Chapter 6
Pharmacogenomics

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Abstract Pharmacogenomics is a rapidly growing field dedicated to identifying genetic markers that will allow practitioners to identify safe and effective therapy that is tailored to the individual patient. As a result, pharmacogenomic testing has the potential to optimize drug therapy for a variety of disease states. The landmark Sequenced Treatment Alternatives to Relieve Depression trial, commonly known as the STAR*D trial, showed that only a disappointing 30 % of patients experience remission from depression symptoms with their initial trial of antidepressant therapy. Furthermore, other studies have shown that 70 % of patients not remitting after their first medication trial may endure symptoms for months before experiencing relief secondary to drug therapy. In the future it is hoped that advancing pharmacogenomics research will help identify the safest and most effective medication for each patient—not only for the treatment of depression but for other disease states as well. Currently pharmacogenomic testing is not widely implemented; however, this is likely to change as clinicians become increasingly familiar with this field. This chapter will familiarize clinicians with the field of pharmacogenomics by (1) building a simple understanding of how genetic variability can alter drug response, (2) discussing current approaches in pharmacogenomics research, (3) describing helpful resources for practitioners, (4) providing an overview of the clinical application of pharmacogenomics and the associated issue of reimbursement, and (5) reviewing opinions on the future of pharmacogenomics in the clinical setting.

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Pharmacogenomics is a rapidly growing field dedicated to identifying genetic markers that will allow practitioners to identify safe and effective drug therapy tailored to the individual patient. As such, pharmacogenomics is a key component of personalized medicine, which is a broad term encompassing preventative, diagnostic, and treatment strategies based on the molecular profile of the individual.

The potential for pharmacogenomics to make a significant impact on the practice of pharmacy is impressive. As an example, for those with depression, the landmark Sequenced Treatment Alternatives to Relieve Depression trial, commonly known as the STAR*D trial, showed that only a disappointing 30 % of patients experience remission from depression symptoms with their initial trial of antidepressant therapy [1, 2]. Furthermore, other studies have shown that 70 % of patients not remitting after their first medication trial may endure symptoms for months before experiencing relief secondary to drug therapy [3]. In the future it is hoped that advancing pharmacogenomics research will help identify the safest and most effective medication for each patient starting a new course of drug therapy. Patients, practitioners, and third-party payers would all be expected to benefit from the impressive amount of time, money, and frustration saved by eliminating this trial and error period.

Currently pharmacogenomics is not widely applied by clinicians; however, with the constant expansion of personalized medicine tailoring therapies and diagnostics to the individual, knowing when pharmacogenomics tests are appropriate, where to order them, and how to interpret and apply the results will be important tools for healthcare practitioners in the near future. The following chapter objectives are structured to familiarize clinicians with pharmacogenomics by (1) building a simple understanding of how genetic variability can alter drug response, (2) discussing current approaches in pharmacogenomics research, (3) describing helpful resources for practitioners, (4) providing an overview of the clinical application of pharmacogenomics and the associated issue of reimbursement, and (5) reviewing opinions on the future of pharmacogenomics in the clinical setting.

6.1 Objective 1: Genetic Variability and Drug Response

Interindividual variation in the DNA sequence occurs approximately once every 300 base pairs, or in roughly ten million locations [4]. By far the most common source of genetic variation, and the source of the above estimate, refers to single-nucleotide polymorphisms (SNPs), commonly referred to as “snips.”

SNPs occur when one of the four DNA base pairs (adenine [A], cytosine [C], thymine [T], or guanine [G]) is substituted for another. In pharmacogenomics literature, SNPs are often designated by their position on the gene of interest and include some indication of the more common base pair, for example, 109T>C or T109C. In this instance the SNP occurs at position 109 on the gene, and the most common

nucleotide found is thymine, followed by cytosine. Therefore, 109T and 109C are different variants of this fictional gene and may occur on one or both alleles (or stands of DNA). In some situations, sets of SNPs that are inherited together due to close proximity on the DNA strand are studied as a group, or haplotype.

Another mechanism of genetic variation that has demonstrated importance in drug response is called a copy number variant (CNV). This type of mutation is observed when large sections of DNA are repeated (or deleted altogether) in an individual's genome. Whereas SNPs are estimated to occur at roughly ten million locations on the human genome, far fewer regions of variable copy number have been identified [4, 5]. In a 2006 analysis of 270 individuals, only 1447 regions of variable copy number greater than 1 thousand base pairs were identified [5]. The estimated occurrence of CNVs per individual has been quoted at anywhere from 11 to 140 [6].

