceutical and biotechnology companies, and the regulating bodies. As it stands right now, application of a personalized medicine approach to healthcare is very costly (Fackler and McGuire, 2009; Leeder and Spielberg, 2009), however conventional medical approaches, i.e. "the one size fits all" approach, has its limitations and pitfalls in a variety of situations (Keyes and Bagshaw, 2008; Munshi et al., 2008; Randall and Ibbott, 2006). This is particularly true in administration of drugs to patients where the entire process relies on determining the right drug, the right dose, the right route and the right frequency of administration. For instance, one of the major problems clinicians face in administering drugs to patients is in trying to find the balance between whether or not a dose is too high or too low for the patient (Benjamin, 2003). Ideally a drug should effectively treat or prevent disease and have no adverse side effects. A meta-analysis of 39 prospective studies from hospitals in the USA conducted by Lazarou and colleagues (1998) showed that 6.7% of in-patients have serious adverse drug reactions and 0.32% have fatal reactions, the latter causing about 100,000 deaths per year in the USA. Of equal relevance is the fact that most presently approved therapies are not effective and safe in all patients and only a subset

of patients receive optimal therapeutic benefits. For example studies conducted to monitor the effects of patients taking antidepressants have been associated with only minimally positive, clinically significant results (Kirsch et al., 2008; Maier and Zobel, 2008) with a response rate of 55-75% (Karasu et al., 2000).

Cancer therapeutics is another relevant example of where conventional approaches to diagnosing and treating patients are limited. The general protocol of when a patient is diagnosed with cancer typically includes collecting biological information about the tumour itself through biopsies, blood tests and other related laboratory work, diagnosing the patient accordingly by identifying the type and at what stage the cancer is in, devising a plan of treatment (usually multimodal) that includes chemotherapy, radiotherapy and/or surgery, and subsequently monitoring and assessing the patient through the progression of treatment. The whole process is very time-consuming (a negatively related aspect to the progression of the disease) and enduring for both the patient and medical personnel. What's more, many complications are associated with disease treatment particularly with chemotherapy. Determination of the right drug or combination of drugs, the ideal dosage, efficacy of reaching its target, dealing with drug resistance and adverse side effects are all important factors to consider in directing chemotherapy. One of the major obstacles to successful chemotherapy in drug-sensitive tumours is the occurrence of resistance resulting in the impossibility of administering the proper curative doses of drugs due to the occurrence of toxicity (Gottesman, 2002; Mihich, 2000). In such instances reducing the intensity of treatment allows for the emergence of cells with the resistant phenotype. Some studies have shown that combinational drug therapy has better outcomes to single-drug therapy (Jing and Waxman, 2007; Mihich, 2000) however this approach still fails in many cases because cancer cells can exhibit simultaneous resistance toward multiple functionally unrelated drugs (Hu and Zhang, 2009). Furthermore, current modes to administer anticancer drugs do not take into account differences among individuals such as pharmacokinetics and pharmacodynamics. Cancer patients typically receive fixed doses that are "normalized" according to the patients' body surface area (Walko and McLeod, 2009). This is a very imprecise approach because of heterogeneity that exists among patients; some patients might benefit from the chemotherapy but others might experience adverse reactions exhibiting no therapeutic advantage. It is illogical for a patient to be administered a drug therapy and exhibit adverse side effects, only to realize that the drug is unsuccessful. Furthermore, applying the trial-and-error method until the "right" drug is found is inhumane. A more effective way of matching the right drug and the optimal dosage to the patient is greatly in need in order to improve clinical outcomes.

It is fair enough to say that conventional ways of medical practice are lacking and that there is a need for better, more accurate, targeted, individualized-based therapeutic approach. Through projects like the HGP and the PGP, genome-based medicine is beginning to find its way into diagnosis, disease staging and medical decision making (Mir, 2009). More specifically, the exciting and vastly emerging field of pharmacogenomics has evolved. The

tenet behind pharmacogenomics is that decoding personal genomes and combining the information with pharmacology drives the decision-making process as to what kind of drug therapies would be feasible and more applicable to patients.

The Promise of Pharmacogenomics

Pharmacogenomics studies the intersection between pharmaceuticals and genetics. The central dogma of pharmacogenomics is how an individual's genetic inheritance affects the body's response to drugs. Differences in DNA sequences that alter the expression or function of proteins that are targeted by drugs can contribute to the variation of response in individuals (Evans and Relling, 2004). Therefore the aim of pharmacogenomics is to define the genetic determinants of drug effects in order to contribute a better understanding of the interaction of drugs and the organism. Even though environmental factors, diet, age, lifestyle, and state of health all can influence a person's response to medicines, the promise of pharmacogenomics is that both the choice of a drug and its dose will be determined by the individuals' genetic make-up leading to personalized, more efficacious and less harmful drug therapy. To clinicians and researchers pharmacogenomics is powerfully attractive. Ideally personalized treatment is the holy grail of medical practice and it brings about a new era in individualized therapeutics.

