ABSTRACT

Human Biological Variation and the Application of Personalized Medicine

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Multidisciplinary advances have progressed the idea that medical therapy may be tailored to the genetics of an individual patient through personalized medicine. The concepts of race, ethnicity, and ancestry have been utilized as ways to describe human biological variation. Race is not a biological classification system but rather a cultural construct that changes through time. The study of DNA sequence, expression of RNA, proteins and their derivatives, and DNA methylation contribute to this growing field. Certain medications are prescribed in a manner tailored to human genetic variation. The anticoagulant warfarin is viewed as a case study of an application of personalized medicine. Further research into the connection between the efficacy of treatments and the ancestry of population groups is needed. This study has examined the connection between the anthropological understanding of human biological variation and the application of personalized medicine with warfarin as a specific example.

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HUMAN BIOLOGICAL VARIATION AND THE APPLICATION OF PERSONALIZED MEDICINE

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By

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TABLE OF CONTENTS

LIST OF FIGURES

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DEDICATION

This endeavor is dedicated to my family for their endless and loving support of my dreams.

Medicine is as close to love as it is to science, and its relationships matter even at the edge of life itself.

Rachel Naomi Remen

CHAPTER ONE

Introduction

An Overview of Human Biological Variation and Race

The art and practice of medicine have a long and complex history that extends from the musings of Hippocrates and ancient healers to modern evidence-based medicine and standards of care. The completion of the Human Genome Project was a major landmark in this history. The collaborative effort carried the hopes of revolutionary advancements in the understanding of disease and treatment and the potential for a paradigm shift in clinical medicine. However, scientists soon realized that the sequenced genome was not an end point. Far more complexity exists in the genetic code than could have been imagined. Though some diseases can now be linked to a definitive genetic cause, other diseases are considered complex and multifactorial. As understanding of human biological variation deepens, hopes for a practice of medicine tailored to the individual and his genome grow stronger. The ideas behind such individualized medicine, widely called personalized medicine, are based on the understanding that individuals differ from each other genetically in ways that significantly impact disease processes. Though it is generally understood that individuals vary genetically more within a given continental population than between populations, different populations may have different predispositions for certain diseases. In addition, the efficacy of medications may vary by population.

This review examines the connection between the anthropological understanding of human biological variation and the application of personalized medicine with warfarin

as a specific example. It also suggests potential implications of this connection. Before delving into applied personalized medicine, it is imperative to establish an understanding of the history of the study of human diversity and the current anthropological standings on the concepts of race, ethnicity, and ancestry. Such concepts have a history of being poorly defined or misunderstood or at times even abused. A firm grasp of the history, growth, and development of these concepts, specifically in the United States, is essential for analyzing their application in the study and clinical practice of personalized medicine.

A Brief Overview of Variation

The fossil record and observed current genetic variation provide the information anthropologists seek to interpret to explain the history of our species (Race 2005). Overall, most anthropologists support the theory that anatomically modern humans evolved in Africa and migrated throughout the world based on the fossil evidence and genetic studies (Richard G. Klein and Hublin 1989; Max Ingman et al. 2000; Underhill et al. 2000; Henrik Kaessmann et al. 1999). African populations exhibit a greater amount of genetic variation than is found in other populations of the world (Tishkoff and Verrelli 2003; Ning Yu et al. 2002; Tishkoff and Williams 2002), but overall humans exhibit less genetic diversity than many other mammalian species (Wen-Hsiung Li and Sadler 1991; Henrik Kaessmann et al. 2001). Geographic, climatic, and historical factors play into the observed genetic diversity while our relatively recent common ancestry and continual gene flow have limited our genetic variation (Race 2005). This recent, common origin and the limited observed variation are important to bear in mind when considering the validity of the concept of race (Jorde and Stephen P. Wooding 2004).

More genetic variation exists within population groups than between population groups. According to genetic data, about 10% of the total species diversity is among major geographic region or populations groups, 5% is among the local populations within these regions, and the remaining 85% is within the local populations. Craniometric variation, which is based on measurement of various dimensions of the skull, follows essentially the same pattern (Relethford 2002).

	60 STR polymorphisms	30 restriction site polymorphisms	100 *Alu* insertion polymorphisms
Between individuals, within continents	90%	87%	86%
Between continents	10%	13%	14%

Figure 1: Distribution of Genetic Variation in Old World Continental Populations
Courtesy of Nature Genetics

Though the distribution of many genetic and physical traits follows this pattern, skin color variation is a notable exception (Anthropology 1996; Keita and Kittles 1997; Relethford 2002). Instead of observing the majority of the variation within a group, only about 10% of variation occurs within a population group and the remaining 90% occurs between groups (Relethford 2002).

The variety of observed skin colors and the fact that skin color seems to correlate with latitude indicate that the trait has experienced strong selective pressure. It has been hypothesized that selection has favored darker skin color in areas at and around the equator for protection from sunburn, skin cancer, the photolysis of folate, and sweat gland damage (Sturm, Teasdale, and Box 2001; Rees 2003). The lighter skin color in higher latitudes may aid the body in forming more vitamin D, which helps predict rickets, or it may simply result from a lack of selective pressure toward darker skin (Jablonski 2004; Harding et al. 2000). Additionally, the strength of the selective pressure on skin color can result in convergent evolution, i.e. populations having similar skin colors

because they have experienced similar selective pressure instead of being closely genetically related (Race 2005).

Despite the differences among populations groups being so small for most traits, these differences can be used to funnel many people into broad, geographically based groups (Race 2005). Computer analyses of hundreds of polymorphic loci taken from samples collected from populations distributed across the globe have shown clustering that is roughly similar to groups that have occupied large continental and sub-continental regions historically (Rosenberg et al. 2002; Bamshad et al. 2003). Problematically, some have tried to argue that these findings validate typical racial categorization because the clusters correspond into the groups of sub-Saharan Africans; Europeans, western Asians, and northern Africans; eastern Asians; Polynesians and other inhabitants of Oceania; and Native Americans (Risch et al. 2002). Sampling design, or simply picking data from certain populations, and the clinal nature of human genetic variation argue strongly against the racial conclusion (Race 2005).

The Evolution of Race, Ethnicity, and Ancestry

The English word "race" may have been derived from the Spanish *raza* meaning "breed or stock." The idea of race gained a foothold during the era of European exploration (Smedley 1999). Up until this point, humans had generally only been capable of traveling small distances at any given time and most frequently travelled over land. Travellers encountered other groups of people that would certainly vary in appearance from them, but they only encountered these changes gradually due to their travelling limitations. All variation in appearance seemed incrementally different until

European maritime exploration. With the nautical revolution, explorers could go for months at sea without encountering anyone before reaching a destination in which the inhabitants would seem categorically different (Brace 2005). At this point, Europeans began to speculate about the reasons for differences in appearance and culture. Additionally, the growth of African slave trade lent incentive to the movement to categorize people into separate groups with the purpose of justifying the way in which African slaves were treated (Milton Meltzer 1971). During this societal attempt at categorization, assumptions claimed a connection between inherited physical differences and inherited intellectual, behavioral, and moral qualities (Banton 1977).

Scientists began investigating the differences between human groups in the eighteenth century (Todorov and Porter 1993). Initially, scientists simply sought to record and describe the differences they observed, as Johann Friedrich Blumenbach did in his 1775 text "The Natural Varieties of Mankind." Even so, this text established the five major divisions of humans that can still be seen in racial categorizations (Race 2005). As the science of anthropology began to develop in the next two hundred years, the search for explanations deepened and expanded into drawing novel connections (Stanton 1960). Anthropologists measured the shape and size of skulls and correlated the results to presumed differences in intelligence or other attributes (Leonard Lieberman et al. 2001).

