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Genomics for Disease Treatment and Prevention

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Abstract

The enormous advances in genetics and genomics of the past decade have the potential to revolutionize health care, including mental health care, and bring about a system predominantly characterized by the practice of genomic and personalized medicine. We briefly review the history of genetics and genomics and present heritability estimates for major chronic diseases of aging and neuropsychiatric disorders. We then assess the extent to which the results of genetic and genomic studies are currently being leveraged clinically for disease treatment and prevention and identify priority research areas in which further work is needed. Pharmacogenomics has emerged as one area of genomics that already has had notable impacts on disease treatment and the practice of medicine. Little evidence, however, for the clinical validity and utility of predictive testing based on genomic information is available, and thus has, to some extent, hindered broader-scale preventive efforts for common, complex diseases. Furthermore, although other disease areas have had greater success in identifying genetic factors responsible for various conditions, progress in identifying the genetic basis of neuropsychiatric diseases has lagged behind. We review social, economic, and policy issues relevant to genomic medicine, and find that a new model of health care based on proactive and preventive health planning and individualized treatment will require major advances in health care policy and administration. Specifically, incentives for relevant stakeholders are critical, as are realignment of incentives and education initiatives for physicians, and updates to pertinent legislation. Moreover, the translational behavioral and public health research necessary for fully integrating genomics into health care is lacking, and further work in these areas is needed. In short, while the pace of advances in genetic and genomic science and technology has been rapid, more work is needed to fully realize the potential for impacting disease treatment and prevention generally, and mental health specifically.

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Introduction

The last decade has brought with it enormous advances in genetics and genomics. In parallel, there has been a growing sense that genomic technologies and discoveries will, sooner rather than later, revolutionize the practice of medicine and bring about a paradigm shift in the way we think of health care, including mental health care, for the individual. Specifically, it has been anticipated that these advances will eventually lead to a new model of health care centered on disease prevention and reinforced by disease treatments that are tailored to the individual. This vision of health care is in stark contrast to our current model, which is largely geared toward acute crisis intervention once disease is present and often progressed to the point of being irreversible. These facts raise a number of important questions. For example, where do things stand in terms of our ability to harness the fruits of genetic and genomic discovery for disease treatment and prevention? In terms of the science, what are the research priorities? Furthermore, although few would, in theory, oppose the adoption of an improved health care system based on personalized medicine, are there social, economic, and policy barriers to moving forward on this front, in particular regarding adoption of policies centered on disease prevention?

Briefly, genomic medicine is the use of information from the genome to guide clinical decision making. Personalized medicine is a more broad concept that refers to a model of health care emphasizing the use of each individual's unique clinical, genetic, genomic, and environmental information for disease prevention and treatment [1]. The state of science and technology is such that we can now examine and measure an individual's entire genome. Hence, individualized risk predictions and treatment decisions based on genomic information are theoretically possible, and in some instances, actually taking place. Personalized medicine draws on genomic medicine to leverage our knowledge of genetics and genomics for preventive health care, as well as administration of personalized, targeted therapies for individuals with existing conditions.

In this article, we begin by providing a brief history of genetics followed by a review of heritability estimates for major chronic diseases as a way of highlighting the putative importance of genetics for disease treatment and prevention. We then provide a brief primer on genetics, genomics, and genome-wide association studies (GWAS), followed by an assessment of the extent to which advances in genetics and genomics are currently being applied clinically, both broadly and specifically in the context of mental health care. We attempt to pinpoint where (sometimes sizable) gaps in the science exist that ultimately preclude additional clinical applications. Next, we propose priority research areas that ultimately will be of critical importance to fully harnessing genetics and genomics for disease treatment and prevention. Finally, we review the current social, economic, and public policy environments, which in some cases do not appear to be conducive to the adoption of genomic and personalized medicine, and suggest possible areas in which changes may be encouraged.

A Brief History of Genetics and Genomics

It is important to note that genetics and genomics are complementary but different disciplines. While genetics is the study of inheritance, or the way traits are passed down from one generation to another, genomics refers to the study of all the genes and gene products in an individual, as well as how those genes interact with one another and the

environment [2]. In 1866, Gregor Mendel published his theories of inheritance based on hybridization experiments in garden peas. Although largely ignored until the early 1900's, his work is considered to form the basic theory of modern genetics. Mendel discovered that when he crossed a white flower and a purple flower plant, rather than being a mix of the two, the offspring were purple flowered. From several successive crosses, he developed the ideas of dominant and recessive inheritance in which dominant factors (purple flowered) will hide recessive factors (white flowered). Later, in the early 1900s, Sir Archibald Garrod described several human diseases that he termed "inborn errors of metabolism" (e.g., albinism), which showed a similar pattern of inheritance to that of the white color in Mendel's hybridization experiments and thus suggested a genetic basis for these diseases [3]. Garrod described the nature of autosomal recessive inheritance (where two copies of an abnormal genetic variant or "allele" are needed to express the disease) with respect to these conditions, and using Mendelian principles illustrated that two parents heterozygous for the disease allele (i.e., who carry only one copy) have a one-in-four chance of producing a child having both disease alleles and, hence, the unwanted disorder.