There are numerous anticipated benefits of pharmacogenomics. The ability to make more powerful medicines that are created on the basis of the proteins, enzymes and RNA molecules that are associated with genes and diseases, allows drug makers to produce more targeted therapies specific to diseases which allows for a maximum therapeutic effect all while decreasing damage to healthy neighbouring cells (Novello et al., 2007). Also, analyzing the patients' genetic profile allows for doctors to prescribe the best available drug therapy for the patient from the beginning consequently eliminating the standard trial-and-error method of matching patients with the right drugs. This allows for a quicker recovery time, increased safety and ultimately eliminates any adverse side effects. This would also allow for more accuracy in determining the proper drug dosage to be administered. Instead of basing dosages on the patients' weight and age, the person's genetics will draw information on how well the body processes the medicine and how long it takes to metabolize it, thereby maximizing the therapeutic value and decreasing the likelihood of toxicity.

Pharmacogenomics can also lead to improvements in the drug discovery and approval processes. Having readily available genetic targets allows for researchers to easily pinpoint drug development in discovering potential therapies. For example, improvements in developing vaccines from genetic material, either from DNA or RNA, makes them more specialized to the individual and unable to cause infection (Poland et al., 2009). Furthermore, clinical trials can be devised as to depict specific genetic populations, which should also facilitate and shorten the drug approval process (Jain, 2002). This would also allow for

significant decreases in clinical trial costs and associated risks as those persons only genetically capable of responding to the drug are targeted. In the time it takes for a drug to be approved onto the market many costs are incurred that stem from increases in: failed drug trials, length of time patients are on medication, the number of medications patients must take in order to find an effective therapy, adverse drug reactions and the effects of a disease on the body. A quicker induction of a new drug onto the market would consequently promote the net decrease in health care costs.

Furthermore, pharmacogenomics opens the door for individuals to have readily available access to advanced screening for disease. This is beneficial as adequate lifestyle and environmental changes can be applied at an earlier stage so as to avoid or lessen the severity of a disease. Many of today's screening tests include the mammogram, PAP test, PSA test, and colonoscopy to name a few, and are applied to populations in order to detect for early onset of disease. In many instances such screens have proved to be inaccurate, as they have often lead to misdiagnosis, overdiagnosis, and created a false sense of security (Grimes and Schulz, 2002; Holden et al., 2010; Welch and Black, 2010). In addition, advanced screening can increase awareness and knowledge of any potential disease susceptibility allowing for careful monitoring and the introduction of treatment at the most appropriate stage thereby maximizing therapy. For example, one of the most readily known (and oldest) examples of advanced pharmacogenomic screening is newborn screening of the genetic disease phenylketonuria (Sahai and Marsden, 2009). Before every newborn baby leaves the hospital in the USA he or she is tested for this genetic abnormality.

Applications of Pharmacogenomics

Pharmacogenomics had its beginnings approximately 50 years ago when researchers realized that some adverse drug reactions could be caused by genetically determined variations in enzyme activity (Meyer and Zanger, 1997). For example, inherited changes in patient's ability to acetylate isoniazid, an organic compound associated with tuberculosis drug therapy, was found to be the cause of peripheral neuropathy caused by this drug. Genetic deficiencies of other drug-metabolizing enzymes such as cytochromes P450 CYP2D6, CYP2C9, CYP2C19 or methyltransferases were discovered later and it was only recently realized that drug receptors such as those of the multidrug resistance gene, MDR1, are subject to genetic variation. Adverse drug reactions in individual subjects and members of their families often were the clinical outcomes that revealed genetic variants of these drug-metabolizing enzymes or drug targets (Evans and Relling, 1999; Meyer, 2000; Meyer and Zanger, 1997; Nebert, 1997).

Tamoxifen is a modulator of the estrogen receptor (ER) and is applied in the treatment of advanced breast cancer (Osborne, 1998). Presence of ER on tumour cells determines the response to Tamoxifen; it has been found that approximately 35% of patients with ER-positive

tumours do not respond to Tamoxifen and this response is explained by drug metabolism enzyme differences present between individuals. More specifically, it is cytochrome P450 CYP2D6 that is primarily responsible for the differences observed in Tamoxifen response between patients (Desta et al., 2004). CYP2D6 is highly polymorphic and has been associated with 46 reported allelic variants, many of which result in the loss of enzyme function (Walko and McLeod, 2009). It has been found that CYP2D6*4 is the most important allele associated with the loss of enzymatic activity and it has been further researched in order to reveal the association between genotype and disease outcome for patients taking Tamoxifen. For example patients who are homozygous and heterozygous for this allele had statistically lower endoxifen (an important by-product of the CYP2D6 enzyme) levels when compared to patients who were homozygous for the wild-type alleles (Jin et al., 2005). Furthermore patients with the homozygous genotype for the variant allele were associated with a shorter time to relapse and shorter disease-free survival when compared with patients with the wild-type genotype. Knowing the presence or absence of the CYP2D6*4 allele allows clinicians to classify patients accordingly. Such genetic information is useful in determining the optimal strategy on how to administer Tamoxifen to patients so as to attain the best possible therapeutic benefit.

