The Foundations of Genomic and Personalized Medicine

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GENOMIC AND PERSONALIZED MEDICINE

The Human Genome Project, completed in 2003, has provided scientists and clinicians with a diverse set of novel molecular tools that can be used to understand health and manage disease. Variation in the human genome has long been the cornerstone of the field of human genetics (see Box 1.1), and its study led to the establishment of the medical specialty of medical genetics (Nussbaum et al., 2007). Now genome sequencing, copy number variation, transcriptional readouts, and comprehensive measurements of micro RNA, protein, and metabolite levels provide a “systems approach” to probe and predict human health and disease states that has greatly broadened the impact of principles of genetics and genomics on clinical medicine. These advances have provided both a conceptual and technological underpinning for the development of the field of genomic medicine as a driver of personalized health care. For the first time in the history of medicine, health care providers as well as patients can use predictive tools to develop a new model for health care based on health planning that is proactive and preventive, as opposed to the current model in health care that is reactive, episodic, and geared toward acute crisis intervention once disease is already manifest and largely irreversible.

The growing transformation of clinical practice in the era of genomic and personalized medicine is perhaps best exemplified today in the field of cancer care, as illustrated in some detail in subsequent chapters of this volume. Oncologists now practice with a suite of genomic testing opportunities that include BRAC1/BRAC2 testing in familial syndromes of breast and ovarian cancers. In colorectal cancer, Hereditary Non-polyposis Colon Cancer (HNPCC) or Lynch syndrome and familial adenomatous polyposis (FAP) coli are conditions for which there is testing for mismatch repair gene mutations (for HNPCC) or APC mutations (FAP) that has been widely adopted. The paradigm for oncology is largely based on the principle that accurate prognosis and proper therapy can be matched to the molecular characteristics of the individual patient’s tumor. Thus, at the time of diagnosis, whole-genome expression data are now being used routinely to identify subtypes of cancer not previously recognized by traditional methods of analysis (Bullinger and Valk, 2005; Dave et al., 2006; Potti et al., 2006a; Staudt, 2003; Valk et al., 2004).

There is now compelling evidence of clinical adoption of genomic testing by oncologists: in 2008, for example, RNA expression signatures were used for risk stratification and prognosis in breast cancer for more than 39,000 “treat” versus “no-treat” decisions (Securities and Exchange Commission, 2009). However, there continues to be a need to develop the
BOX 1.1 Genetics and Genomics

Throughout this and the many other chapters in this Essentials volume, the terms "genetics" and "genomics" are used repeatedly, both as nouns and in their adjectival forms. While these terms seem similar, they in fact describe quite distinct (though frequently overlapping) approaches in biology and in medicine. Having said that, there are inconsistencies in the way the terms are used, even by those who work in the field. To some, genetics is a subfield of genomics; to others, genomics is a subfield of genetics. Arguably, depending on the perspective one has in mind, both may be right!

Here, we provide operational definitions to distinguish the various terms and the subfields of medicine to which they contribute.

The field of genetics is the scientific study of heredity and of the genes that provide the physical, biological, and conceptual bases for heredity and inheritance. To say that something—a trait, a disease, a code, or information—is genetic refers to its basis in genes and in DNA.

Heredity refers to the familial phenomenon whereby traits (including clinical traits) are transmitted from generation to generation, due to the transmission of genes from parent to child. A disease that is said to be inherited or hereditary is certainly genetic; however, not all genetic diseases are hereditary (witness cancer, which is always a genetic disease, but is only occasionally an inherited disease).

Genomics is the scientific study of a genome or genomes. A genome is the complete DNA sequence, containing the entire genetic information of a gamete, an individual, a population, or a species. As such, it is a subfield of genetics when describing an approach taken to study genes. The word “genome” originated as an analogy with the earlier term “chromosome,” referring to the physical entities (visible under the microscope) that carry genes from one cell to its daughter cells or from one generation to the next. Genomics gave birth to a series of other “-omics” that refer to the comprehensive study of the full complement of genome products—for example, proteins (hence, proteomics), transcripts (transcriptomics), or metabolites (metabolomics). The essential feature of the “-omes” is that they refer to the complete collection of genes or their derivative proteins, transcripts, or metabolites, not just to the study of individual entities. While formally the field of genomics refers to the study of genomes (and hence, DNA) only, it sometimes takes on the broader meaning of referring to any large-scale approach; the less specific term “genome sciences” is also sometimes used to refer to all of the -omics to connote global and comprehensive approaches to the study of biology and medicine.