The marriage of the science studying differences in people groups and the societal beliefs about the connection between inherited physical differences and attributes like inherited intelligence became known as the "ideology of race," and it alleged that races are "primordial, natural, enduring, and distinct" (Smedley 1999). This meant that the

races were seen not as recent developments but as having arisen at the beginning of human evolution. It also meant that different races were believed to be genetically distinct. The concept of polygenesis, or the belief that *Homo sapiens* had several distinct evolutionary origins, was in debate at this time. Ancient races could combine to form admixed groups, but even these could be broken down to their ancestral races (Race 2005). The polygenic viewpoint was promoted by Carleton Coon in his 1962 book *The Origin of Races* in which he suggested the five major races of modern humans evolved in parallel at different times and rates from *Homo erectus* even though most anthropologists were highly skeptical of the race concept by this time (Caspari 2003).

Central to the ideology of race are the interrelated concepts of essentialism, clades, and biological determinism. Carl Linnaeus put forth the foundation for the Western race ideology in 1758 in *Systemae Naturae* when he separated humans into five subgroups with specific morphology and behavioral characteristics. These characteristics were understood to be essential to the intrinsic biology of the races. The race concept also encompassed the way in which races were considered monophyletic groups, or a group that included ancestral taxon and all its descendants. Human groups were considered small separate species, and this allowed for the differences between human groups to be accounted for by independent evolution. Biological determinism established a causal relationship between biology and culture (Caspari 2003).

Even before racial ideology took root, spread, and manifested in terrible ways worldwide like eugenics, campaigns of oppression, ethnic cleansing, and genocide, the shortcomings of the concept, particularly in America, were obvious (Race 2005). Immigrants came to the New World from a variety of locations in the Old World, and

these groups began to mix among each other and among indigenous populations. This mixing has led to surprising amounts of genetic admixture in populations, of which individuals are frequently unaware (Race 2005). For example, in the United States many people who identify themselves as African American have some European ancestry—one genetic marker that varies by continent indicates up to 23% (Parra et al. 1998). Attempts to classify the mixed American population into discrete categories have been problematic because the racial identity of a person can change over time and the race with which a person identifies can be different from the race that person would be assigned by administrators or practitioners in the health care field (Spickard 1992; Kressin et al. 2003). Latinos took issue with the way in which they were required to report their race on the United States census before 2000 because they could only identify one race despite the history of mixing in Latin and Central America. Consequently in the 2000 census, 42% of Latino respondents simply indicated "some other race" instead of identifying with one of the provided categories (Mays et al. 2003).

As the negative connotation of the word "race" grew during the twentieth century, "ethnicity" was asserted as a better way to describe different groups of people (Huxley, Haddon, and Carr-Saunders 1936; Hutchinson and Anthony D. Smith 1996). Instead of focusing on the genetic makeup of an individual, the concept of ethnicity seeks to encompass more. The idea of ethnicity attempts to include a person's cultural, socioeconomic, religious, and political qualities. Ethnicity can describe everything from language to diet, to customs, to territorial identity (Cornell and Hartmann 2006).

Unfortunately, the concept of ethnicity has drawbacks as well. Using a single descriptor or ethnic category for a group of people may imply more uniformity than

actually exists within the group. For example, Americans who trace their relatives or ancestors to anywhere in South or Central America are collectively referred to as Hispanic or Latino. A large amount of variation exists within this massive grouping of people (Hayes-Bautista and Chapa 1987). Just as with race, ethnicity is a flexible concept that is influenced by historical and social context (Waters 1990; Smelser, Wilson, and Mitchell 2001). Ethnic identification may change over the course of an individual's lifetime, and a government official, clinician, or researcher may assign an ethnicity to an individual that is different from the one that person would choose (Kressin et al. 2003). Despite the attempts to distinguish "race" and "ethnicity," the two terms are problematically still used interchangeably (Oppenheimer 2001). Though the idea of ethnicity is less focused on biology, like racial groups, ethnic groups may believe they share common ancestors (Cornell and Hartmann 2006). Marriage within ethnic groups can maintain a degree of relatedness whether or not it existed ancestrally (Race 2005).

Ancestry is the concept that has arisen in an attempt to categorize humans as an alternative to race or ethnicity. Ancestry can be defined geographically (e.g. Asian), geopolitically (e.g. Norwegian), or culturally (e.g. Apache). Ancestry can be assigned to a person by an observer, like a physician or government worker, it can be chosen by the individual, or it can be calculated from genetic data using loci with allele frequencies that vary geographically (Race 2005). In biomedical research, a person's self-identified ancestry usually agrees with the genetic estimates (Tang et al. 2005). The definition of ancestry attempts to be more objective, but still has limitations (Elliott and Brodwin 2002). A survey in Georgia noted that 40% of approximately 100 respondents did not know how one or more of their grandparents would identify himself or herself ancestrally

(Condit et al. 2003). Race, ethnicity, and ancestry are attempts to describe the complexity of human groups on a biological and social level (Race 2005).

The Efficacy of Population Classifications

Despite the social issues surrounding human classification described thus far, individuals may be separated into population groups based on genetic information with accuracy (Jorde and Stephen P. Wooding 2004). Recall that only about 10% of variation occurs within a population group and the remaining 90% occurs between the major continental groups of Africa, Asia, and Europe, regardless of the autosomal loci examined (Relethford 2002; Jorde and Stephen P. Wooding 2004). Despite this fact, racial categories continue to be used in a variety of contexts, including forensic databases, medical research, and clinical practice (Jorde and Stephen P. Wooding 2004). Biomedical scientists are divided in their opinions on race. Some view it as a scientifically invalid concept while others believe it to be a useful concept in clinical decision making and research design (Haga and Venter 2003; Risch et al. 2002; Esteban González Burchard et al. 2003; Wood 2001).

Despite differences in appearance, culture, and behavior, humans are on average quite similar genetically, especially compared to other mammals. The average nucleotide diversity, or proportion of nucleotide differences between two randomly selected humans, is estimated to be between 1 in 1,000 and 1 in 1,500 (Fischer et al. 2004; Wen-Hsiung Li and Sadler 1991). The human genome contains approximately three billion nucleotide base pairs, so any two random humans differ from each other by on average approximately two or three million base pairs (Jorde and Stephen P. Wooding 2004).

Comparisons of populations are open to criticism because putting individuals into groups in order to study them can superimpose a structure that influences the outcome of a genetic study. As already described, populations can also be defined in a variety of often-arbitrary ways. Comparing individuals instead of comparing populations is a method to avoid these issues. Individuals may be compared by analyzing the genetic similarity between all possible couplings of the individuals in a study then looking for the clusters of most similar individuals (Jorde and Stephen P. Wooding 2004). Studies based on a robust amount of loci demonstrate that individuals tend to cluster according to ancestry or geographic origin (Bamshad et al. 2003; Rosenberg et al. 2002; Shriver et al. 2004). Even a more statistically sophisticated method known as the structure program provides similar results (Pritchard, Stephens, and Donnelly 2000). Evaluating more loci provides more accurate and detailed classification results, adding strength to the method of evaluating individuals (Edwards 2003).