Warfarin therapy is another example of how genetic variation between patients determines the efficacy of the drug. Warfarin is an anticoagulant drug that is one of the most commonly used agents for the prevention and treatment of venous and arterial thromboembolism (Walko and McLeod, 2009). Known causes of individual variability observed in Warfarin therapy include a variety of genetic and non-genetic factors. The latter includes variability between patients for food and alcohol intake, hepatic and renal insufficiency as well as differences in interactions with other drugs (Holbrook et al., 2005). Genetic variations are observed with allelic differences of the drug-metabolizing enzyme CYP2C9 and clinical studies have implicated the alleles CYP2C9*2 and CYP2C9*3 as the main determinants of phenotypic differences to Warfarin therapy (Higashi et al., 2002; Takahashi and Echizen, 2001). Patients with at least one of these alleles is at higher risk of internal bleeding (one of the severe side-effects associated with Warfarin), they take longer to reach an Internal Normalized Ratio (INR) (a measurement of the extrinsic pathway of coagulation) in the therapeutic range, and they require less maintenance dosage of the drug. The drug metabolism differences observed account for approximately 17% of the differences associated with Warfarin, an additional 25% of the differences can be explained with genetic differences in the gene VKORC1 (Walko and McLeod, 2009). This gene encodes the enzyme VKORC1 that is important in Vitamin K activation, which in turn is responsible for producing various blood-clotting proteins. When Warfarin is present, this disrupts the VKORC1 gene, which results in the production of clotting factors with impaired coagulation activity often leading to internal bleeding (Rost et al., 2004). In a retrospective study of patients taking Warfarin, 10 single-nucleotide polymorphisms (SNPs) were identified in noncoding regions of the VKORC1 gene that were found to be associated in 5% of the patient population and used to describe five major haplotypes (Rieder

et al., 2005). The results allowed patients to be stratified into low-, medium- and high-dose Warfarin groups thus allowing for administration of the right dosage to each patient group and decreasing any associated adverse drug reactions. Furthermore, the genotypic information obtained from the genes that affect Warfarin metabolism, CYP2C9 and VKORC1, has contributed invaluable insight into the dose requirements and effects of Warfarin. Along with other factors such as age, weight and drug interactions, an algorithm has been created and is now applied in the clinic for correctly directing Warfarin therapy (Lenzini et al., 2007).

The above examples illustrate that genetic or allelic variations between individuals are reflective in drug therapy outcome. Thus specific genes and/or associated polymorphisms are important factors and much sought after for further determining the relationship between genetic variants and the effects of therapy.

Finding Markers for Pharmacogenomics

The anticipated benefits of pharmacogenomics reveal a promising future but specific tools are needed in order to realize the promise of pharmacogenomics. The techniques of genomics and proteomics help researchers to understand disease and to discover new drug targets. The efforts of the HGP have resulted in, among other things, the identification and mapping of hundreds of thousands of single-nucleotide polymorphisms (SNPs). About 12 million SNPs have been identified to date (Voisey and Morris, 2008) and turning these SNPs into useful markers of drug response is the goal of researchers in the field of pharmacogenomics. Ultimately researchers turn SNPs into markers of drug response that promise to dramatically alter the practice of medicine and drug development.

SNPs are common genetic variations present in DNA that are thought to account for most of the genetic variations that occur between individuals. They typically occur throughout the human genome with an average frequency of 1 SNP per 1000 base pairs (Brookes, 1999). There are two basic approaches to exploit SNPs in order to uncover markers of drug response: candidate gene studies and random whole linkage disequilibrium (LD) mapping. The candidate gene approach uses experimental approaches and *a priori* knowledge of a drug pathway, metabolism or disease pathogenesis to identify genes that may have possible relevance to drug response (Tabor et al., 2002). The SNPs identified in these genes are then applied and assessed in populations of patients exposed to the drug of interest and tested for statistical association or correlation with drug response. If these genes are found to be associated, then the “susceptible genes” are hypothesized to directly influence an individual’s likelihood of responding to the drug. The success of this approach lies in the ability to identify relevant candidate genes, and once identified further experimental procedures can be employed in order to elucidate gene characteristics and any particular markers involved in drug metabolism. This approach allows for great success in identifying common genetic determinants of disease. For example, allele comparisons of candidate genes between

individuals with the disease versus those without the disease can become good markers in positive identification of disease presence. An example of a disease gene in which SNPs have been correlated with response to therapy is the Alzheimer's disease gene, apolipoprotein E (APOE) (Kwon and Goate, 2000). Carriers of the E4 allele of the APOE gene, a risk factor for developing Alzheimer's disease, have been shown to respond differently to several cholinesterase inhibitors (Poirier et al., 1995; Richard et al., 1997) when compared to non-carriers.

An alternative to the candidate gene approach is a whole genome analysis of random SNPs using linkage disequilibrium (LD) mapping. This is a more direct approach than candidate gene studies, because the aim is to uncover a non-random association between SNPs in proximity to each other (Kwon and Goate, 2000). In other words, scanning genomes of individuals usually affected by the same disease results in SNPs being identified in similar genetic regions associated or "in linkage" with the disease. The affected individuals essentially share certain marker variants (i.e., alleles) located in those regions more frequently than would be expected by chance. These regions can then be isolated, or cloned, for further analysis and characterization of the susceptible genes.