The presence of an SNP or CNV alone is not enough to confer impact on clinical outcome with respect to drug response. In fact, the vast majority of SNPs and CNVs likely have no impact on pharmacogenomics. As illustrated in the upcoming examples of pharmacogenomics research, genetic variants that are most likely to impact drug response often have one of the following characteristics: they change the activity of enzymes important for medication metabolism, they occur in a site important to the mechanism of action (such as in the binding pocket of a drug target or a change in the promoter region of the gene that regulates expression), or they impact a medication's side effect profile. The outcomes that are measured and assumed to be due to genetic variability are called phenotypes. Phenotypes are a reflection of the impact of a person's genotype. Common phenotypes in pharmacogenomic studies include treatment response, tolerability, side effects, and drug pharmacokinetics.

An additional consideration unique to pharmacogenomics research is variant frequency. Genetic variants often differ in occurrence by ethnicity, and for a study to be feasible with respect to participant size, a variant typically needs to be present in at least 5 % of the general population. Otherwise, the number of study participants necessary to show a statistically significant impact becomes unattainable for many investigators (in the thousands depending on expected clinical impact). Examples of methods used in pharmacogenomics research to detect and analyze SNPs, haplotypes, and CNVs will be discussed in more detail in the following section.

6.2 Objective 2: Current Approaches in Pharmacogenomic Research

6.2.1 Targeted Genotyping

The targeted genotyping method is employed when a predetermined SNP is linked to a disease or drug response phenotype. Identification of candidate genes is particularly useful when disease pathophysiology or drug mechanism of action is known. Often for these studies, one or more genes are sequenced, and a few SNPs are examined in relation to the identified phenotype.

An example of utilizing a candidate gene approach in pharmacogenomics of mental health is defining the mechanism of antidepressant-associated sexual dysfunction (SD). Sexual dysfunction is a frequently described side effect of antidepressants, specifically those associated with the serotonergic pathway [7]. Selective serotonin reuptake inhibitors (SSRIs) are first-line agents for the treatment of depression but have a reported SD rate that approaches 40 % [8]. Males typically describe a decrease in desire and ability to achieve orgasm, while females report a decrease in arousal that is attributed to SSRI use. As a result of SD, clinicians report decreased compliance with antidepressant treatment [9]. Most research on SSRI-associated SD has focused on the *5-HTTLPR* variant, which is a 44 base pair insertion/deletion in the promoter of the gene *SLC6A4* [10, 11]. This gene encodes a serotonin transporter 5-HTT and, due to its involvement in the serotonergic pathway, is a logical gene to interrogate by the candidate gene approach in this population. Upon sequencing the *SLC6A4* loci, analysis showed that the longer *5-HTTLPR* variant (44 bp insertion present) is associated with greater SSRI efficacy; however, the long allele is also associated with greater SD in carriers [12–15]. Clinically, we may find that although homozygous carriers of the long *5-HTTLPR* variant respond well to antidepressant therapy, compliance may become an issue as the patient is likely to experience SD [11, 16].

6.2.2 Genome-Wide Association Studies (GWAS)

The majority of pharmacogenomics research has generally focused on genes related to drug metabolism. However, as sequencing technology improves along with our understanding of disease pathophysiology, we find a greater need to understand additional pathways that may determine treatment response. GWAS uses array chip technology to associate specific phenotypes with genetic variants, or SNPs, across the entire genome [17]. Unlike candidate gene studies, the GWAS method does not require prior knowledge of the pathophysiology of the disease state and has the potential to identify novel candidate variants.

GWAS design requires several elements. DNA is required from a large phenotypically relevant population in addition to the ability to detect polymorphic alleles that can be genotyped and have adequate coverage of the genome [18]. Importantly, GWAS also requires rigorous statistical methodology to determine genetic associations [19]. For many recent GWA studies, the few common associated SNPs show a small effect size and explain small portions of genetic risk [20]. Aside from monogenic diseases, or an inherited disease controlled by a single pair of genes, the genetic cause of more complex disease may need to consider a graded quantitative genetic risk that includes the involvement of high-risk and low-risk genes. In many cases, researchers feel that current GWAS methods are only the first step in the identification of target genes [21]. Additionally GWAS investigations can examine the accumulation of gene variants in a specific network that may result in complex disease.