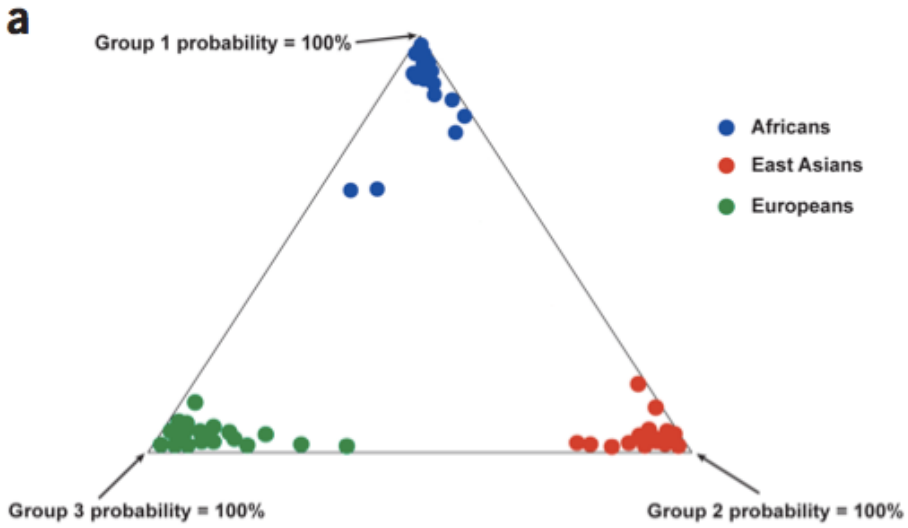

Figure 2: Clusters Determined by the Structure Program
Courtesy of Nature Genetics

In light of the possibility of accurately group individuals based on genetic markers into groups, e.g. European, sub-Saharan African, and East Asian, it may be tempting to

use the results of genetic studies to validate traditional ideas about race discussed in the section about the ideology of race. When a group of South Indians is added to the study, the results become more muddled. South Indian individuals overlap with both East Asian and European groupings and do not fit into a typical racial category (Jorde and Stephen P. Wooding 2004).

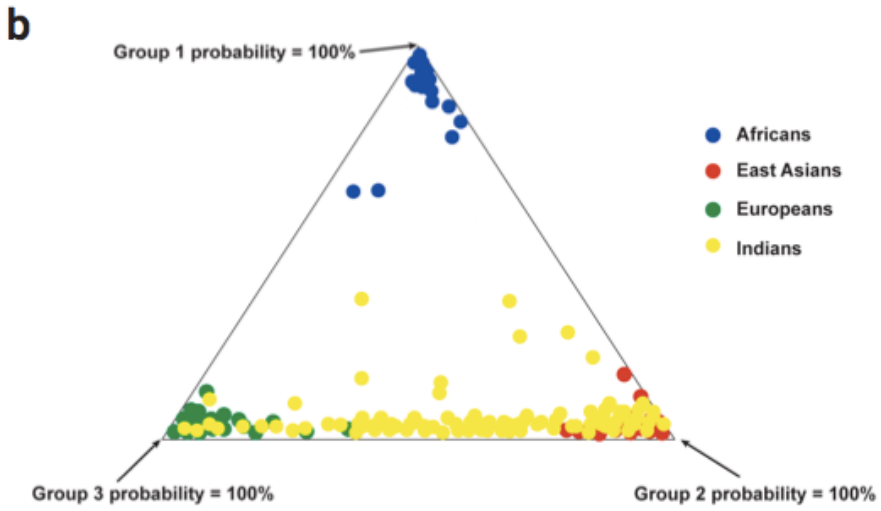

Figure 3: Problematized Clusters Determined by the Structure Program
Courtesy of Nature Genetics

Further analysis of results of the classifications involving posterior probabilities reveals that individuals share most but not all of their ancestry with other members of the cluster (Bamshad et al. 2003). Again, the results of genetic studies demonstrate that individuals cannot be divided into stark, clearly delineated categories. Ancestry is a more subtle reflection of the complexity of an individual's genetic history than race. The migrating and mixing of human groups throughout human history makes for a storied genetic history. Mixing contributes to the way in which variation is generally distributed in a continuous manner instead of within distinct groupings. The importance of evaluating many different loci in an attempt to even approximate ancestry cannot be understated. Failing to use a sufficiently robust number of loci can produce misleading

results. No group can ever truly be considered pure, and all groupings are to some degree inaccurate and arbitrary (Jorde and Stephen P. Wooding 2004). Charles Darwin's words ring true today, as he says "It may be doubted whether any character can be named which is distinctive of a race and is constant" (Darwin 1871).

CHAPTER TWO

Methods and Materials

Ways in Which to Study Variation

The primary field that addresses personalized medicine is pharmacogenomics, which is described by the *Report of the Secretary's Advisory Committee on Genetics, Health, and Society* as the way in which genetic differences influence responses to drugs (Teutsch et al. 2008). This field, also widely referred to by its abbreviation PGx, arises from the intersection of pharmacology, genetics, and human genomics. Providing clinicians with meaningful, applicable, and appropriate tools is the long-term goal of developments in pharmacogenomics. These tools would allow the clinician to assess risks and benefits associated with medications and to select treatments tailored to the genetics of individual patients. Two important aspects of personalized medicine are the desire to avoid adverse drug reactions and the desire to increase the safety and efficacy of drug treatments. Personalized medicine carries the potential to shift the focus in pharmaceutical development, basic research, and clinical practice. Multidisciplinary advances have provided the research foundation for personalized medicine. These fields include genomics, transcriptomics, proteomics, metabolomics, and epigenomics, and the combination of them all—systems biology. Aims of these fields include quantifying the differences between individuals on the molecular level and applying these differences to understanding disease states and drug reactions (Isaac S. Chan and Ginsburg 2011). The

possibility for applied personalized medicine rests on the knowledge acquired from these specific but interrelated methods of studying human biological variation.

Genomics

Recently, the focus in human variation is on the study of DNA sequences and changes that may occur. Variation in the human genome arises from several types of mutations including point mutations, in which the sequence of the bases changes at one specific point, and structural rearrangements, in which larger chunks of DNA move or are deleted (Feero et al. 2010; Redon et al. 2006). Point mutations are also known as single-nucleotide polymorphisms, or SNPs. The majority of what scientists and anthropologists currently know about human biological variation is derived from study of the sequence of DNA (Isaac S. Chan and Ginsburg 2011).

The first person to receive his fully sequenced genome was James Watson, Ph.D., co-discoverer of the helical structure of DNA, on May 31, 2007 at Baylor College of Medicine in Houston, Texas. The landmark 13-year-long, $2.7 billion International Human Genome Project paved the way for this accomplishment. The sequencing of Dr. Watson's genome required only 2 months and $1 million (SoRelle 2007). As of 2010, an individual's genome could be sequenced for $10,000. It is hoped that a person's genome will be able to be sequenced for approximately $1000 in the coming years so that the price of sequencing will be comparable in price to existing medical tests. An outstanding monetary prize is available to the innovator who can accomplish this (Bonetta 2010; Bentley 2006; Robert 2006). Sequencing technology has advanced to be more efficient and more accurate than it was when the first human genome was sequenced in the Human Genome Project. The next-generation method was used to sequence Dr. Watson's

genome (Samuel Levy et al. 2007; Pushkarev, Neff, and Quake 2009; Jun Wang et al. 2008; Wheeler et al. 2008).