By analogy with genetics and genomics, epigenetics and epigenomics refer to the study of factors that affect gene (or, more globally, genome) function, but without an accompanying change in genes or the genome. Some typical epigenetic factors involve changes in DNA methylation or modifications to chromatin that change genome structure and hence influence gene expression even in the absence of changes in the DNA sequence. The epigenome is the comprehensive set of epigenetic changes in a given individual, tissue, tumor, or population. It is the paired combination of the genome and the epigenome that best characterize and determine one's phenotype.

Medical genetics is the application of genetics to medicine with a particular emphasis on inherited disease. Medical genetics is a broad and varied field, encompassing many different subfields, including clinical genetics, biochemical genetics, cytogenetics, molecular genetics, the genetics of common diseases, and genetic counseling. Medical genetics is one of 24 medical specialties recognized by The American Board of Medical Specialties, the preeminent medical organization overseeing physician certification in the United States. As of 2007, there were approximately 2500 board-certified medical geneticists in the United States.

Genetic medicine is a term sometimes used to refer to the application of genetic principles to the practice of medicine and thus overlaps medical genetics. However, genetic medicine is somewhat broader, as it is not limited to the specialty of Medical Genetics but is relevant to health professionals in many, if not all, specialties and subspecialties. Both medical genetics and genetic medicine approach clinical care largely through consideration of individual genes and their effects on patients and their families.

By contrast, genomic medicine refers to the use of large-scale genomic information and to the consideration of the full extent of an individual’s genome, proteome, transcriptome, metabolome, and/or epigenome in the practice of medicine and medical decision-making. The principles and approaches of genomic medicine are relevant well beyond the traditional purview of medical genetics and include, as examples, gene expression profiling to characterize tumors or to define prognosis in cancer; genotyping variants in the set of genes involved in drug metabolism or action to determine an individual’s correct therapeutic dosage, scanning the entire genome for millions of variants that influence one’s susceptibility to disease, or analyzing multiple protein biomarkers to monitor therapy and to provide predictive information in presymptomatic individuals.

Finally, personalized medicine refers to a rapidly advancing field of health care that is informed by each person’s unique clinical, genetic, genomic, and environmental information. The goals of personalized medicine are to take advantage of a molecular understanding of disease to optimize preventive health care strategies and drug therapies while people are still well or at the earliest stages of disease. Because these factors are different for every person, the nature of disease, its onset, its course, and how it might respond to drug or other interventions are as individual as the people who have them. In order for personalized medicine to be used by health care providers and their patients, these findings must be translated into precision diagnostic tests and targeted therapies. Since the overarching goal is to optimize medical care and outcomes for each individual, treatments, medication types and dosages, and/or prevention strategies may differ from person to person—resulting in unprecedented customization of patient care.

The principles underlying genomic and personalized medicine and their applications to the practice of clinical medicine are presented throughout the chapters that comprise this volume.

evidence that these signatures will enhance outcomes across a broad population of women with breast cancer. A prospective cooperative group clinical trial has been initiated in Europe (MINDACT) that aims to measure the effectiveness of a gene expression predictor of breast cancer prognosis to guiding adjuvant chemotherapy when compared to predictions based solely on the traditional clinical parameters for prognoses (Bogaerts et al., 2006). A study sponsored by the US National Cancer Institute (TAILORx) aims to use an RNA signature to identify low risk breast cancer patients unlikely to benefit from
chemotherapy (Sparano, 2006). Similar studies are getting started for prognostic signatures in lung cancer (Potti et al., 2006a). These are exemplars of the approach of genomic and personalized medicine and serve as clear examples where a genome-based approach has resulted in the opportunity to redefine disease phenotypes and at the same time redefine therapeutic strategies.