In 1909 Wilhelm Johannsen coined the term "gene", and in 1915, Thomas Morgan Hunt showed that genes, which exist on chromosomes, are the basic units of inheritance [4]. Over the next several years, many additional examples of diseases inherited in an autosomal recessive manner were discovered, including phenylketonuria and cystic fibrosis. Autosomal dominant diseases (where only one copy of an abnormal allele is needed to express the disease) were also described, including Huntington's disease and Marfan's syndrome. X-linked recessive and X-linked dominant traits (see Glossary of Terms) were also discovered and described. Importantly, disorders that follow these patterns of inheritance, termed "Mendelian disorders", have been among the easiest to analyze and the best understood. Arguably, these disorders and modes of inheritance also have led to a common fatalistic view among lay people that genes are deterministic and that if one inherits a disease allele, one will inherit an unwanted disorder. This view stands in opposition to more recent notions of the "susceptibility allele", based in large part on findings from the field of genomics, specifically GWAS, in which inheritance of a specific genetic variant does not guarantee the emergence of a disease, but merely confers some environmentally and/or other genetic factor mediated probability of developing a disease [5].

In 1920 Hans Winkler coined the term "genome" to refer to all the genes in an organism by combining the words gene and chromosome [6]. Building on evidence that DNA, or deoxyribonucleic acid, was the primary component of chromosomes and genes, in 1953 James Watson and Francis Crick, with the help of Rosalind Franklin, discovered the double helix structure of DNA, and in 1966 Marshall Nirenberg was credited with "cracking the genetic code" and describing how it operates to make proteins [7]. From these important discoveries, several downstream events occurred that began to reflect progression from the study of inheritance to the study of how genomic profiles could be used in medicine and in other arenas. For instance, in 1978, the biotechnology company Genentech, Inc. genetically engineered bacteria to produce human insulin (the first drug made through the use of recombinant DNA technology) for the treatment of diabetes [8], and in 1983 scientists identified the gene responsible for Huntington's disease, which led to the first genetic test for a disease. In 1984, Sir Alec John Jeffreys developed DNA profiling or "fingerprinting" to be used in paternity testing and forensics, and in 1986, Richard Buckland was the first person acquitted of a crime based on DNA evidence. In 1989, Stephen Fodor, who later co-founded the gene chip company Affymetrix, developed the first DNA "microarray" and scanner, which would eventually lead to a method for testing hundreds of thousands of genetic variants simultaneously and thus foreshadowing the upcoming era of genome-wide association studies (GWAS) [9].

More recently, two major research initiatives have led to the present day "post-genomics" era – i.e., the Human Genome Project (HGP) and the International HapMap Project. The goal of the HGP was to draft a reference human genome delineating the sequence of chemical base pairs which make up DNA, as well as to determine the location of the roughly 25,000 genes thought to populate the human genome. In 2000 a draft sequence was released [10,11] and in 2003 the final version was published. Relatedly, the goal of the International HapMap Project [12,13] was to create a genome-wide database cataloging patterns of common human sequence variation within and across both individuals and populations. Importantly, an explicit aim of the HapMap was to facilitate identification of commonly occurring complex (i.e., non-Mendelian) disease causing genetic variants based on the "common disease, common variant" hypothesis [14], a hypothesis that incidentally has been called into question for explaining the genetic contributions to mental illness [15]. This hypothesis suggests that genetic influences on complex diseases are attributable to common allelic variants present in more than 5% of the population. These variants represent "risk factors" or "susceptibility variants" for disease, as opposed to the more deterministic variants governed by Mendel's principles. Taken together with technological developments enabling cost effective applications of DNA microarrays capable of measuring hundreds of thousands of genetic variants at once, these two initiatives led to the first [16] of many GWAS to be published. While GWAS have some weaknesses, which will be discussed in later sections of this article, it is this research paradigm (now together with whole-genome sequencing) that has generally been thought of as laying the groundwork for the era of genomic and personalized medicine.

Heritability of Major Chronic Diseases

It is important to make explicit the reasons for considering genetics and genomics to have substantial utility for disease treatment and prevention, especially given the obvious role of environmental (including behavioral) factors in the etiology of many conditions (e.g., the role of smoking in the development of lung cancer), including neuropsychiatric disorders. Essentially, from family, twin, and adoption studies, researchers have been able to estimate the proportion of variance due to genetics (i.e., "heritability") and the proportion of variance due to environment for a range of chronic diseases and other phenotypes. A heritability estimate of 1.0 indicates that all of the variation in a trait can be accounted for by genetics, and a heritability estimate of 0 indicates that all of the variation in a trait can be accounted for non-genetic factors (e.g., environment). Table 1 gives heritability estimates for chronic disorders of aging, aging phenotypes, and major neuropsychiatric disorders. These estimates range from 0.25 for human longevity [17,18] to 0.85 for Bipolar disorder [19,20], indicating a strong genetic component with respect to many chronic diseases and phenotypes relevant for human health, including mental health. Ultimately, the large extent to which human disease can be attributable to genetic factors underscores the importance of genetics and genomics research for impacting health care [21].

Genetics, Genomics, and GWAS Primer

There are many study designs that have been successfully applied to genetic analyses. Here we provide a primer that is primarily focused on GWAS, given that it is this paradigm that has recently provided a means of assessing the entire genome in order to identify specific genetic differences among human beings that contribute to variation in disease susceptibility.