Whole genome LD mapping and candidate gene studies are also associated with some major drawbacks. The candidate gene approach relies on current knowledge of a disease or drug response to choose which genes to examine, whereas the whole genome approach makes no assumptions as to what the underlying genes are (Kwon and Goate, 2000). The whole genome LD mapping approach, on the other hand, requires very large sample sizes and is associated with higher genotyping costs. The two methods outlined are both aimed at finding genes that account for differences in drug response and although different approaches, they are complimentary strategies that together provided the best overall strategy in identifying markers.

Genome Wide Association Studies

It is well established by now that pharmacogenomics can unlock a new area in the field of pharmacology by pinpointing genetic factors involved in drug response. Previously outlined examples have shown the role of SNPs as useful markers of drug response, however the ability of translating genetic variants into risk factors for common disease still remains elementary. Various prevalent diseases such as type I and type II diabetes, coronary heart disease, rheumatoid arthritis, Chron's disease, bipolar disorder, and hypertension, are very complex in their etiology consisting of a combination of environmental factors and a variety of genetic components. Until recently, there was little progress in finding the genetic risk factors that underlie such traits. In 2007 the Wellcome Trust Case Control Consortium (WTCCC) was the first to carry out genome wide association studies (GWAS) on seven common diseases (listed above) in order to detect genetic risk factors associated with these diseases (Wellcome

Trust Case Control, 2007). Although LD and candidate gene association studies have lead to some success in determining genetic markers (Hirschhorn and Daly, 2005), GWAS provide the newest tool for unlocking the genetic basis of common diseases.

GWAS normally require two groups of participants: those that are healthy and those with the disease in question. The genomes of all the participants are scanned for any markers, i.e. SNPs, and the information is then used to survey and detect for associations of markers of genetic variation. Some recent advances have allowed for GWAS to be carried out more precisely and on a greater scale. First, the International HapMap Project greatly facilitates both the design and analysis of association studies because it provides a database of a haplotype map (HapMap) of the human genome by documenting any previously found LD and genomic-wide-variation, along with any new SNPs derived from European, African and Asian populations (International HapMap, 2005). Second, technological advances of dense population genotyping chips now containing sets of greater than 1 million SNPs provide good coverage of the human genome, that allows GWAS for thousands of cases and controls to be conducted in one sample, in less time and more cost-effectively (Ragoussis, 2009). Third, clinical samples of common diseases are gathered and well-characterized giving useful biological information (Wellcome Trust Case Control, 2007).

The conception of GWAS has proved to be very successful in identifying genes in many common diseases. The WTCCC represented the initial and largest of GWAS for seven common diseases and was able to identify susceptibility genes for bipolar disorder, coronary heart disease, Crohn's disease, type I and type II diabetes and rheumatoid arthritis (Wellcome Trust Case Control, 2007). Other GWAS have also been published, which include among them those that have been useful in identifying genetic traits for asthma (Moffatt et al., 2007), diabetes (Diabetes Genetics Initiative of Broad Institute of et al., 2007), schizophrenia and bipolar disorder (Williams et al., 2010), obesity (Scherag et al., 2010), and cancer (Barnholtz-Sloan et al., 2010; Slattery et al., 2010). GWAS are an important discovery tool and their success has opened new horizons for exploration into genomic architecture. As more genetic variants are discovered amongst common diseases with GWAS, as this is only the beginning, further extensive follow-up to map each region, investigation of the underlying biological mechanism underpinning the association, and testing the optimal markers for assessing risk for a disease or its outcome is required.

Microarray Technology in Pharmacogenomics

Microarray analysis has also been a very useful tool in determining genetic markers in common diseases and in some instances applications for directing drug therapy is already being applied in the clinic. For instance gene expression analysis of breast cancer tumours has provided a new method for gaining insights into development of the disease in the individual patient (Fan et al., 2006; Sotiriou and Pusztai, 2009) and one of the most readily

known examples of this is the MammaPrint test. This microarray based test classifies tumours in breast cancer patients as low or high risk of reoccurrence and directs therapy accordingly (Glas et al., 2006). This test is based on a 70-gene expression signature (also known as the "Amsterdam Signature") that was developed in order to stratify patients genetically into groups that would benefit from adjuvant chemotherapy versus those that would not (van 't Veer et al., 2002). It was observed that 70-80% of patients receiving adjuvant chemotherapy for metastatic breast cancer would have survived without it. Thus the MammaPrint is beneficial in determining which patients are actually in need and will benefit from treatment, versus those who do not have to follow treatment thereby also eliminating the experience of dealing with associated adverse drug reactions.