As another way to study genetic variation, data from the International HapMap Project, completed in 2005, provide a haplotype map of the human genome (Isaac S. Chan and Ginsburg 2011). A haplotype may be described as a combination of alleles for different genes that are located near each other on the same chromosome. These combinations tend to be inherited together. Due to the genetic phenomenon, the presence of a single SNP may provide information about the presence of other SNPs. This characteristic is known as linkage disequilibrium (Kenneth M. Weiss and Andrew G. Clark 2002). The haplotype map was developed to detect regions with larger amounts of linkage disequilibrium and smaller amounts of haplotype diversity. The haplotype map can be a powerful tool for disease gene mapping, and the data have formed the basis for genome-wide association studies (Isaac S. Chan and Ginsburg 2011; Gabriel et al. 2002).

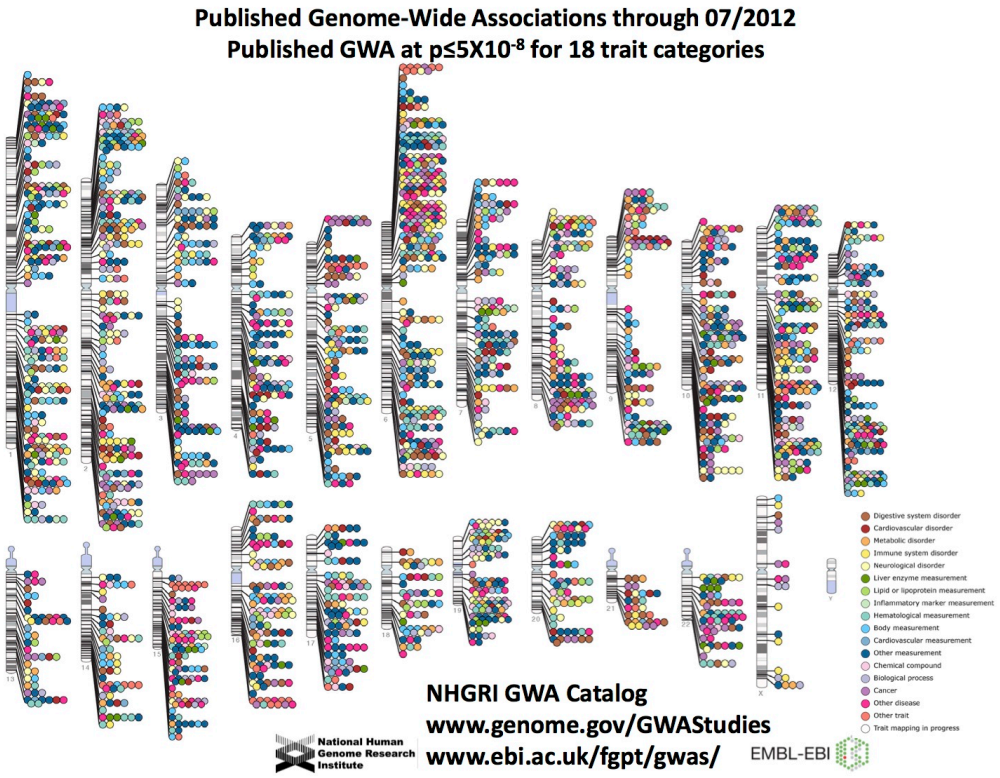

Figure 4: The National Human Genome Research Institute Genome-Wide Association Catalog
Courtesy of the National Human Genome Research Institute

Genome-wide association studies (GWASs), which can produce results like those pictured in Figure 1, compare SNPs between disease populations and control populations. GWASs are a way to further the study of genetic variation in the direction of understanding the genetics of disease. As demonstrated by Figure 1, hundreds of GWASs have been published and compiled on over 150 human diseases and traits. Studies are compiled on the project's website, and findings are freely available to the public. These studies have reported over 2,400 SNPs with statistically significant associations and odds ratios (Isaac S. Chan and Ginsburg 2011; Hindorff et al. 2011; Andrew D. Johnson and Christopher J. O'Donnell 2009). Such studies have found at least thirty variants that contribute to Crohn's disease, an autoimmune disorder characterized by inflammation of the intestines. A GWAS helped identify specific variants at NOD2 and IL23R as being associated with an increase in disease risk (Barrett

et al. 2008). At least twenty variants have been identified for type 2 diabetes (Feero, Guttmacher, and Mark I. McCarthy 2010; Sladek et al. 2007). More than 100 variants have been identified that may be associated with coronary artery disease risk. Several studies have independently noted the importance of the 9p21.2 locus (Helgadottir et al. 2007; J. J. McCarthy et al. 2004; McPherson et al. 2007; Samani et al. 2007). The connection between coronary artery disease and the genes at this location is not fully understood, but the gene is thought to have some influence on inflammatory response (Isaac S. Chan and Ginsburg 2011). Identifying specific variants that contribute to disease could lead to more specific and hopefully more effective treatment. The success of the use of GWAS data has been demonstrated in treatments for age-related macular degeneration (Isaac S. Chan and Ginsburg 2011). Targeted therapeutics were developed for the complement-mediated inflammatory pathways identified in GWASs (Yuxiang Huang et al. 2008; Robert J. Klein et al. 2005).

The odd ratios of alleles associated with disease phenotype determined by GWAS are not usually very strong. Frequently, the odds ratio associated with disease phenotype are less than 2, meaning they may not make a significant contribution to disease risk (Isaac S. Chan and Ginsburg 2011). One example of a more significant connection is a polymorphism discovered by GWAS on chromosome 19, 3kb upstream of IL-28B. This gene encodes interferon-lambda-*3* and was found to have a twofold effect on treatment response for hepatitis C (Ge et al. 2009). A second study analyzed the genotypes of patients being treated for hepatitis C and found the same variation is a predictor of sustained virologic response in patients with hepatitis C (OR 5.2; 95% CI 4.1-6.7) (Thompson et al. 2010). Also, a GWAS located a polymorphism on *SLCO1B1* that

regulates hepatic uptake of statins was associated with an increased risk of myopathy after a patient was treated with statins (OR 4.5; 95% CI 2.6-7.7) (Link et al. 2008). GWASs have not yet provided a vast amount of clinical implications, but they have provided contributions demonstrating the role of new genes in pathogenesis, or the mechanism that causes disease. Deeper understanding of the mechanisms of disease may still lead to new therapies or refinements of current therapies, as is described in the case of warfarin in the following chapter (Isaac S. Chan and Ginsburg 2011).

Transcriptomics

Transcriptomics approaches the analysis of biological variation by studying RNA expression, from messenger RNA to noncoding RNA, in a cell, tissue, or biological fluid (Isaac S. Chan and Ginsburg 2011). Analysis of RNA and investigation of genes that are expressed at the same time can aid in understanding current disease or predict future disease (R. Simon 2003). Microarray data have been used to assist in diagnosis, estimate prognosis, and evaluate response to treatment in breast cancer and lymphoma patients (Joel S. Parker et al. 2009; Rosenwald et al. 2002). RNA analysis led to the discovery of distinct molecular subclasses in cancers like breast cancer, lung cancer, blood-based lymphomas, and melanoma. Treatment can be tailored to a patient's specific microarray type (Alizadeh et al. 2000; Bhattacharjee et al. 2001; Bittner et al. 2000; Van't Veer et al. 2002). Microarray technology has also been applied to complex diseases like cardiovascular disease, rheumatic disease, neurologic disease (multiple sclerosis), and psychiatric disorders (schizophrenia, biopolar disorder, and major depression) (Bray

2008; Comabella and Martin 2007; Goes, Sanders, and Potash 2008; Kittleson and Hare 2005; Divya Mehta, Menke, and Binder 2010; Van Baarsen et al. 2009).