Of equal if not greater importance in achieving the goal of personalized treatment is an ability to predict response to specified therapies, particularly for those regimens that are part of routine clinical practice today. The selection of therapy for many cancer patients is still largely empiric and guided by large randomized clinical trials on populations of patients. Estimates of benefits from this approach for individuals are extrapolations from the effects seen in these large trials and do not necessarily apply to individual patients.

Genomic signatures that predict response and resistance to a spectrum of cytotoxic chemotherapies may now allow assignment of patients to effective treatment regimens best suited to the unique characteristics of their tumor (Potti et al., 2006b). Genomic predictors of chemotherapy response thus provide an opportunity to determine which drug would be optimal for an individual patient in clinical scenarios for which past studies have not shown a clear superiority for any of the currently available drugs.

Beyond cancer, other fields of medicine are also benefiting from whole-genome approaches that are defining both susceptibility to complex disease through genome-wide association studies (GWAS) or genome resequencing (see below), as well as signatures that define disease states and predictive outcomes based on analyses from both disease tissues and from blood (Alizadeh et al., 2000; Golub et al., 1999). Blood-based expression profiling is particularly important as it presents the opportunity to report on disease processes from remote and often inaccessible sites for direct analyses. Instead of analyzing single genes, global gene expression provides a “molecular signature” that may distinguish between one disease state and another. In addition to identifying signatures or patterns of gene expression that represent a disease state, analyses can be constructed to identify representative pathway genes that might point to novel pathophysiology relevant to the underlying disease state. Peripherial blood gene expression signatures have now been reported in a variety of conditions described in subsequent chapters, including rheumatoid arthritis (Lequerre et al., 2006; Shou et al., 2006), systemic lupus erythematosis (Rus et al., 2004), multiple sclerosis (Bomprezzi et al., 2003; Singh et al., 2007), asthma (Brutsche et al., 2002), malignancies (Alizadeh et al., 2000; Golub et al., 1999), solid organ transplantation (Baron et al., 2007; Horwitz et al., 2004), as well as environmental exposures (Dressman et al., 2007; Lodovici et al., 2007; Meadows et al., 2008; Wu et al., 2003). Many of these conditions have an inflammatory component and thus affect immune cells in the vascular compartment. It is hypothesized that these cellular changes are the basis for the differences in gene expression that is observed in RNA extracted from whole blood specimens or from specific circulating cell types. The greatest potential of this approach would be the enhancement in accurately classifying patients by the type and severity of their disease and to individualize the therapy based on the biology of the disease in an individual patient. Significant power can be anticipated from approaches that combine both assessment of an individual’s constitutional genome and evaluation of gene expression signatures of one’s health status (Figure 1.1) (Hardy and Singleton, 2009).
GENES, GENOMES, AND DISEASE

In the context of genomic and personalized medicine, a key question is to what extent genetic variation influences the likelihood of disease onset; determines or signals the natural history of disease; and/or provides clues relevant to the management of disease. Variation in one’s constitutional genome can have a number of different direct or indirect effects on gene expression, thus contributing to the likelihood of disease (Frazer et al., 2009). It is not, however, just the human genome whose variation is relevant to an individual’s state of health, but there are thousands of microorganisms, both symbiotic and pathogenic, whose genomes are also relevant to human phenotypes, and sequence determination of their genomes is providing new insights and approaches for the diagnosis, study, and treatment of infectious disease (see Box 1.2).

Contemporary frameworks for considering the impact of variation in the human genome on disease build on decades of success in establishing the role of individual, typically rare, mutations as causal determinants of now more than 2000 simple Mendelian diseases (Online Mendelian Inheritance in Man, 2009). As a result of that success, much of which paralleled the development of technologies in the early stages of the Human Genome Project (Altschuler et al., 2008; Peltonen and McKusick, 2001), attention has now turned to the genes presumed to underlie susceptibility to common complex diseases, which are the subject of many of the subsequent chapters in this book.