The MammaPrint™ test developed by Agendia was the first of its kind of microarray-based prognostic and treatment outcome tests. Since its incorporation onto the market, MammaPrint™ along with four other gene expression tests for breast cancer are currently commercially available in the USA: Oncotype DX™ (a 21-gene RT-PCR assay; Genomic Health), Mammostrat™ (developed by Applied Genomics Inc. and currently offered by the Molecular Profiling Institute), the Molecular Grade Index (Aviara MGISM; AviaraDx, Inc.) and the Breast Cancer Gene Expression Ratio (as originally offered by Quest Diagnostics under license; currently offered by AviaraDx, Inc. as Aviara H/ISM). These tests outlined above do not only illustrate the discovery of genetic variations and their usefulness in related assays, but have brought with them business opportunities in molecular diagnostics and personalized medicine.

Commercialization of Pharmacogenomics

From the predominant focus on single genes and disease-related variants has emerged the technology to assay the genome in its entirety, as well as the induction of new companies enabling broad access to whole genome information. A number of 'consumer genetics' companies, mostly from the USA, already offer genotyping (such as 23andMe, Navigenics and deCODEme) and sequencing (Knome) services direct to the public. Over the last five years, more than 30 companies have begun to market genetic tests directly to consumers (Samuel et al., 2010). Companies like 23andMe offers genetic testing for disease, health and ancestry (www.23andme.com) by sequencing 500,000 SNPs across the genome. They provide, what is known as a "Personal Genome Service™" that begins with consumers purchasing a "kit" online that is then sent to them. This kit contains information about the company and the service they provide as well as a plastic tube that the consumer must fill with their saliva. Upon doing so, consumers send the DNA sample back to the company, 23andMe technicians analyze the sample, and in 6-8 weeks the consumer can have readily online access to the results. Furthermore, some companies that offer direct-to-consumer personal genome scans have recently partnered with physician groups to make their services

available to patients and their health care providers (Fackler and McGuire, 2009) as to apply acquired genetic knowledge into the personalized medicine approach.

While accessibility to molecular diagnostic companies is relatively easy, the cost of it certainly does not come cheap. Tests like the MammaPrint™ come with a price tag of 4200USD (in Europe it costs 2675EUR) while getting your genome sequenced and analyzed by companies like 23andme can run 400-500USD. Based on our limited knowledge of the genotype–phenotype relationship of complex traits in humans at this time, it is debatable whether these services offer value for money. It is no secret that personalized medicine is steadily emerging as the new healthcare paradigm, however it is still in its early stages. PricewaterhouseCoopers currently estimates the total market for personalized medicine in the USA at $232 billion and is projected to grow 11% annually, nearly doubling in size by 2015, to a total of $452 billion (http://www.pwc.com/personalizedmedicine). Furthermore, the core segment of the market – comprised primarily of diagnostic tests and targeted therapies – is estimated at $24 billion, and is expected to grow by 10% annually to $42 billion by 2015. Certainly such promising growth potential provides optimism to the current big players of the pharmaceutical and diagnostic industry (such as: Merck KGaA, GlaskoSmithKline, Pfizer, Roche, Johnson and Johnson, and Novartis) for further advances in research and development, however this also means that many new players will be attracted onto the market, which will also inevitably lead to developments of new business models.

Ethical Considerations and Limitations to Pharmacogenomics

Many greet the evolving era of pharmacogenomics and personalized medicine with optimism however this sentiment is not universally shared. Some key concerns include exposure of the personal genome and the social ramifications and privacy issues that come along with its exposure. More specifically, concerns lie with whether or not individualized medicine will be used ethically. First and foremost, as the personal genome becomes more readily accessible and available to the public, government policies should be assessed and changed accordingly in order to ensure medical privacy at all times and to avoid any misuse with the power of knowledge. Furthermore, public access to online companies such as those illustrated above, must be approached with caution. Individuals are capable of not fully understanding and misinterpreting such data. It must be stressed that genes are not the only key to cures and the individuals' environment is also a key factor. This means that all fears should not be put aside because an individual possesses a specific genetic code matching the "right" drug; variation in drug response is not limited to polymorphisms. Dietary and lifestyle behaviours are likely to still affect the safety and efficacy of medicines for particular individuals. Ultimately, diagnostic companies that directly link the information with physicians is a better approach for dealing with personal genomic data. This way the individual is better educated through the professional knowledge of the doctor rather than drawing misinformed

conclusions. This will only succeed, however, if the physicians will take advantage of new testing methods and are willing to readily apply them to their conventional methods.

Genome-wide information is technology based which also means there are associated limitations. At present there is a tremendous influx of genetic information, like that obtained through the identification and mapping of hundreds of thousands of SNPs. Right now, there is a race to catalog as many of these genetic variations found within the human genome as possible. Perhaps there is even more information available than researchers know what to do with at present and traditional gene sequencing technology is very slow and expensive and has therefore impeded the widespread use of SNPs as a diagnostic tool. Therefore development of analytical tools to deal with high volumes of data, data mining and data integration is well needed. Furthermore, with all the new information coming in there is a need for cataloguing and annotating it.

Fundamental research is important in identifying and uncovering specific biological markers in the drug discovery process. Limitations to biological knowledge contribute to limitations to pharmacogenomics. This is because there are complexities of gene regulation, of proteomics, of gene-environment interactions especially when investigating disease mechanisms. GWAS is a good tool to uncover specific biomarkers associated with common diseases, however limitations also exist here due to classification strategies and sample sizes.