The human genome sequence is comprised of roughly 3 billion nucleotide bases (6 billion if one considers its diploid nature). Although more than 99% of that sequence does not differ from person to person, it is the differences in sequence that are of interest because it is these differences that, along with environmental/behavioral differences, contribute to phenotypic

divergence. Variation in the DNA sequence can take different forms. By far the most common form of variation is characterized by sites in the sequence where individuals differ by a single base. These differences are known as single nucleotide polymorphisms or "SNPs," and they occur, on average, about one site per 300 bases [22]. More than 10 million SNPs are thought to be present in the human genome. SNPs are also relatively common such that, by definition, the minor allele of any given SNP is present in at least 5% of individuals. GWAS have traditionally focused on using high-throughput genotyping to assess SNP variation across the genome to identify sites where frequency differences exist between individuals with and without disease (or with and without a certain phenotype). One can imagine that genotyping 10 million sites in the genome could potentially be very expensive and time-consuming. The genome, however, exhibits a structural property known as linkage disequilibrium (LD) whereby large sections of DNA sequence within a given chromosome are highly correlated. This structural property allows a shortcut that makes GWAS cost-effective and feasible in that representative SNPs ("tag" SNPs) from each section of correlated sequence can be genotyped and then used to infer genotypes at other unmeasured bases within the same section of sequence. These sections of correlated sequence are known as "haplotypes." This method of genotyping tag SNPs across known haplotypes means that GWAS studies are possible with genotyping of only 500,000 to 1 million SNPs. Indeed, using this method, over the past 5 years or so more than 400 GWAS have been published identifying over 150 risk variants for more than 60 common diseases and traits [23].

Missing Heritability

GWAS have been a powerful tool for conducting unbiased scans of the genome to identify SNPs implicated in common, complex diseases, and represent an important advance compared to candidate gene studies. There is a wide gap, however, between the proportion of variance in disease susceptibility explained by the results of GWAS (usually between 1–10%) and the proportion of variance in disease susceptibility thought to be due to genetics based on heritability estimates (see Table 1) [24,25], which can be as high as 50% or greater. Furthermore, this is particularly true for neuropsychiatric disorders where GWAS have been less successful relative to studies of other common chronic aging-related diseases [26]. Many reasons for this missing heritability have been proposed including the need for much larger sample sizes to detect additional SNPs of smaller effect that are yet to be found. In addition, rare variation (<1% frequency) and structural variation (e.g., copy number variants, insertions, deletions, inversions, and translocations), forms of variation that are not well-captured with most genotyping chips currently in use, likely account for some fraction of the unexplained genetic variability. Finally, low power to detect gene-gene interactions, inadequate examination of gene-environment interactions, phenotypic heterogeneity or imprecise phenotypic definition, and epigenomic alterations such as imprinting or parent-of-origin effects have also all been proposed as explanations for missing heritability [25]. Some of these explanations (e.g., phenotypic heterogeneity) may be particularly relevant for explaining missing heritability in neuropsychiatric disorders. Furthermore, with regard to mental illness in particular, the common disease, common variant hypothesis has been called into question, and it has been proposed that an alternative evolution-informed framework, characterized by the importance of gene-environment interactions and rare variants is more tenable for these types of disorders [15]. To some extent, it is this issue of unexplained genetic variance that has hindered the use of genomic information from GWAS for the development of clinically useful predictive tests for common, complex (non-Mendelian) diseases. This, in turn, has limited the development of more targeted prevention strategies. We propose that one priority research area for leveraging genomics for disease prediction and prevention should be development of new strategies for finding and investigating the remaining heritability, especially in the area of neuropsychiatric diseases.

Sequencing and Other Research Strategies

DNA sequencing, which involves measuring each nucleotide base as opposed to just SNP variation and tag SNPs, is one approach for finding missing heritability that has wide support in the genetics community. This approach has the enormous benefit of providing information about all the different forms of common, as well as rare, genetic variation within the genome, including SNPs, copy number variations, insertion/deletions, inversions, and unique *de novo* single base mutations. Furthermore, although sequencing is currently limited to candidate genes, it is rapidly becoming more refined and cost-effective, such that whole genome sequencing will like become more widely available and feasible in the near future. In the aging and neuropsychiatric literature, there is little precedent for sequencing on a large scale; however, one recent example of this approach is a study by Halaschek-Wiener and colleagues in which they sequenced 24 candidate aging genes in healthy adults aged 85 years or older. Of note, 41% of the genetic variants they identified were not previously recorded in existing genetic reference databases [27]. This suggests that previous genetic strategies such as GWAS and candidate gene studies are likely unable to detect much of the genetic variation that underlies complex diseases and phenotypes, and that DNA sequencing will be critical in this regard. A number of studies utilizing this approach for studying neuropsychiatric diseases are also ongoing, including studies in schizophrenia, biopolar disorder, and anorexia nervosa [28]. In addition to sequencing, meta- and combined data set analysis (i.e., “mega-analysis”) of comparable, and in many cases publically-available data [29,30], can be leveraged to increase sample sizes and power to detect variants of smaller effect. Also, future GWAS studies can be improved by including more precisely measured phenotypes rather than the common “case-control” design, as well as measures of environmental exposures. Gene-gene interactions can also be investigated via a priori hypothesis testing. Finally, family data can be leveraged to better elucidate gene-environment interactions as well as parent-of-origin effects. We propose that accounting for the missing heritability in common chronic diseases, including neuropsychiatric diseases, will be an important hurdle to overcome in the use of genomics for making reliable and valid individual disease risk predictions and designing complementary targeted disease prevention strategies.

Applications of Genetics and Genomics in Disease Prevention and Treatment

Below we discuss some of the major areas in which genetics and genomics are poised to make (and in some cases already have made) strong impacts on the practice of medicine.