There are two distinct, but nonexclusive models for thinking about human genetic variation and disease (Altschuler and Clark, 2005; Fearnhead et al., 2005; Florez et al., 2003; Pritchard, 2001). One – the “common allele, common disease” hypothesis – posits that variation common in the population accounts for the relatively higher or lower risk that some individuals (and their families) have for a particular condition. Under this model, the collection of 10–15 million common variants in the genome (see Chapter 2) underlies the range of susceptibility that one finds in the general population, modulated by the particular and often variable environmental inputs and factors that are present in that population and that may, in fact, shift or even obscure the relative impact of inherited factors. An alternative model – the rare variant hypothesis – argues that genetic susceptibility to disease is due to the accumulated risk conferred by multiple rare variants in an individual’s genome, variants therefore not likely to be captured by study of the common variants identified by studies to date (Goldstein, 2009).

These two hypotheses suggest different approaches that will likely be informative for delineating the genetic contribution to disease, both for designing research studies and for eventual clinical surveillance. It is worth emphasizing that these two hypotheses are not mutually exclusive and are each likely to be correct in some cases; indeed, there is already evidence supporting each for different diseases (Frazer et al., 2009).

Genome-Wide Association Studies

The common allele, common disease hypothesis has been explored with notable success in a number of conditions, utilizing large cohorts of well-phenotyped patients and high-throughput methods to genotype up to 500,000 or a million variants (so-called single nucleotide polymorphisms [SNPs], see Chapter 2) in the genome (Manolio et al., 2008). These

BOX 1.2 The Genomes Within

The human genome is not the only genome relevant to the practice of medicine.

Both in states of health and disease, our own genome is vastly outnumbered by the genomes of a host of microorganisms, many living peacefully and continuously on various body surfaces, especially throughout the gastrointestinal tract, others wreaking havoc as adventitious viral, bacterial, or fungal pathogens.

The genomes of thousands of microorganisms have been determined and are being utilized to provide rapid diagnostic tests in clinical settings, to predict antibiotic or antifungal efficacy, to identify the source of airborne, water, or soil contaminants, to monitor hospital or community environments, and to better understand the contribution of microbial ecosystems and various environmental exposures to diverse human phenotypes.

The human colon contains more than 400 bacterial species comprising some $10^{12}$–$10^{14}$ microorganisms. Each adult’s gut provides a unique environment – the microbiome – whose origins and impact on human disease are just being explored. The microbiotic gene set is significantly different from that of the human genome and thus has the capacity to alter the metabolic profile of different individuals or different populations, with clinically meaningful effects on drug metabolism, toxicity, and efficacy (Gill et al., 2006; Li et al., 2008; Palmer et al., 2007). The applications to microbiomes of approaches in genomics (as well as proteomics and transcriptomics) are revolutionizing clinical diagnostics, for example, to identify unknown viral infections (Delwart, 2007; Long et al., 2004; Wang et al., 2003) or to diagnose antibiotic-resistance infections such as methicillin-resistant Staphylococcus aureus (MRSA) (Francois et al., 2007).

The field of metagenomics explores this heterogeneous ecosystem by comprehensive sequence analysis of the collected genomes from biological specimens (such as stool, urine, sputum, water sources, and air), followed by both taxonomic and bioinformatic analysis to deconvolute the many genomes contained in such specimens and to define the different organisms, their genes, and genome variants. This approach is particularly informative for characterizing organisms that cannot be cultured in standard microbiology labs. A number of diseases have been associated with large-scale imbalances in the gut microbiome, including Crohn’s disease, ulcerative colitis, antibiotic-resistant diarrhea, and obesity (Frank and Pace, 2008; Ley et al., 2006; Turbaugh et al., 2006).

Undoubtedly, the states of health and disease are determined in part by the balance of genomes both within us and external to us. The full complement of genomic information from both of these sources of genomes will provide insights into defining the states of health and disease and the basis for unsurpassed precision in both the prevention of disease and its treatment.
GWAS report the statistical association of one or more variants in a narrow genomic region (which may or may not contain an annotated gene) with the presence or absence of the clinical condition. The reported SNPs define immediately accessible risk factors for that condition, at least in the population(s) under study and can provide novel insights into the biology of the disease. It should be stressed, however, that in most instances, causality of the reported SNP(s) and the increased risk has not been proved; it may be that the actual causal variant is not the SNP itself but is a currently undetected variant that lies in linkage disequilibrium with the SNP (Frazer et al., 2009).