One of the biggest limitations to pharmacogenomics is from the economics standpoint. Pharmaceutical companies may not see pharmacogenomics as an incentive for drug discovery because their “one size fits all” approach has made them very successful. It costs billions of dollars to bring a drug to market and a pharmacogenomics approach would mean that pharmaceutical companies would incur costs to develop a drug that would only serve a small part of the population making designer drugs too costly at first for all to benefit. Government resources as well as health care systems would also incur tremendous costs, as current pharmacogenomic strategies of implementing personalized assays are very expensive. Until technology improves as to minimize such costs, personalized medicine will be accessible to only the economically privileged. In addition, cost-effectiveness ratios of incorporating personalized medicine into conventional methods of medical practice will have to be extensively appraised for its overall benefit.

Future Perspectives

The era of individualized, efficacious treatments is almost within reach and this is because we are entering the genomic era of medicine. Pharmacogenomics and its applications in personalized medicine is the new area of biomedical research. Some remain skeptical about whether or not this is “too good to be true.” Perhaps it is just a mirage. However the beginning of this era has been marked by revolutionary changes in patient-oriented research, data processing and integration. This has been made possible through tremendous breakthroughs in genomic research such as, the Human Genome Project and mapping of SNPs nevertheless we must not forget that this is a very complex process and the final picture is still evolving.

While only limited research exists regarding the potential and feasibility of pharmacogenomics, a handful of noteworthy studies have indicated that the future of pharmacogenomics is bright. For instance, studies on Tamoxifen and Warfarin therapy as well as GWAS for uncovering genetic variants have proved exceptionally useful. Over the next several years, the numbers of SNPs found to be associated with drug responses will grow at an unprecedented rate. Sorting through the relevant SNPs and demonstrating clinical validity and utility of these SNPs as pharmacogenomic markers is a challenge that lies ahead. This goes hand-in-hand with the challenge for developing analytical tools to deal with high volumes of data as well as bridging knowledge between genomics and proteomics.

As the progress of pharmacogenomics is brought to the clinic, it becomes necessary to address increasingly complex ethical issues in patient-oriented research and in treatment design and delivery. Personalized medicine is able to deliver significant value to individuals, to industry, and to the health care system overall, and that it should continue to grow in importance. Further research can lift the barriers that impede its adoption and build incentives to encourage its practice. We are now able to obtain a plethora of information from the genome, perhaps even more that we know what to do with at the moment; good clinical practice and ethics must be at the forefront.

References

Barnholtz-Sloan, J.S., Shetty, P.B., Guan, X., Nyante, S.J., Luo, J., Brennan, D.J., and Millikan, R.C. (2010). FGFR2 and Other Loci Identified in Genome-Wide Association Studies are Associated with Breast Cancer in African American and Younger Women. Carcinogenesis.

Benjamin, D.M. (2003). Reducing medication errors and increasing patient safety: case studies in clinical pharmacology. J Clin Pharmacol *43*, 768-783.

Brookes, A.J. (1999). The essence of SNPs. Gene *234*, 177-186.

Buchanan, J.A., Carson, A.R., Chitayat, D., Malkin, D., Meyn, M.S., Ray, P.N., Shuman, C., Weksberg, R., and Scherer, S.W. (2009). The cycle of genome-directed medicine. Genome Med *1*, 16.

Church, G.M. (2005). The personal genome project. Mol Syst Biol *1*, 2005 0030.

Desta, Z., Ward, B.A., Soukhova, N.V., and Flockhart, D.A. (2004). Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. J Pharmacol Exp Ther *310*, 1062-1075.

Diabetes Genetics Initiative of Broad Institute of, H., Mit, L.U., Novartis Institutes of BioMedical, R., Saxena, R., Voight, B.F., Lyssenko, V., Burtt, N.P., de Bakker, P.I., Chen, H., Roix, J.J.*, et al.* (2007). Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science *316*, 1331-1336.

Evans, W.E., and Relling, M.V. (1999). Pharmacogenomics: translating functional genomics into rational therapeutics. Science *286*, 487-491.

Evans, W.E., and Relling, M.V. (2004). Moving towards individualized medicine with pharmacogenomics. Nature *429*, 464-468.

Fackler, J.L., and McGuire, A.L. (2009). Paving the Way to Personalized Genomic Medicine: Steps to Successful Implementation. Curr Pharmacogenomics Person Med *7*, 125-132.

Fan, C., Oh, D.S., Wessels, L., Weigelt, B., Nuyten, D.S., Nobel, A.B., van't Veer, L.J., and Perou, C.M. (2006). Concordance among gene-expression-based predictors for breast cancer. N Engl J Med *355*, 560-569.

Glas, A.M., Floore, A., Delahaye, L.J., Witteveen, A.T., Pover, R.C., Bakx, N., Lahti-Domenici, J.S., Bruinsma, T.J., Warmoes, M.O., Bernards, R.*, et al.* (2006). Converting a breast cancer microarray signature into a high-throughput diagnostic test. BMC Genomics *7*, 278.