Particular attention is now being given to the expression patterns of noncoding RNA like small interfering RNA (siRNA) and microRNA (miRNA) (Isaac S. Chan and Ginsburg 2011). Coding RNA like messenger RNA (mRNA) goes on to be translated into proteins, but noncoding RNA serves different purposes. Usually only twenty-two nucleotides in length, miRNA form a complex that silences post-transcription expression by binding to untranslated target regions of mRNA (Bartel 2004; Rosalind C. Lee, Feinbaum, and Ambros 1993). Studies indicate microRNA sequences may influence the regulation of proliferating cancers, development of cardiomyopathies, immune response, schizophrenia, and hepatitis C viral replication (Jinong Feng et al. 2009; Iorio and Croce 2009; Jopling et al. 2005; Kathryn A. O'Donnell et al. 2005; Antony Rodriguez et al. 2007; Tatsuguchi et al. 2007). It is hypothesized that variably expressed miRNAs could have clinical application in diagnosis and prognosis of disease (Budhu, Junfang Ji, and Xin Wang 2010; Calin and Croce 2006; Kartha and Subramanian 2010). Because they have an interesting role in gene regulation, miRNA targets and miRNAs are being tested for therapeutic efficacy. Restoration of deficient miRNA demonstrated the possibility for therapeutic use in gastric cancer (Qing Ji et al. 2008). The therapeutic use of siRNAs via targeted nanoparticle delivery is showing promising results in refractory solid tumor treatment (Mark E. Davis et al. 2010). A potential issue with the use of miRNAs is lack of specificity. Instead of acting as the targeted treatment desired, miRNAs can also lead to unintended side effects in the inhibition of other genes. Their small size allows them

to affect many different mRNA sequences (Lewis et al. 2003; Thomas, Judy Lieberman, and Lal 2010).

Just as the sequencing of the human genome is providing information about underlying biology and pathology, sequencing of the transcriptome will add to the understanding of the complexity of DNA expression. Because DNA contains large noncoding regions, examining the transcriptome could be a more targeted study technique. Technologies like RNA sequencing (RNA-Seq) are being used to analyze whole human transcriptomes and increase the understanding of transcription regulation (Core, Waterfall, and Lis 2008; Yiping He et al. 2008; Pan et al. 2008; Sugarbaker et al. 2008; Sultan et al. 2008). System-wide understanding will hopefully lead to applications in the understanding of disease as RNA-Seq has been used to investigate gene fusion and translocation in melanoma, breast, prostrate, and gastric cancers (Guffanti et al. 2009; Maher et al. 2009; Palanisamy et al. 2010; Zhao et al. 2009).

Proteomics, Metabolomics, Epigenomics, and Systems Biology

The large-scale study of all proteins and their various derivatives produced by cells defines the study of proteomics. In relation to healthcare, scientists try to identify all the proteins and protein derivatives associated with a disease state. This search continues to be an important area for biomarker discovery and molecular research (Isaac S. Chan and Ginsburg 2011). Historically, stable isotope markers have been the dominant method of research, but label-free methods are becoming more prevalent. Label-free methods involve measuring the concentration of a peptide and comparing it to the concentration of the peptide in other samples. Higher throughput and fewer required manipulations of the sample make this an advantageous advancement (Du et al. 2008;

Issaq and Timothy D. Veenstra 2008). Simpler, less time-intensive tests should enable unprecedented growth in this field, which is currently relatively immature in application to human health (Isaac S. Chan and Ginsburg 2011).

Metabolomics measures changes in the approximately 5000 nonprotein small molecule metabolites. Mass spectroscopy and nuclear magnetic resonance spectroscopy measure changes in the nonprotein molecules related to a biological or physiological state. Enzymatic drug targets can be immediately suggested by the identification of a metabolic change. The potential for applications of this approach is seen in particularly challenging chronic diseases like diabetes, obesity, cardiovascular disease, cancer, and mental disorders (Bain et al. 2009; Griffin and Shockcor 2004; Kaddurah-Daouk et al. 2007; Newgard et al. 2009). Metabolite profiles have been established for ischemia and coronary artery disease (Sabatine et al. 2005; Shah et al. 2009). Metabolomics can also be used to directly assess drug toxicity which could be useful in relation to the goal of finding better ways to make drug treatments safer (Ebbels et al. 2007; Keun 2006; Nicholson et al. 2002).

The field of epigenomics is concerned with the consequences of DNA methylation, a method of control of DNA expression (Sharma, Kelly, and Peter A. Jones 2010). Methylation, or the addition of a methyl group, usually prevents the active transcription of DNA, and heavily methylated genes are referred to as silenced genes. Only the base cytosine can be methylated (Bird 1986; Prendergast and Ziff 1991). Some tumors demonstrate hypomethylation, a low level of methylation, of oncogenes and hypermethylation, a high level of methylation, of tumor suppressing genes (Archey et al. 2002; Feinberg and Vogelstein 1983; Rosty et al. 2002). Altered methylation states have

been demonstrated in chronic diseases like type 2 diabetes, cardiovascular disease, and autoimmune diseases like systemic lupus erythematosus (Corwin 2004; Devaskar and Thamotharan 2007; Januchowski, Prokop, and Jagodzinski 2004; Lu et al. 2002). The Human Epigenome Project, an international private and public collaboration, is currently underway and aims to identify and assess DNA methylation patterns of all human genes in the major tissues (Bernstein, Meissner, and Lander 2007; Peter A. Jones et al. 2008; Eckhardt et al. 2006).

Systems biology combines genomics, transcriptomics, proteomics, metabolomics, and epigenomics in an attempt to study the biological system as a whole. Systems biology addresses the study of humans in such a way as to appreciate the integration of genetics and its dynamic operation (Ginsburg and Willard 2008). Inextricably related and integrated chemical and biological processes determine health and disease. Each system can be analyzed individually, but no system acts independently *in vivo* (Isaac S. Chan and Ginsburg 2011). Analysis of blood or tissue can provide integrated information about disease state and the potential for developing therapeutic targets (Gonzalez-Angulo, Hennessy, and Mills 2010; Roukos 2010; Kai Wang et al. 2010).

The search for understanding of human variation and human disease has many tools, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics, and systems biology. Genomics has the most storied history and the most current applications, but each field holds the potential for novel breakthroughs in the understanding of underlying biology, etiology of disease, and the development of new treatments. Discoveries from these research fields play into pharmaceutical development that aims to become increasingly individualized, safer, and more effective.

CHAPTER THREE

Results

Warfarin as a Current Clinical Application

As a result of the research into underlying genetic variation, successful current applications of personalized medicine are approved and in use. The anticoagulant warfarin may be viewed as a case study for the development of a personalized therapy. Key genetic variations in the CYP2C9 and VKORC1 genes factor into warfarin metabolism and dosing, and some of the genetic variation differs by ancestry.

Warfarin is a coumarin-based anticoagulant prescribed for more than one million patients annually who are at risk for dangerous blood clots. It functions as a vitamin K antagonist (Higashi et al. 2002; Mark J. Rieder et al. 2005). Approved by the FDA over sixty years ago, warfarin is the most widely used oral anticoagulant with 25 million users (Raul Altman and Vidal 2011; Cabral, J. Ansell, and E. M. Hylek 2011; Nita A. Limdi 2012; Schirmer et al. 2010; Tzeis and Andrikopoulos 2012; Ann K. Wittkowsky 2011). Proper dosing is influenced by complex factors like age, diet, and underlying conditions, but proper dosage is important to avoid serious complications (Teutsch et al. 2008). Patients taking warfarin require first a stabilization dose to initiate treatment then a different maintenance dose to continue treatment to prevent blood clots (Mark J. Rieder et al. 2005).