In the most favorable cases, the associated SNP may be a nonsynonymous variant, leading to a pathological amino acid change in the relevant gene (Thorleifsson et al., 2007), or may be a variant in an RNA splice site, leading to a clinically meaningful change in the production of the gene’s transcript(s) (Heinzen et al., 2007). But in most instances, the functional impact of the associated SNP is obscure, notwithstanding very clear genetic evidence of a role of genome variation in susceptibility to the particular condition. SNPs are but one of several types of genome variation that can influence gene expression and/or disease (see Chapter 2). Copy number variants have also been associated with some disorders (reviewed in Estivill and Armengol, 2007), and it will require integrated genomic, genetic and functional studies to elucidate the precise basis for the role(s) of genome variation in different diseases.

Medical Resequencing in Search of Rare Variants

While GWAS certainly establish that common alleles do indeed increase susceptibility to common disease in some instances, they do not allow one to conclude that this is always the case. Indeed, in most (but not all) cases to date, the common SNPs found to be associated with disease only explain a small fraction of the total genetic variation, implicating an as yet undiscovered (and presumably rarer) basis for most genetic variation underlying a given condition. While such association is sufficient to conclude that a particular variant does indeed contribute to disease in the population under study, such a finding is insufficient to say anything declarative about the cause of our likelihood of disease in a particular case. This conclusion is, of course, highly relevant to the prospects of genomic and personalized medicine.

An alternative or complementary approach to genome-wide genotyping of common variants is to resequence specific genes in a cohort of affected individuals, in an effort to uncover rare variants responsible for (or at least statistically associated with) the disease in question. To date, most efforts have focused on one or several genes that were believed to be strong candidates for the phenotype understudy; the notable exception thus far is exemplified by the whole-genome resequencing of the HuRef genome and correlation of novel variants detected in that study with his family and personal medical histories (Levy et al., 2007). Rare variants, including nonsynonymous variants, in relevant candidate genes have been detected at a statistically significant higher frequency in the genomes of patients with colorectal adenomas (Fearnhead et al., 2004), with low-plasma high-density lipoprotein cholesterol (HDL-C) (Cohen et al., 2004), with triglyceride levels in the lowest quartile (Romeo et al., 2007), and with familial cases of X-linked mental retardation (Tarpey et al., 2009).

These successes point to a strategy of resequencing relevant genes in individuals at the extremes of the population distribution for measurable traits (Topol and Frazer, 2007) in which the only limiting parameters are the cost of sequencing and the quality of the phenotypic or quantitative data. In a proof-of-principle for this case-control approach, a recent study sequenced coding exons and splice junctions of 58 genes in nearly 400 obese and lean individuals, at the >95th or <10th percentile of body mass index (Ahituv et al., 2007). Of the ~1000 variants detected, most were rare variants, including over 270 nonsynonymous mutations; many were found only in the obese cohort and thus become strong functional candidates for a role in obesity.

Searching for Somatic Mutations

While GWAS are restricted to inherited variation, medical resequencing studies can target either inherited or somatic variants. In cancer especially, it is of interest to use medical resequencing to search for somatic mutations in tumor tissue in order to identify genes potentially relevant to cancer development and/or progression (Stratton et al., 2009). Two important points emerge from such studies (Greenman et al., 2007; Jones et al., 2009; Sjoblom et al., 2006). First, the genes implicated by virtue of discovering rare somatic variants in multiple cases of a particular cancer tend to be different from those identified in previous genetic studies as inherited risk factors. This provides novel insights into the biology of human cancer and suggests candidates for further exploring mechanisms of tumorogenesis or metastasis or for developing therapeutic approaches. Second, however, the large number of mutations uncovered by this approach introduces the need for caution, as many will be “bystander” or “passenger” mutations only associated with cancer, not genes involved directly in cancer.

FROM THE GENOME TO PERSONALIZED MEDICINE

Of all the promises of the current scientific and social revolution stemming from advances in our understanding of the human genome and its variation, genomic and personalized medicine has been the most eagerly awaited. The prospect of examining an individual’s entire genome (or at least a significant fraction of it) in order to make individualized risk predictions and treatment decisions is an attractive, albeit challenging, one (Bentley, 2004; Kraft and Hunter, 2009; Willard et al., 2005).