Gottesman, M.M. (2002). Mechanisms of cancer drug resistance. Annu Rev Med *53*, 615-627.

Grimes, D.A., and Schulz, K.F. (2002). Uses and abuses of screening tests. Lancet *359*, 881-884.

Higashi, M.K., Veenstra, D.L., Kondo, L.M., Wittkowsky, A.K., Srinouanprachanh, S.L., Farin, F.M., and Rettie, A.E. (2002). Association between CYP2C9 genetic

variants and anticoagulation-related outcomes during warfarin therapy. JAMA *287*, 1690-1698.

Hirschhorn, J.N., and Daly, M.J. (2005). Genome-wide association studies for common diseases and complex traits. Nat Rev Genet *6*, 95-108.

Holbrook, A.M., Pereira, J.A., Labiris, R., McDonald, H., Douketis, J.D., Crowther, M., and Wells, P.S. (2005). Systematic overview of warfarin and its drug and food interactions. Arch Intern Med *165*, 1095-1106.

Holden, D.J., Jonas, D.E., Porterfield, D.S., Reuland, D., and Harris, R. (2010). Systematic review: enhancing the use and quality of colorectal cancer screening. Ann Intern Med *152*, 668-676.

Hu, C.M., and Zhang, L. (2009). Therapeutic nanoparticles to combat cancer drug resistance. Curr Drug Metab *10*, 836-841.

International HapMap, C. (2005). A haplotype map of the human genome. Nature *437*, 1299-1320.

International Human Genome Sequencing, C. (2004). Finishing the euchromatic sequence of the human genome. Nature *431*, 931-945.

Jain, K.K. (2002). Personalized medicine. Curr Opin Mol Ther *4*, 548-558.

Jin, Y., Desta, Z., Stearns, V., Ward, B., Ho, H., Lee, K.H., Skaar, T., Storniolo, A.M., Li, L., Araba, A.*, et al.* (2005). CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst *97*, 30-39.

Jing, Y., and Waxman, S. (2007). The design of selective and non-selective combination therapy for acute promyelocytic leukemia. Curr Top Microbiol Immunol *313*, 245-269.

Karasu, T.B., Gelenberg, A., Merriam, A., and Wang, P. (2000). American Psychiatric Association practice guideline for the treatment of patients with major depressive disorder. Am J Psychiatry *157*, 1-45.

Keyes, R., and Bagshaw, S.M. (2008). Early diagnosis of acute kidney injury in critically ill patients. Expert Rev Mol Diagn *8*, 455-464.

Kirsch, I., Deacon, B.J., Huedo-Medina, T.B., Scoboria, A., Moore, T.J., and Johnson, B.T. (2008). Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med *5*, e45.

Kwon, J.M., and Goate, A.M. (2000). The candidate gene approach. Alcohol Res Health *24*, 164-168.

Lazarou, J., Pomeranz, B.H., and Corey, P.N. (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA *279*, 1200-1205.

Leeder, J.S., and Spielberg, S.P. (2009). Personalized medicine: reality and reality checks. Ann Pharmacother *43*, 963-966.

Lenzini, P.A., Grice, G.R., Milligan, P.E., Gatchel, S.K., Deych, E., Eby, C.S., Burnett, R.S., Clohisy, J.C., Barrack, R.L., and Gage, B.F. (2007). Optimal initial dose

adjustment of warfarin in orthopedic patients. Ann Pharmacother *41*, 1798-1804.

Maier, W., and Zobel, A. (2008). Contribution of allelic variations to the phenotype of response to antidepressants and antipsychotics. Eur Arch Psychiatry Clin Neurosci *258 Suppl 1*, 12-20.

Meyer, U.A. (2000). Pharmacogenetics and adverse drug reactions. Lancet *356*, 1667-1671.

Meyer, U.A., and Zanger, U.M. (1997). Molecular mechanisms of genetic polymorphisms of drug metabolism. Annu Rev Pharmacol Toxicol *37*, 269-296.

Mihich, E. (2000). New leads in cancer therapeutics: a keynote address. Medicina (B Aires) *60 Suppl 2*, 4-8.

Mir, K.U. (2009). Sequencing genomes: from individuals to populations. Brief Funct Genomic Proteomic *8*, 367-378.

Moffatt, M.F., Kabesch, M., Liang, L., Dixon, A.L., Strachan, D., Heath, S., Depner, M., von Berg, A., Bufe, A., Rietschel, E.*, et al.* (2007). Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature *448*, 470-473.

Munshi, A., Ni, L.H., and Tiwana, M.S. (2008). Complementary and alternative medicine in present day oncology care: promises and pitfalls. Jpn J Clin Oncol *38*, 512-520.

Nebert, D.W. (1997). Polymorphisms in drug-metabolizing enzymes: what is their clinical relevance and why do they exist? Am J Hum Genet *60*, 265-271.

Niccol, A. (1997). Gattaca (USA).

Novello, S., Longo, M., and Levra, M.G. (2007). Toward therapies tailored to patient characteristics. J Thorac Oncol *2*, S38-41.