Pharmacogenomics and Treatment Response

Pharmacogenomics is the study of genetic variation that is associated with the variable responses of individuals to any given drug treatment [1], including individual differences in drug efficacy and susceptibility to adverse effects. This area of genomics provides possibly the best and clearest example of how genomics can be used to bring about more targeted and individualized treatments and actually influence clinical care. This area has already made a number of significant impacts in this regard. Specifically, over the past several years, many associations between genetic variants and drug response have been discovered, including, for example, the now well-known association between CYP2C9 and VKORC1 gene variants and Warfarin [31].

Warfarin is one of the most commonly used anticoagulant medications and is prescribed worldwide to prevent stroke and venous thromboembolism [32]. Unfortunately, however, dosing of Warfarin is highly complex due to many factors that affect its metabolism, including clinical (drug-drug interactions, dietary interactions, age, and body surface area)

and genetic factors, in particular variants in the genes CYP2C9 and VKORC1 [33,34]. In fact, it is estimated that consideration of combined genotypes across variants in these genes, together with factors such as age and body size, are estimated to account for 35–60% of the variability in Warfarin dosing requirements. Evidence for the importance of these variants in influencing Warfarin metabolism led the U.S. Food and Drug Administration (FDA) to update the labeling of Warfarin in 2007 to include a statement acknowledging the importance and potential of genotyping during the early phase of dosing [35]. This particular update, however, did not dictate how physicians should change the dosage based on genotype. Based on additional research since then, the FDA again updated its Warfarin labeling in 2010 to include specific ranges of initial doses assigned to each genotype representing the expected steady state maintenance doses.

To the extent that pharmacogenomic research efforts and resulting label updates by the FDA lead to improved drug safety and efficacy, this represents a real step forward in the use of genomics for disease treatment (and prevention of adverse effects) and for ushering in a new era of personalized medicine. Other examples of pharmacogenomic associations and FDA label updates are included in Table 2 [35]. Briefly, Azathioprine and 6-MP are immunosuppressants used to treat some cancers, as well as autoimmune diseases such as rheumatoid arthritis and Crohn's disease. Genetic testing for variants in the TPMT gene have been found to be associated with adverse side effects, including severe myelotoxicity, and the 6-MP label was the first label to be updated in the last decade based on pharmacogenomic information. A similar association was found between Irinotecan, an anti-cancer chemotherapy drug, and variations in the gene UGT1A1. This was the first label update to recommend a specific dosing reduction based on pharmacogenomics because of an increased risk of neutropenia in patients with certain genotypes. In terms of mental health and applications to neurological disorders, Carbamazepine, an anticonvulsant and mood stabilizer used in the treatment of epilepsy, bipolar disorder, trigeminal neuralgia, and other neuropsychiatric disorders, has shown an association with variants in HLA-B*1502. Specifically, genotyping of variants in HLA-B*1502 can identify individuals at risk for Stevens-Johnson syndrome and toxic epidermal necrolysis, two forms of rare but potentially fatal skin diseases [36]. Similarly, associations between Abacavir and variants in HLA-B*5701, have also been shown to predict adverse drug effects. Finally, another notable pharmacogenomic association is that between genetic variants in CYP2C19 and metabolism of Clopidogrel, which is used in at-risk patients to prevent strokes and heart attacks. In 2010, the label of Clopidogrel was updated with a warning that patients carrying variants associated with poor metabolism of the drug may be less responsive to the medication and thus fail to receive full protection from heart attacks, stroke, and cardiovascular death [37].

While pharmacogenomic research and findings have led the FDA to take major steps forward in translating genomic findings into better, individualized disease treatments, there is still much work to be done. For example, with respect to pharmacogenomics in psychiatry, limited evidence from twin and family studies suggests that response to antipsychotic and antidepressant medications are heritable traits. Specifically, studies on single pairs of monozygotic twins observed similar response to treatment with antipsychotics [38] and similar levels of drug-induced weight gain [39], and studies on siblings and first-degree relatives observed similarities in treatment-induced tardive dyskinesia and response to antidepressants [40,41]. Furthermore, genetic variants in the HLA complex have been associated with risk of drug-induced agranulocytosis, which led a biotechnology company to develop and offer a genetic test for the determination of high (1.5%) or low (0.5%) risk in conjunction with prescription of clozapine [42]. This test, however, has not been widely adopted by physicians [43], and the FDA has not updated labels of major antidepressants or antipsychotics, in part, due to difficulties replicating findings in this area and a lack of large-scale controlled studies. Another issue that may

inhibit translation of pharmacogenomic findings into the clinic is a lack of adequate training of community physicians in pharmacogenomics. Furthermore, the clinical availability of genetic testing for pharmacogenomic variants is still limited in many areas, and there remain important questions with respect to insurance reimbursement and who will pay for testing.

Although not a pharmacogenomic association *per se*, another genetic association that may have implications for the treatment of unipolar depression is the well-studied gene-environment interaction between the promoter region of the serotonin transporter gene (5-HTTLPR) and stressful life events. In a large cohort, childhood abuse and stressful life events were associated with a high risk of becoming depressed in individuals with the short allele of the 5-HTTLPR, but had little effect on the development of depression among long allele homozygotes [44]. Further work stemming from this initial report suggests that the finding has more general implications in that this variant is likely not directly associated with depression, but that the 5-HTTLPR, together with polymorphisms in other genes such as BDNF and CRHR1 [45], are more broadly associated with personal dispositions that are more or less sensitive to environmental surroundings. In terms of treatment for depression, psychological therapy and antidepressant medications have, on average, comparable efficacy in unselected groups of patients diagnosed with depression. Importantly, however, the potential gene-environment interaction involving 5-HTTLPR suggests that individuals who are more sensitive to environmental stimuli may respond better to psychological treatments versus antidepressant medication [45,46]. Although this particular gene-environment interaction has been called into question in recent years [47], these findings illustrate the potential importance of further study of gene-environment interactions in other contexts, as well as the potential implications of such findings for disease treatment and prevention in psychiatry. Another issue particularly relevant for mental health conditions such as depression is that of placebo effects and the cyclical nature of the conditions themselves, which both have implications for drug and pharmacogenomic discovery in this particular disease area.