Having access to the reference human genome sequence has been transformational for the fields of human genetics and
sequences may have been the first, they have been rapidly followed by several others (see Chapter 2), and numerous additional genomes are already in various sequencing pipelines.

What remains unsettled for now is what degree of genome surveillance will be most useful, either for research or for clinical practice, a topic that is discussed frequently in subsequent chapters. Some have argued that, while whole-genome sequencing is increasingly possible, it is unlikely to provide more information about established disease associations than would high-density, genome-wide genotyping to detect both SNP and copy number variation. Targeted resequencing of, for example, exons and known regulatory regions would allow detection of rare variants in portions of the genome most relevant to disease at a fraction of the cost of whole-genome sequencing (Hodges et al., 2007).

The availability of associated clinical data is variable among the studies announced to date, but there exists, at least among some participants, a strong sense of “health-information altruism” to contribute to the much needed large-scale correlation of genotype and phenotype (Kohane and Altman, 2005). Notwithstanding individual’s willingness to make genome sequence data (much less medical information) available more or less publicly, substantial concerns have been raised about privacy, since a surprisingly (to some) small number of SNPs or other genome variants are sufficient to allow identification of individuals (Lin et al., 2004; McGuire and Gibbs, 2006; McGuire et al., 2008). Absolute privacy and anonymity may be an impossible standard.

A Consumer Revolution

While the genome revolution has without doubt been driven by technological improvements and by an explosion in the availability of genome data, the push for incorporation of genome information into clinical practice may come as much or more from consumers as from professionals. A half dozen or more companies are already offering genome-wide SNP profiles to the public, some with associated risk estimates for relevant clinical conditions. At least a few companies will also sequence individual genomes for a cost that, while high currently, is not out of reach for some individuals. There is a clear and important research agenda that needs to be developed in concert with these technological breakthroughs that allows health providers and the public to understand the information and more so to believe that it is accurate, informative, and actionable (Feero et al., 2008; Hunter et al., 2008; McGuire et al., 2007, 2008). With the vast amount of information contained in the human genome sequence, the stakes are high for patients, physicians, and the public to ensure proper reading, interpretation, and communication of the information are carried out (Janssens et al., 2008). This may be a “disruptive technology” in health care delivery with the provision of health and disease risk information to consumers without physician intervention and guidance. It will not be long before a patient will bring a report of a whole genome to a physician’s office and ask for guidance. What will the physicians of today, armed with a paucity of genomic training, tell them?

CHALLENGES IN THE TRANSLATION OF GENOMICS TO HUMAN HEALTH

Despite the clear advances in technology to bring genomic information closer to physicians, patients, and the public, looming ever closer are issues that are outside of the sphere of the scientists that have been involved in the discovery and early translational activities. In the United States, the Institute of Medicine has convened a Roundtable on Translating Genomics to Health (Institute of Medicine, 2007), the Centers for Disease Control has independently developed a pilot project on the Evaluation of Genomic Applications in Practice and Prevention (EGAPP, 2004), and the Genomic and Personalized Medicine Act of 2007 (Personalized Medicine, 2007) was introduced in Congress to also address similar issues.

Recently, Scheuner et al. (2008) carried out an extensive meta-analysis of studies using genomics toward clinical application in chronic disease. This study aimed to understand the current state of translation focusing on the following questions: “What are the outcomes of genomic medicine? What is the current level of consumer understanding about genomic medicine and what information do consumers need before they seek services? How is genomic medicine best delivered? What are the
challenges and barriers to integrating genomic medicine into clinical practice?”

Using a total of 68 articles in their analysis, the authors synthesized information on the delivery of genomic medicine for common adult-onset conditions (Scheuner et al., 2008). The major findings of the study were not surprising in terms of the genome policy issues that have been previously summarized (Haga and Willard, 2006).

- Education – The primary care workforce feels woefully unprepared to integrate genomics into regular practice. Consumers are also unclear about genetics and genetic testing for common diseases.

- Privacy – Consumers are worried about the possible adverse consequences of genetic testing, particularly the privacy issues and discrimination against receiving employment and health insurance.