The goal of treatment is to establish anticoagulation within the target International Normalized Ratio range of 2.0-3.0, but the dosage required to meet this goal may vary up

to twenty-fold between patients (Nita A. Limdi 2012). Appropriate dosing is vital because a therapeutic level must be established without causing under-anticoagulation leading to risk of thrombosis or over-anticoagulation leading to risk of dangerous hemorrhaging (Elaine M. Hylek and Rose 2009; Elaine M. Hylek and Singer 1994; Elaine M. Hylek et al. 1996; Elaine M. Hylek et al. 2000; Webinar, Roundtable, and Part 2004; Ann K. Wittkowsky 2011). The risk for hemorrhage is especially notable when treatment is first initiated and also when INR exceeds 4.0 (Nita A. Limdi 2012). Bleeding complications may occur at a rate around 8 per 100 patient years (Palareti et al. 1996). In the United States, warfarin accounted for 33% of drug-related hospitalizations for adverse events between 2007 and 2009 (Budnitz et al. 2011). Increased focus on the known genetic variation that influences warfarin metabolism may help avert the risk of hemorrhage for some patients.

CYP2C9 Variation

Specific genetic mutations are known to affect the way the body processes warfarin. The CYP2C9 gene encodes cytochrome P-450 enzyme 2C9 which is the main enzyme involved in warfarin metabolism. SNP variants of this gene can influence the ability of a patient's body to remove the drug from his system (Nita A. Limdi 2012; Mark J. Rieder et al. 2005). The wild-type, or CYP2C9*1, is most common. A number of studies have demonstrated that two common variants reduce the body's metabolism of warfarin. The variant CYP2C9*2 reduces the body's metabolism of warfarin by 30% to 50%, and the variant CYP2C9*3 reduces it by around 90% (Craig R. Lee, Joyce A. Goldstein, and Pieper 2002; Daly and King 2003). A study indicated that mean doses of

5.6, 3.9 and 2.9 mg/day were reported in Caucasians with the CYP2C9*1/*1, *1/*2 and *1/*3 genotypes respectively (Scordo et al. 2002). Overall, patients with CYP2C9*2 and CYP2C9*3 variants may require significantly lower maintenance doses of warfarin, take a greater amount of time to achieve dose stabilization, and experience increased risk for serious and life-threatening bleeding than patients without these variants (Higashi et al. 2002).

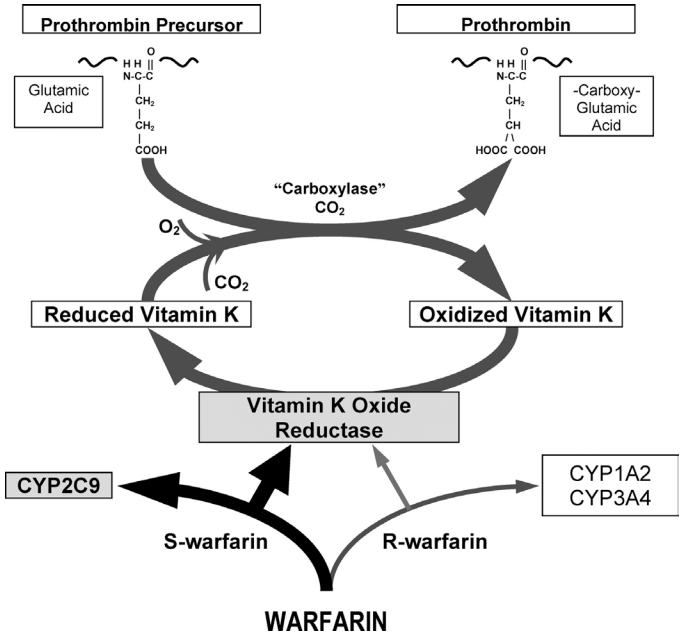

Figure 5: Warfarin Pathway
Courtesy of *Chest Journal: Official Publication of the American College of Chest Physicians*

The presence of the variants varies by ancestry. More than 30% of European and Caucasian populations possess one or both of the CYP2C9*2 or CYP2C9*3 alleles, having respective allele frequencies of 0.1 and 0.08 (Daly and King 2003). However, the presence of the two variants is rare in Asian and African American populations, with greater than 95% of these groups expressing the wild-type genotype CYP2C9*1 that does not reduce warfarin metabolism (Craig R. Lee, Joyce A. Goldstein, and Pieper 2002). According to a meta-analysis, studies on CYP2C9 variants have tended to focus on

Caucasian populations. Continued study is needed to determine if different variations, or possibly even different genes, affect non-Caucasians in the dosing of warfarin (Sanderson, Emery, and Julian Higgins 2005).

VKORC1 Variation

The target enzyme of warfarin is the vitamin K epoxide reductase complex 1, and it is encoded by the VKORC1 gene (Nita A. Limdi 2012). A set of SNPs commonly inherited as a group in this gene also influences the efficacy of warfarin therapy. The common G allele is replaced by an A allele in the VKORC1 1639 (or 3673) SNP. People with an A allele or the A haplotype naturally produce less VKORC1 than those with the G allele non-A haplotype. Therefore, people with the A haplotype require lower warfarin doses to inhibit VKORC1 and to produce the desired anticoagulant effect with a target INF range of 2.0-3.0. The prevalence of these variants varies by ancestry, with 37% of Caucasians and 14% of Africans carrying the A allele (Mark J. Rieder et al. 2005).

Current Warfarin Dosing

The American College of Chest Physicians (ACCP) provides the guidelines for warfarin dosing, and the FDA generally adopts their recommendations (Jack Ansell et al. 2008). The guidelines currently allow flexibility in selecting a starting dose of warfarin, suggesting a physician start a patient with 5–10 mg. The ACCP guidelines recommend lower (2.5–5 mg) doses when age, comorbidity, nutritional status and drug interactions are a concern. However, the ACCP recommends against pharmacogenetic guidance or

tailoring in dosing until more is known about the effects (Ageno et al. 2012; Jack Ansell et al. 2008). Physician discernment and trial and error are currently central determinants.

The most commonly used standard initial warfarin dose is 5 mg/day. Considering clinical and demographic factors alone improves dosing predictions (Nita A. Limdi 2012). This ability to predict dosage independent of knowledge of genotype may call into question the need for genetic testing, but randomized clinical trials have suggested that knowledge of CYP2C9 and VKORC1 genotypes is a clinically useful predictor of warfarin dose (Jeffrey L. Anderson et al. 2007; Jeffrey L. Anderson et al. 2012). The FDA provides a genotype-stratified warfarin dosing table (Figure 6) to assist in dosing if the patient's VKORC1 and CYP2C9 genotype are known (Nita A. Limdi 2012). The table is easy to use and provides a more accurate dose prediction than empiric data alone (Finkelman et al. 2011).

Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes†

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

Figure 6: FDA Recommendations for Warfarin Dosing
Courtesy of the US Food and Drug Administration

Algorithms that consider genetic variation are also available for clinicians to assist in the dosing of warfarin. Algorithms that consider genotype provide better dosage prediction than clinical algorithms like the table supplied by the FDA or the standard 5mg/day dosage (T. E. Klein et al. 2009; Jeffrey L. Anderson et al. 2007; Jeffrey L. Anderson et al. 2012). Using an algorithm to predict dosage that considers the CYP2C9

and VKORC1 variants can provide a substantial gain in improvement of dose prediction in about half of patients (T. E. Klein et al. 2009). A website (warfarindosing.org) is also freely available to clinicians. As Figure 7 demonstrates, this site allows input of phenotypic data, race and ethnicity, lifestyle qualities, and several genetic variants if known (B. F. Gage et al. 2008).