Predictive and Disease Susceptibility Testing

The clinical validity and utility of predictive testing for disease based on genetic information currently varies dramatically depending on the mode of inheritance of the disease, what is known about the specific genetic variants implicated, protective variants that may be important, as well as the degree of redundancy of genetic information with other traditional risk factors that are routinely, easily, and more inexpensively assessed clinically (e.g., family history of disease). For instance, work that has uncovered the genetic variations involved in diseases that are inherited according to simple Mendelian principles has led to the development and availability of predictive genetic tests that have nearly 100% accuracy. Thus, a decade after the Huntington's disease (HD) gene was mapped to chromosome 4, the pathogenic mutation was localized and identified as a CAG-repeat expansion [48] for which testing is now available to offspring of individuals with the disease. This predictive test has high reliability, validity, and clinical utility given the mode of inheritance of the disease and the fact that the causal mutation is known and can be measured. Furthermore, test results indicating the presence of the CAG-repeat provide information that is not redundant with standard clinical risk factors such as family history (i.e., one can have a family history and still not inherit HD), and therefore, has high clinical and personal utility.

Similarly, genetic linkage studies in families with hereditary breast, ovarian, and colon cancers have identified several important high penetrance genetic variants, which are now currently being used for screening, disease risk counseling, and preventive treatment programs for breast cancer [49]. For example, although breast cancer is a complex disease (i.e., non-Mendelian), the high penetrance susceptibility genetic variations identified, specifically variations in the BRCA1 and BRCA2 genes, confer a 50–80% chance of

developing breast cancer by age 70 [50]. Thus, a positive test result in this case provides critical additional information (beyond clinical risk factors) with respect to degree of disease risk. Furthermore, based on genetic test results, changes in surveillance practices (e.g., frequency of mammography) or even decisions as to whether to undergo prophylactic surgery to decrease risk are often recommended [51] by health care providers.

In contrast, susceptibility testing in the case of common, complex diseases for which no high penetrance risk variants have been identified is highly controversial (though currently performed in some contexts). As alluded to previously, it is likely that most complex diseases are caused by multiple environmental factors and multiple low penetrance common genetic factors, possibly together with rare variations that are yet to be identified. This is illustrated by the fact that most of the risk variants underlying complex diseases that have been identified through GWAS thus far have been characterized by effect sizes that are small, with odds ratios typically between 1.1 and 1.5. In addition, for most diseases, the variants identified explain little of the total genetic variance known from heritability estimates (Table 1). Nevertheless, work in this area continues in order to determine the feasibility of combining information from many small-effect risk variants in order to develop more complex algorithms that can accurately predict an individual's genetic risk for common, complex diseases [52], including risk for neuropsychiatric disease [53]. Early studies suggest, however, that while the use of combined genotypes of small-effect variants identified to date is informative, this approach does not necessarily confer improved risk predictions when compared with traditional clinical risk factors alone [54] as there is often much redundancy. Thus, this hinders, to some extent, broader-scale preventive efforts based on susceptibility testing for complex diseases using genomic information derived from GWAS.

Susceptibility testing using genomic information may also benefit from utilization of protective genetic variants; however, research to discover such variants is incomplete. For example, although much work is ongoing to identify variants associated with healthy aging, findings are controversial [55] and to our knowledge, broadly applicable algorithms to predict longevity that take into account the frequency of the phenotype have not been constructed. In addition, identification of genetic variants associated with protective traits such as optimism and resilience [56] may serve to further clarify risk predictions, particularly for neuropsychiatric disorders; however, to date there has been a lack of needed studies in this area.

Personal/Consumer Genomics

Although highly controversial [57], leveraging recent findings from GWAS together with high-throughput SNP genotyping technology, a number of companies [58–61] now offer commercially available tests that aim to calculate an individual's genetic risk for between 20–40 common, complex diseases using genome-wide genotyping. The purchase of these tests is ultimately initiated by consumers without the obligatory involvement of a health care provider [62]. Costs currently range from $100 to over $2,000 per individual depending on the specific test and the company from which the test is purchased. Neurological/ neuropsychiatric disorders which are represented across testing panels for the major personal genetic testing companies include Alzheimer's disease, multiple sclerosis, and amyotrophic lateral sclerosis.