Osborne, C.K. (1998). Tamoxifen in the treatment of breast cancer. N Engl J Med *339*, 1609-1618.

Poirier, J., Delisle, M.C., Quirion, R., Aubert, I., Farlow, M., Lahiri, D., Hui, S., Bertrand, P., Nalbantoglu, J., Gilfix, B.M.*, et al.* (1995). Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer disease. Proc Natl Acad Sci U S A *92*, 12260-12264.

Poland, G.A., Ovsyannikova, I.G., and Jacobson, R.M. (2009). Application of pharmacogenomics to vaccines. Pharmacogenomics *10*, 837-852.

Ragoussis, J. (2009). Genotyping technologies for genetic research. Annu Rev Genomics Hum Genet *10*, 117-133.

Randall, M.E., and Ibbott, G.S. (2006). Intensity-modulated radiation therapy for gynecologic cancers: pitfalls, hazards, and cautions to be considered. Semin Radiat Oncol *16*, 138-143.

Richard, F., Helbecque, N., Neuman, E., Guez, D., Levy, R., and Amouyel, P. (1997). APOE genotyping and response to drug treatment in Alzheimer's disease. Lancet *349*, 539.

Rieder, M.J., Reiner, A.P., Gage, B.F., Nickerson, D.A., Eby, C.S., McLeod, H.L., Blough, D.K., Thummel, K.E., Veenstra, D.L., and Rettie, A.E. (2005). Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med *352*, 2285-2293.

Ring, H.Z., Kwok, P.Y., and Cotton, R.G. (2006). Human Variome Project: an international collaboration to catalogue human genetic variation. Pharmacogenomics *7*, 969-972.

Rost, S., Fregin, A., Ivaskevicius, V., Conzelmann, E., Hortnagel, K., Pelz, H.J., Lappegard, K., Seifried, E., Scharrer, I., Tuddenham, E.G.*, et al.* (2004). Mutations in VKORC1 cause warfarin resistance and multiple coagulation factor deficiency type 2. Nature *427*, 537-541.

Sahai, I., and Marsden, D. (2009). Newborn screening. Crit Rev Clin Lab Sci *46*, 55-82.

Samuel, G.N., Jordens, C.F., and Kerridge, I. (2010). Direct-to-consumer personal genome testing: ethical and regulatory issues that arise from wanting to 'know' your DNA. Intern Med J\ *40*, 220-224.

Scherag, A., Dina, C., Hinney, A., Vatin, V., Scherag, S., Vogel, C.I., Muller, T.D., Grallert, H., Wichmann, H.E., Balkau, B.*, et al.* (2010). Two new Loci for body-weight regulation identified in a joint analysis of genome-wide association studies for early-onset extreme obesity in French and german study groups. PLoS Genet *6*, e1000916.

Slattery, M.L., Herrick, J., Curtin, K., Samowitz, W., Wolff, R.K., Caan, B.J., Duggan, D., Potter, J.D., and Peters, U. (2010). Increased risk of colon cancer associated with a genetic polymorphism of SMAD7. Cancer Res *70*, 1479-1485.

Sotiriou, C., and Pusztai, L. (2009). Gene-expression signatures in breast cancer. N Engl J Med *360*, 790-800.

Tabor, H.K., Risch, N.J., and Myers, R.M. (2002). Candidate-gene approaches for studying complex genetic traits: practical considerations. Nat Rev Genet *3*, 391-397.

Takahashi, H., and Echizen, H. (2001). Pharmacogenetics of warfarin elimination and its clinical implications. Clin Pharmacokinet *40*, 587-603.

Turnbaugh, P.J., Ley, R.E., Hamady, M., Fraser-Liggett, C.M., Knight, R., and Gordon, J.I. (2007). The human microbiome project. Nature *449*, 804-810.

Valet, G., and Tarnok, A. (2004). Potential and challenges of a human cytome project. J Biol Regul Homeost Agents *18*, 87-91.

van 't Veer, L.J., Dai, H., van de Vijver, M.J., He, Y.D., Hart, A.A., Mao, M., Peterse, H.L., van der Kooy, K., Marton, M.J., Witteveen, A.T.*, et al.* (2002). Gene expression profiling predicts clinical outcome of breast cancer. Nature *415*, 530-536.

Voisey, J., and Morris, C.P. (2008). SNP technologies for drug discovery: a current review. Curr Drug Discov Technol *5*, 230-235.

Walko, C.M., and McLeod, H. (2009). Pharmacogenomic progress in individualized dosing of key drugs for cancer patients. Nat Clin Pract Oncol *6*, 153-162.

Welch, H.G., and Black, W.C. (2010). Overdiagnosis in cancer. J Natl Cancer Inst *102*, 605-613.

Wellcome Trust Case Control, C. (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature *447*, 661-678.

Williams, H.J., Norton, N., Dwyer, S., Moskvina, V., Nikolov, I., Carroll, L., Georgieva, L., Williams, N.M., Morris, D.W., Quinn, E.M.*, et al.* (2010). Fine mapping of ZNF804A and genome-wide significant evidence for its involvement in schizophrenia and bipolar disorder. Mol Psychiatry.