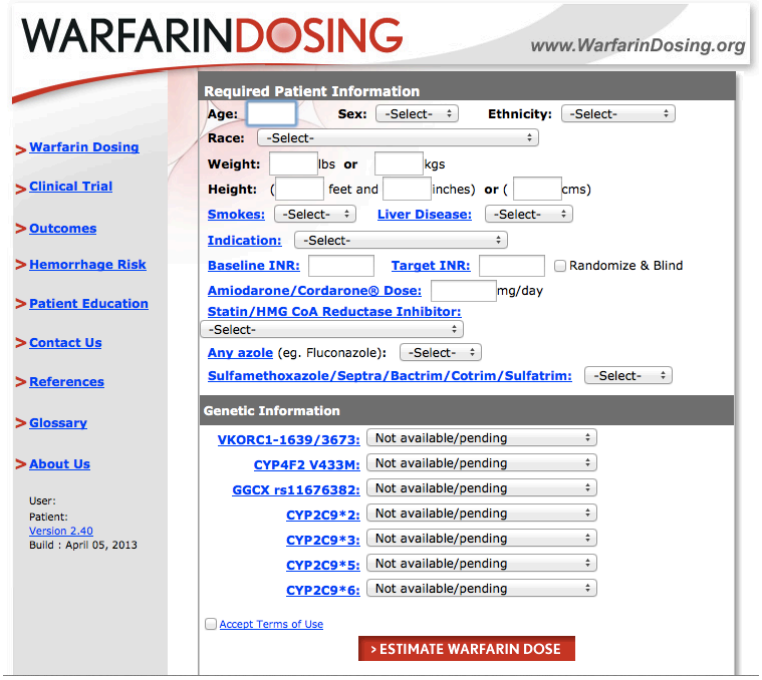

Figure 7: Data Input for Warfarin Dosing Algorithm
Courtesy of warfarindosing.org

Guidelines developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) of the National Institutes of Health Pharmacogenomics Research Network can help clinicians interpret genotype data to estimate therapeutic warfarin dosing aiming to achieve an INR of 2.0-3.0 (J. A. Johnson et al. 2011).

Robust GWASs of Europeans have confirmed the influence of VKORC1 and CYP2C9 on warfarin dosage. They have also indicated CYP4F2 may be influential, but its genome-wide significance has yet to be confirmed. Based on the comprehensive

nature of these studies, the identification of additional common variants in other genes with such impact as CYP2C9 and VKORC1 is unlikely in Caucasians (Gregory M. Cooper et al. 2008; Nita A. Limdi 2012; Takeuchi et al. 2009). The known variants mentioned thus far have less influence on warfarin dosing in non-Caucasians, so The International Warfarin Pharmacogenetics Consortium (IWPC) initiated a GWAS in such a group. Plans for a GWAS meta-analysis for multiple population groups—Whites, Asians, African American, Japanese, and Middle-Eastern—are also underway (Nita A. Limdi 2012). Despite the advances in warfarin dosing due to genetic insight, a large proportion, about 40% in Caucasians and 60% in non-Caucasians, of the variability in warfarin dosage remains unaccounted for. The influence of genetics is even less understood in the Hispanic population. It is possible that further genetic exploration like exome sequencing or whole-genome sequencing will provide more heritable clues, but the influence of lifestyle and environment should not be neglected.

Furthermore, the effect of pharmacogenetic guidance of warfarin dosing on anticoagulation control is still being evaluated. Such dosing has resulted in a higher proportion of time in the target coagulation range in a limited clinical trial (Jeffrey L. Anderson et al. 2012). The improvement noted in pharmacogenetic-dosing is greater than the improvement noted in patients who were treated in specialty anticoagulation clinics versus under typical medical care (Nita A. Limdi 2012). Observational cohort studies have shown that patients with a CYP2C9 variant allele have a higher risk of hemorrhage (Aithal et al. 1999; Margaglione et al. 2000; Higashi et al. 2002; N. A. Limdi et al. 2007). Warfarin dosage can be more accurately predicted using pharmacogenetics, but a link to decreased risk of hemorrhage is yet to be clearly demonstrated. Many trials

are underway, but a sufficiently robust and randomized trial has yet to be completed. The FDA has approved four CYP2C9/VKORC1 rapid throughput genotyping platforms, but clinical application is limited, and the cost of application has yet to be sufficiently evaluated (Nita A. Limdi 2012).

Warfarin in Patients of Non-European Ancestry

The standard warfarin results in over- or under-anticoagulation in 60% of Caucasians and an even higher percentage of African-Americans (T. E. Klein et al. 2009). The dosage these patients require can take a longer amount of time to achieve, leaving the patients open to dangerous risk of thrombosis or hemorrhage for longer periods of time. Unfortunately, the African American population is significantly under-represented in the pharmacogenetic studies of warfarin. Hispanics are even less represented than African Americans. Algorithms that are designed for Caucasians may not be as effective for patients of different ancestry (Cavallari and Perera 2012). The VKORC1 and CYP2C9 variants discussed thus far that are associated with lower required warfarin doses are significantly less common in African Americans compared with Caucasians and Asians. Because they are studied less, more mystery surrounds dose requirements in Hispanics, but the limited data available suggest that Hispanic and non-Hispanic Caucasians may require similar warfarin doses (Cavallari and Perera 2012; Cavallari et al. 2011). African Americans and Hispanics have generally worse outcomes from adverse affects of warfarin treatment than Caucasians, so it is especially important to study and establish safer and more effective guidelines for these populations (Cavallari and Perera 2012).

CHAPTER FOUR

Discussion and Conclusion

Pharamcogenomics and Beyond

Personalized medicine is an important intersection of the fields of modern medicine and physical anthropology. The differences between individuals can seem discrete and quantifiable when looking on a microscopic level but turn out to be continuous and shifting on a holistic level. As personalized medicine seems to be one of the frontiers of the field, examining its methods and applications closely is a valuable and worthwhile task.

Human biological variation has a storied and complex history. Analysis of the fossil record and genetic structure has led to the consensus belief that anatomically modern humans evolved in Africa and migrated in waves to populate the rest of the world. Our relatively recent common ancestry and continual gene flow have led to a low amount of variation within our species. Genetic information indicates that about 10% of the total species diversity is among major geographic regions or populations groups, 5% is among the local populations within these regions, and 85% is within the local populations. Many physical characteristics like craniometrics follow this pattern of variation, but skin color is an interesting and notable exception. Evolutionary pressure is hypothesized to have influenced skin color variation with dark to lighter shades generally being noted from the equator outward. This correlation between visible variation and to some extent genetic variation and geographic origin has led to attempts throughout

history at discrete grouping and characterizing of humans, but the clinal nature of variation resists neat and tidy groupings. Anthropologists today are still trying to overcome the troubled history of the field, and the practice of medicine feels the impacts.

The race concept began to take root during the era of European exploration when people expanded their capacity for long distance travel. Explorers began to understand the natives they encountered as categorically different from themselves. Connections between physical appearance and culture became a part of general mentality. A direct connection was assumed between physical difference and inherited intellectual, behavioral, and moral qualities. Natural philosophers began to try to observe and record differences between people groups, but observations fed into racial categorization. The "ideology of race" entailed belief in the enduring, natural, and fundamental differences between members of different races. It was even suggested that the races evolved in parallel at different times and rates from distinct ancestors. The races were considered different enough to be separate species. Inherent shortcomings in the idea of race have led to the understanding that an individual's race is a cultural construct rather than a biological reality.