This type of testing is hotly debated for the reasons cited above, as well as because of the small effect sizes of SNP variants identified from GWAS and the fact that these variants explain only a small fraction of the total genetic variance and only confer small increases in disease risk. Even so, personal genetic testing proponents argue that providing this type of information directly to consumers can empower them to take control of their health by

improving their compliance with health screening practices and by making more healthful lifestyle choices (i.e., make efforts to modify their disease risk). On the other hand, critics are concerned that there is a lack of research on how best to present this type of risk information to individual consumers to ensure adequate understanding of the results [63], as well as on how individual consumers are likely to respond to their results. Researchers focused on the ethical, legal, and social implications of such testing have noted that it is an open question as to whether this type of susceptibility testing would lead consumers to (a) make positive health behavior changes in response to their results; or (b) adopt more fatalistic attitudes and/or experience high levels of anxiety in response to estimates of high risk; or perhaps worse yet, (c) be falsely reassured by inaccurate or incomplete estimates of low risk. This becomes particularly problematic in light of recent evidence calling into question the consistency and accuracy of the risk estimates provided [64,65]. In fairness to genetic studies, however, it is important to emphasize that all clinical testing and health care guidance from physicians and other health care providers (e.g., routine blood chemistries) suffer from some degree of variability and inconsistency. Studies are ongoing, including our own Scripps Genomic Health Initiative (SGHI), to shed light on some of these issues, in particular the behavioral and psychological response to testing [66] and genomic risk disclosure.

Diagnosis, Prognosis, and Monitoring

In addition to DNA sequence-based testing, which is stable and does not change over the course of a person's lifetime, genomic biomarkers such as whole-genome gene expression are now starting to be used in diagnosis, prognosis, and monitoring of disease. Such transcriptomic, proteomic, and/or metabolomic profiles, combined with other testing and clinical factors may provide assistance in diagnosing individuals at the earliest possible subclinical stages of disease when preventive strategies can be employed and treatments are more effective, or after a diagnosis has been made but differentiation of disease subtype is needed to guide intervention and drug treatment plans. The use of such markers for diagnosis and subtype differentiation in neuropsychiatric disorders may be particularly useful given the difficulties often encountered in differential diagnosis.

There are some instances in which genomic biomarkers are currently being used in clinical care. For instance, whole-genome gene expression data are now being used routinely to identify subtypes of cancer, including new subclasses of tumors within acute myeloid leukemia [67], as well as distinguishing between Burkitt's lymphoma and diffuse B-cell lymphoma [68]. Moreover, in the clinical management of cancer, genomic signatures are even moving beyond classification and diagnosis and are further being used to predict prognosis and response to therapy. For example, gene expression signatures have been used to develop profiles that can predict prognosis in early-stage non-small-cell lung cancer [69], as well as predict sensitivity and response to individual chemotherapeutic drugs, which can help with monitoring and guide the use of these drugs alone and in combination with existing therapies [70,71]. Additional work with respect to disease monitoring has been in the use of gene expression in peripheral blood mononuclear cells for predicting graft rejection in the area of solid organ transplantation [72].

In many ways, cancer provides an ideal opportunity for the use of biomarkers such as those obtained from whole-genome gene expression data because the disease lesion usually resides in an accessible tissue (i.e., the tumor) that can be biopsied and measured directly. Generally, affected tissues in neuropsychiatric and other diseases that affect mental health (e.g., the brain) are less accessible and more difficult to measure in living patients, making the development of preventive and treatment opportunities based on such biomarkers difficult. The general strategy in regards to the development of biomarkers for neuropsychiatric disorders is to measure gene expression or other markers in surrogate

tissues, such as blood or cerebrospinal fluid. For example, artificial neural networks analysis of blood gene expression patterns was recently used to classify 52 antipsychotics-free schizophrenia patients and 49 controls with almost 88% accuracy [73], suggesting that blood-based gene expression may have utility as a diagnostic tool for schizophrenia. In addition, similar studies have been performed in Parkinson's disease [74], Huntington's disease [75], and Alzheimer's disease [76]; however to our knowledge, none of these expression profiles are currently being used clinically. Recently, studies of telomeres, which are DNA sequences at the ends of chromosomes that are thought to protect chromosomes from damage, have also been prominent in disorders of aging, and to some extent in neuropsychiatric disease. For instance leukocyte telomere length has been associated with many diseases and phenotypes, including risk of Alzheimer's disease, cognitive aging, cardiovascular disease, and post-stroke mortality [77].

Social, Economic, and Policy Issues for Genomic Medicine

As we have described thus far, there are significant scientific challenges that still need to be overcome for the vision of genomic and personalized medicine to become a reality, and this is true to an even greater degree for the area of mental health. In addition, however, it is important to consider other issues outside of genomic science that may be at play, such as social, economic, and policy issues.

Pharmaceutical, Biotechnology, and Insurance Companies

Early in the drug development process, pharmaceutical and biotechnology companies often use genomic and other biomarkers to aid in research and development; however, it is only in some cases that they develop these markers as commercially available companion diagnostics that can be used to identify a patient's likelihood of responding to a drug or experiencing an adverse event. Although there are a number of reasons for this and the process of drug development is complex, one primary reason is that there is often considerable risk in the development of such personalized medicine tests for a given drug since these tests can serve to divide the treatable patient population into subsegments, which can then decrease market share [78] and potential profits. Some research has suggested that companies are most likely to include companion diagnostics for "later-to-market" drugs that enter into crowded markets. For instance, if two drugs are already on the market and are relatively undifferentiated, the third drug on the market is likely to capture a relatively small market share. A companion diagnostic for the third drug, however, that identifies a segment of the patient population that will respond particularly well or experience fewer adverse events, could generate higher pricing and thus added value [79].