- Evidence – There needs to be outcome data for genetic testing and chronic disease to assess whether patients who receive the test do better clinically.

- Cost – Cost uncertainty (both in terms of delivery and reimbursement) is an important issue to many of the stakeholders of genomic issues.

Health Professional and Public Education

Education of health professionals and the public will be essential to advancing the use of genomics into health care (Frueh et al., 2005). With all of the rapid advancements in genomics research and technologies, it will be challenging to keep health professionals informed about the benefits, risks, and limitations of new tools as they become available. In addition, the public and health care workforce will need to understand the appropriate applications of genomic tools, including their benefits, risks, and limitations; how they may improve clinical management; inherited versus acquired genomic variations (e.g., implications for family members); and privacy and confidentiality. Although several surveys have documented the below average physician knowledge of genetics (Metcalfe et al., 2002), none has assessed knowledge of the newer field of genomics. But, several papers have been published recognizing the importance of pharmacogenetics (Frueh and Gurwitz, 2004), and steps are underway to develop more educational materials in this area.

Privacy Fears

There has been ongoing debate about the uniqueness of genetic information and whether it warrants special protections beyond those in place for standard medical information (Haga and Willard, 2006). In the United States, fear of discrimination by employers and health insurers is the main concern, whereas in the United Kingdom, use of genetic information by life insurers is the major concern (Apse et al., 2004; HAll et al., 2005). Despite the outcome of these debates, the attention paid to genetics by the popular press and public has raised concern about genetic information. The potential for genetic discrimination has been a major concern for researchers, health professionals, patients, and the public. In order for genomic biomarkers to be integrated into routine clinical practice, associated fears with this type of testing must be put to rest. In 2008, the United States enacted legislation to protect against genetic discrimination by employers and health insurers. This is an important step in allaying public fears that may otherwise hinder a comprehensive genomic and personalized approach to medicine.

Building the Evidence for Clinical Utility

Perhaps the most important factor hindering the appropriate integration of genomics into clinical practice is the lack of evidence for its clinical utility (i.e., evidence that use of a genomic technology actually improves health outcomes). Evidence generation needs to be more practicable and practical. There is also a need for greater collaboration among stakeholder groups and for innovation in both study design and analysis methods. Clinical outcome studies are needed that demonstrate the clinical utility of genomic interventions that are linked to specific, actionable clinical recommendations, or practice guidelines. Public–private partnerships are likely to be required to generate the evidence base for genomic medicine. These collaborations are desirable because no single stakeholder group is likely to have sufficient resources or expertise to conduct the necessary studies.

Cost Issues

As with any new innovation, genomic testing must be demonstrated to be clinically useful and cost effective and of value. But, because genomic technologies inherently involve diagnostic or prognostic testing, in addition to the complexities of incomplete gene penetrance and multiple gene × environment interactions, their assessment can be more challenging. In addition, perhaps more than in any other area of medicine, questions have arisen in regard to the economic incentives to develop these technologies. Formal health economics frameworks can be used to gain insights into these issues and provide guidance for research and development (Carlson et al., 2005; Flowers and Veenstra, 2004; Stallings et al., 2006). It is important to examine the drivers of cost effectiveness of genomic technologies and to consider approaches that include value-based reimbursement for genomic testing technologies. A particularly challenging area is pharmacogenomics, in which the economic incentives for developing diagnostics linked to therapeutics in the pharmaceutical industry are unclear. An integrated business model is needed that will be favorable for the effective delivery of genomic information to patients and clinicians.

THE FUTURE OF PERSONALIZED MEDICAL CARE

While the human genome sequence is now available, it is important to acknowledge that our knowledge of the genome and its biological complexity is nowhere near complete, and the use of genomic protocols in standard clinical care faces many challenges. There are a host of clinical, economic, insurance, privacy, and
commercialization concerns that will need to be addressed and that vary substantially among different countries. As a field, we can confront those with the certainty that the science behind genomic medicine is sound and the practice of medicine that it informs is evidence based. These issues are being dealt with systematically, and the prospects of using genomic information to offer patients health care that is truly personalized in nature—as will clearly see in the subsequent chapters—is finally within our reach.

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