Discussions about race gave way to discussions about ethnicity in the twentieth century. The idea of ethnicity sought to encompass more of a person's cultural identity than simply his biology. Language and customs as well as territorial identity were to be wrapped together into the concept of ethnicity. Some of the problems with ethnicity are common to the problems with any approach to categorize humans. Identity is a fluid concept that is affected by historical and social context. Additionally, the terms "race"

and “ethnicity” are still frequently used interchangeably. These issues with the terms led to the development of a new way to describe variation.

Anthropologists now tend to describe people in terms of ancestry, which may be defined geographically, geopolitically, or culturally. Ancestry may be assigned, chosen, or calculated genetically. The idea of ancestry attempts to be more objective than past classification systems have been, but any attempt at describing the complexity of human groups and connections has its limitations. It is possible to determine population groups with some degree of accuracy based on genetic information, which is helpful for medical research and practice. Evaluating the way in which clusters form from the analysis of genetic data of individuals is a good method for looking for population groups, but genetic analysis still supports the conclusion that individuals cannot be divided into starkly delineated groups.

Bearing the shifting nature of cultural identification of individuals in mind, concrete ways to evaluate individuals have developed. These fields include genomics, transcriptomics, proteomics, metabolomics, and epigenomics, and systems biology. Genomics focuses on variation in the DNA sequence. The completion of initiatives like the Human Genome Project and the International HapMap Project has propelled new research and discovery in this field. Genome-wide association studies search for genetic explanation of disease. Transcriptomics studies RNA expression and can be used to identify molecular subclasses of disease. Noncoding RNA like small interfering RNA (siRNA) and microRNA (miRNA) may also play a role in disease. Proteomics or the study of proteins and their derivatives, metabolomics or the study of nonprotein small molecules, and epigenomics or the study of the consequences of DNA methylation also

have the promising ability to make contributions to what is known about biological variation. Systems biology combines all these fields of research in order to study the biological system as a whole. The chemical and biological processes of the body are interwoven and intertwined, so analyzing them as a whole may provide even more insight than the analysis of the parts. Personalized medicine hopes to integrate these findings into the field of pharmacogenomics to assess risks and benefits associated with medications and to select treatments tailored to individual patients. Personalized medicine also hopes to have the capacity to avoid adverse drug reactions and increase the safety efficacy of drug treatments.

Warfarin is an anticoagulant whose use may be made safer and more effective by the application of personalized medicine. Warfarin has a narrow therapeutic index (INR 2.0-3.0), but the dosage required to accomplish an INR in this range can vary twenty-fold between patients. Tens of millions of Americans are currently taking warfarin to prevent thrombosis, but dangerous side effects can result if the patient is not receiving a proper dose. Under-anticoagulation can increase the risk of thrombosis, and over-anticoagulation can increase the risk of hemorrhage. Two main SNPs are known to affect the efficacy of warfarin. The CYP2C9 gene encodes cytochrome P-450 enzyme 2C9 which is the main enzyme involved in warfarin metabolism. Two main variants of this gene decrease the ability to clear the drug from the body. The VKORC1 gene encodes the vitamin K reductase complex 1. A variant haplotype of this gene leads to less of warfarin's target enzyme in circulation, so a lower dose of warfarin is required to obtain the target INF range. Current dosing can be made more accurate using pharmacogentic guidance. The FDA provides a simple table to guide clinicians, and more specific

algorithms can be used online free of charge. It remains to be demonstrated that this more accurate dosing leads to improved outcomes. Additionally, the influence genetic variation on warfarin dosing has mainly been studied in Europeans and Caucasians. More research is needed to see how warfarin dosing is influenced in other population groups like African Americans and Hipanics by the same variants in the same genes, different variants in the same genes, or perhaps novel variants in genes that have yet to be identified. Finally, studies must be conducted to see if improved warfarin dosing in these population groups in fact improves outcomes as well.

The conduct of these studies is one of the most important connections between human biological variation and personalized medicine. Studies are at times lax in detailing the way in which race, ethnicity, or ancestry is assigned. Researchers may not even specify whether they are attempting to describe a person's race, ethnicity, or ancestry in a study. Individuals are frequently referred to as either black or white. Cleary such broad categorizations do not carry enough meaning to be used in rigorous scientific research. Researchers and clinicians alike would benefit from education about the nuances of human biological variation because their results and treatments may not be as valid or effective as hoped if their groupings of people are not accurate or meaningful. Ideally, the specific population for which a treatment is prescribed would be the same population that participates in genetic research. Logistically this may not be possible, so representative groups should be carefully selected and evaluated. Most importantly, broad generalizations should not be made when the data cannot support them. Such generalizations have the possibility to do more harm than good in terms of the goals of personalized medicine.

Finally, an interesting consideration in light of the possibilities of personalized medicine is patient reaction. Researchers and clinicians must contemplate when personalized medicine becomes a clinically applicable reality, in whatever form it takes, if patients will want genetically personalized treatments. Three hundred and eighty-seven patients were recruited from a Baltimore outpatient center to participate in an experimental study based on vignettes. Butrick et al. point out that previous exploratory investigations into how patients would receive personalized medical treatments indicated suspicion of race-based therapeutics. In this randomized experimental study, patients were told to imagine seeing a friendly doctor and finding out they had a common but serious condition. Each was given lifestyle recommendations and a medication that was conventional, race-based, or genetically personalized. Participants rated the race-based vignettes less positively but rated the genetically personalized and conventional vignettes comparably well. However, minority participants expressed notable reluctance to adhere to genetically personalized treatment.

Trust and communication will be of utmost importance in the implementation of personalized medicine. The physician-patient relationship must be the foundation for the use of personalized medicine. Trust between the patient and physician is essential if the physician hopes for the patient to adhere to the prescribed treatment (Butrick et al. 2011). The physician must be open to listening to the patient's concerns about cost, privacy, and discrimination and must be knowledgeable enough to put concerns to rest.

The possibilities of personalized medicine seemed almost limitless at the completion of the Human Genome Project, but these ambitious dreams have been slow to materialize. Human biological variation is incredibly complex, but the differences

between individuals transcend the differences in their biology. Personalized medicine may someday be able to address the genetic differences between individuals or perhaps even populations, but the socioeconomic and cultural influences on health and disease must not be ignored. Responsible and equitable use of personalized medicine may be almost as hard to realize as effective applications. Cost, quality, and access of basic care are already weighty issues in the American health care system and beyond. As amazing possibilities are realized, personalized medicine and health care in general should be offered in a manner that continues to serve the population as a whole.

The field of anthropology intends to evaluate the human species as a whole, while physicians must treat patients one by one. Though these two fields have markedly different emphases, the connections between them are strong in the target of their study and practice—human beings. Physicians would do well to note the danger in drawing conclusions based simply on skin color or ethnic appearance. Anthropologists would do well to note the deep interest in the implications of minor genetic variation in the realm of disease study. The issues of ancestry in biomedical study, clinical practice, and limited personalized medicine will continue until personalized medicine is perfected or the population of earth has become increasingly homogenous. If personalized medicine technology advances to the point that it can become the dominant clinical model, clinicians will no longer be constrained to making frequently unfounded assumptions based on the appearance of and individual. Until then, increased dialogue between the fields of anthropology and medicine will benefit both fields.

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