Similarly, although it has been widely predicted that personalized medicine will dramatically reduce health care costs, insurance companies have been reluctant to provide reimbursements for "personalized medicine tests." Several reasons have been put forth for this reluctance [78], including an inability to easily identify tests that truly reduce costs. Briefly, per patient savings (i.e., the difference between the cost of treating the disease and the cost of the treatment intervention indicated by the test), as well as the likelihood that a test suggests an intervention for any particular patient, are two primary factors that determine a test's cost-effectiveness. Tests that help to avoid the use of expensive therapies, minimize costly adverse events, or delay expensive procedures can be cost-effective; however, tests that only save a small amount per patient or that have a low probability of identifying patients requiring an intervention (e.g., testing all-comers for a rare disease) are not cost-effective. In addition, adoption is further complicated by the high customer turnover experienced by many insurance companies in the U.S., which is particularly salient in terms of reimbursement for prophylactic tests and preventive interventions. Specifically, this high-turnover makes it less economical for companies to reimburse for tests and interventions that

minimize the likelihood of conditions that will occur much later in life (i.e., when a customer may have switched their coverage to another company). Other concerns that have been expressed by payers include difficulties in enforcing standard protocols to ensure that physicians follow through with appropriate patient care based on test results, and also, potential misuse of test information (particularly in the early stages of development) in ways that could harm patients [78]. Further, companies are impacted by the fact that agencies like the U.S. FDA often struggle with what constitutes evidence that a drug should really only be given to a certain group of individuals. For instance, are restricted trials required or is retrospective data sufficient?

Clearly there are some instances in which there are incentives for both pharmaceutical/biotechnology and insurance companies to invest in personalized medicine; however, it is also apparent that there are a number of situations in which it is currently economically disadvantageous for them to do so. It is an open question as to whether these relevant "stakeholders" will be willing to work together and with regulatory bodies to reshape incentive structures.

Physicians and Legislation

Potential issues have also been raised regarding provider (e.g., physician) incentives/disincentives for adopting personalized medicine. In particular, there are concerns due to the fact that the current, procedure-based reimbursement system confers economic rewards to providers based on performing increasing numbers of procedures. As such, providers may be more likely to adopt personalized medicine tests that increase the number of procedures performed post-testing (e.g., they may be more likely to adopt genetic susceptibility testing for colon cancer if it might lead to more frequent colonoscopies for a given patient) [78]. Tests that ultimately decrease the likelihood of future procedures (or are neutral), however, may be less likely to be adopted. Another potential issue concerning physicians is reflected by recent findings that only one in 10 physicians felt he or she had the necessary training and knowledge in genomics [80] to provide adequate care in this area to their patients. Thus, lack of appropriate training and education in genomics may be a significant hindrance to adoption of personalized medicine tests as well, although, it is encouraging that there are some recent initiatives to bring about changes in this area [81].

In terms of legislative initiatives, there is evidence that personalized medicine is a priority healthcare issue for the U.S. (see Table 3). For instance, recent enactment of the Genetic Information Non-Discrimination Act (GINA) to ensure genetic privacy, the Health and Human Services Personalized Health Care Initiative to support research addressing individual aspects of disease prevention, and the Genomics and Personalized Medicine Act introduced in Congress, all suggest the support of many policy makers for personalized medicine [1]. In addition, it is notable that the Ethical, Legal, and Social Issues (ELSI) branch of genome science [82] was initiated specifically to deal with outcomes and "fall-out" from the Human Genome Project. There are few other areas of science where similar programs have been initiated for such reasons. However, more work is needed, especially to the extent that government-sponsored initiatives can encourage other relevant stakeholders (e.g., insurance companies) to work together to update existing policies.

Public Health Genomics

While the pace of genetic and genomic technology has been rapid, many have noted that the complementary work in behavioral and public health arenas needed to translate findings into clinical applications for disease treatment and prevention has lagged far behind [83]. One obvious reason for this is that there is much disagreement about whether genomic discovery is at a point where translation into clinical applications is appropriate (e.g., the controversial

"personal genetic testing" described previously). To begin to address this gap, in 2008 the National Human Genome Research Institute (NHGRI) convened a 2-day workshop that brought together a group of 50 scientists representing a broad range of disciplines including public health, communication, behavioral and social sciences, genetics, epidemiology, medicine, and public policy. When asked to recommend forward-looking priorities for translational research, the group identified three priority research areas, including (1) improving the public's "genetic literacy" in order to enhance consumer skills; (2) gauging whether genomic information improves risk communication and adoption of healthier behaviors more than current approaches and public health interventions; and (3) exploring whether genomic discovery in concert with emerging technologies can elucidate new behavioral intervention targets [83]. It is anticipated that these themes may help inform development of funding priorities, and this effort on the part of the NHGRI underscores the attention being given to and importance being placed on development of behavioral and public health efforts needed for translation of genomic discoveries.

Conclusions and Future Directions

We have reviewed the status of genomic scientific discovery, current applications of genomics for disease treatment and prevention, and relevant social, economic, and policy issues in genomics. Through this, we have attempted to highlight exciting areas where genetic and genomic discoveries are already being used in the clinic to improve health care, including mental health care (e.g., pharmacogenomics). We also, however, have tried to pinpoint where sizable gaps in the science exist that ultimately preclude additional clinical applications (e.g., lack of validity and utility of susceptibility testing for common, complex disease based on information derived from GWAS) and to suggest priority areas for further research (e.g., DNA sequencing in neuropsychiatric disease, public health genomics). We also note the important role of non-scientific issues (e.g., insurance reimbursement policies, level of physician education in the area of genomics) that will no doubt play a pivotal role in the speed with which genetics and genomics are, and continue to be, harnessed to bring about personalized medicine. In short, while the pace of genetic and genomic science, technology, and discovery has been rapid, more work is needed to fully realize the potential for impacting disease treatment and prevention generally, and mental health specifically.

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Glossary of Terms

Allele	an alternative form of a genetic variant
Autosomal dominant	a pattern of inheritance in which an affected individual has one copy of an abnormal allele and one normal allele on a pair of non-sex chromosomes
Autosomal recessive	a pattern of inheritance in which an affected individual has two copies of an abnormal allele on a pair of non-sex chromosomes
Biomarker	a substance used as an indicator of a biological state (e.g., DNA sequence, gene expression)

Copy number variant (CNV)	a DNA sequence of hundreds to thousands of base pairs that is present a variable number of times across individuals
Complex disorder	disorder with a genetic component, but without a clear-cut pattern of inheritance
DNA sequencing	refers to sequencing methods for measuring and determining the order of all the nucleotide bases in a molecule of DNA
Epigenomics	an emerging area of genomics that involves the study of changes in the regulation of gene activity and expression that are not dependent on gene sequence
Genomic medicine	the use of information from the genome to guide clinical decision making
Haplotype	a region of the genome on a given chromosome containing strongly correlated SNPs
Heritability	the proportion of phenotypic variation in a population that is attributable to genetic variation among individuals
Human Genome Project	a 13-year effort coordinated by the U.S. Department of Energy and the National Institutes of Health to identify all the approximately 20,000–25,000 genes in human DNA, determine the sequences of the 3 billion chemical base pairs that make up human DNA, store this information in databases, improve tools for data analysis, transfer related technologies to the private sector, and address the ethical, legal, and social issues that may arise from the project
International HapMap Project	a multi-country effort to identify and catalog genetic similarities and differences in human beings across individuals and populations and to identify chromosomal regions where genetic variants are shared
Linkage disequilibrium	the nonrandom association of alleles at two or more sites on the same chromosome
Mendelian disorder	disorder caused by a single gene defect, which tends to occur in either dominant or recessive inheritance patterns
Personal/consumer genomics	controversial genetic testing services in which internet-based companies provide, for a fee, information on an individual's genomic makeup and risk for 20–40 common, complex diseases with varying levels of detail and interpretation
Personalized medicine	a broad concept that refers to a model of health care emphasizing the use of each individual's unique clinical, genetic, genomic, and environmental information for disease prevention and treatment
Pharmacogenomics	the branch of pharmacology and genomics that deals with the influence of genetic variation on drug response in patients by correlating DNA sequence variants or other biomarkers with a drug's efficacy or toxicity
Public health genomics	the branch of genomics that studies and promotes the integration of genomics into public health research, policy, and

	practice in order to prevent disease and improve the health of all people
Single nucleotide polymorphism (SNP)	a site within the genome that differs by a single nucleotide base across different individuals
X-linked dominant	a pattern of inheritance by which a dominant allele is carried on the X-chromosome
X-linked recessive	a pattern of inheritance in which an allele on the X-chromosome causes the phenotype to be expressed (1) in males and (2) in females who are homozygous for the allele

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Table 1

Heritability estimates for chronic disorders of aging, aging phenotypes, and neuropsychiatric disorders

Disorder/Phenotype	Heritability Estimate	Reference
Obesity	0.77	[84,85]
Coronary Heart Disease	0.57	[86]
Type II Diabetes	0.64	[87]
Colorectal Cancer	0.35	[88]
Prostate Cancer	0.42	[88]
Breast Cancer	0.27	[88]
Alzheimer's Disease	0.74	[89]
Longevity	0.25	[17,18]
Schizophrenia	0.81	[90]
Bipolar Disorder	0.85	[19,20]
Unipolar Depression	0.37	[91,92]
Anxiety Disorders	0.32	[93,94]

Table 2

Select pharmacogenomic medication label updates by the Food and Drug Administration in the past 10 years

Genetic Variant	Medication	Rationale for Testing and Label Update
TPMT	Azathioprine/6-MP	Can identify individuals at increased risk for severe, life-threatening myelotoxicity.
UGT1A1	Irinotecan	Can identify individuals at increased risk of neutropenia.
CYP2C9 & VKORC1	Warfarin	Can more precisely identify appropriate initial doses for individuals in order to avoid well-known risks of minor and major bleeding.
HLA-B*1502	Carbamazepine	Can identify individuals at increased risk for potentially life-threatening dermatological side effects.
HLA-B*5701	Abacavir	Can identify individuals with increased risk of hypersensitivity reaction.
CYP2C19	Clopidogrel	Can identify individuals who are less responsive and may not receive full protection from heart

Data From References [35,37].

Table 3

Legislative acts and initiatives supporting genomic medicine

Legislative Acts/Initiatives	Description	Reference
Genetic Information Non- Discrimination Act (GINA)	Protects against discrimination based on genetic information regarding health insurance and employment.	[95]
HHS Personalized Health Care Initiative	Provide federal leadership supporting research addressing individual aspects of disease and disease prevention. Goal is to shape preventive and diagnostic care to match each person's unique genetic characteristics.	[96]
Genomics and Personalized Medicine Act	A bill to improve access to and appropriate utilization of valid, reliable and accurate molecular genetic tests by all populations.	[97]
Ethical, Legal, and Social Issues (ELSI) Research in Genomics	The U.S. Department of Energy (DOE) and the National Institutes of Health (NIH) devote 3% to 5% of their annual Human Genome Program budgets toward studying the ethical, legal, and social issues (ELSI) surrounding availability of genetic information. This represents the world's largest bioethics program.	[82]

Data from Reference [1].