Genome-wide association studies have been widely utilized to identify target genes responsible for varying treatment response phenotypes in psychiatric medicine. The STAR*D trial, previously mentioned, provided the largest cohort of DNA from patients with major depressive disorder (MDD) [2]. One of STAR*D's goals was to determine the effectiveness of alternate therapies for patients who were nonresponders to initial antidepressant treatment, and a genetic portion of the trial examined how differences in patient response may be explained in part by pharmacogenetics [22].

To do this, researchers examined DNA sequences from 68 suspect genes collected from 1297 STAR*D participants, comparing those who responded to treatment with citalopram as opposed to nonresponders [23]. This initial analysis established a response relationship with a variant of the *HT2RA* gene (rs7997012), which is a serotonin receptor. A later analysis of the STAR*D trial expanded the population to include 1816 patients and duplicated the analysis between the citalopram responders and nonresponders [24]. This study reproduced the previous association with the *HT2RA* variant and treatment response but additionally found an association of the *GRIK4* gene variant (rs1954787) with the higher likelihood of treatment response. This was the first report that highlighted the role of *GRIK4,* a glutamate receptor, in the pathogenesis and treatment outcome of MDD.

6.2.3 Whole-Exome Sequencing (WES)

Out of the approximate three billion base pairs that configure the human genome, only 1 % of this sequence actually translates into protein [25]. An exon is the protein-coding portion of the gene and the exome consists of all the genome's exons. Therefore, whole-exome sequencing is a technique in which genomic DNA binds to a predefined target of sequences that correspond to the protein-coding portion of the genome. As next-generation sequencing platforms become cheaper and more available, it is now possible to cost-effectively target variation in the coding portion of the genome [26]. The obvious drawbacks to WES are that structural changes and intergenic and promoter sequences that may influence gene transcription or splice variants will be excluded from analysis. Additionally, our current understanding of the genome limits our analysis as parts of the genome not currently recognized as translatable will not be interrogated by this method [27]. Despite these limitations, WES has been shown to be highly effective at identifying high-penetrance exonic mutations causing disease.

Much like the GWAS STAR*D trial, which examined the genetics of nonresponders to SSRIs, WES has also been employed to investigate pharmacogenomics of antidepressant treatment. Wong and colleagues compared the effectiveness of fluoxetine and desipramine therapy in a prospective pharmacogenetic study in first-generation Mexican Americans to identify specific SNPs that correlated with treatment response [28]. Although the study showed that fluoxetine was generally more effective after 8 weeks of treatment, whole-exome sequencing was performed for 36 treatment responders and 29 subjects who did not respond to treatment.

Pharmacogenetic analysis showed that exm-rs1321744 achieved significance for the treatment remission group. Interestingly, the location of the variant suggests an epigenetic function, as it's situated in a brain-methylated DNA immunoprecipitation sequencing site, which further implicates its functional role in antidepressant treatment response.

6.2.4 Whole-Genome Sequencing

Most loci identified by genome-wide association analysis do not result in amino acid substitutions in proteins or may not even locate to an exome sequence [29]. Instead, these mutations can potentially alter gene expression and translational activity or affect gene splicing. Current array-based methodologies such as WES identify common allele variants in a population, but these may only have minor effects on phenotype or have variable penetrance due to epigenetic confounders. Whole-genome sequencing offers the most comprehensive picture of an individual's genome by providing both uncommon variant sequence data as well as structural data. As the cost of genome sequencing continues to decrease, experts predict a shift from array-based technologies to whole-genome sequencing approaches [30]. Whole-genome sequencing analysis requires redundant sequencing of millions of short DNA fragments [31]. Construction of the genome can be performed de novo but is more commonly done with the aid of the reference genome. The most important element of whole-genome sequencing is the quality of the genome assembly defined by the assembly and alignment algorithms.

Whole-genome sequencing is now employed to identify variants in pharmacogenomic biomarkers for commonly prescribed drugs [32]. Mizzi and colleagues analyzed whole-genome sequences from 482 unrelated individuals of mixed ethnic backgrounds. Analysis revealed over 400,000 variants in 231 pharmacogenes associated with the absorption, distribution, metabolism, excretion, and toxicity (ADMET) of several drugs. Of these variants, 26,807 were in exon sequences and regulatory regions, whereas 16,487 were previously undetected. Interestingly, when authors focused their analysis on defined pharmacogenes, *CYP2D6*, *CYPC9*, *VKORC1*, *UGT1A1*, and *TPMT*, 11 novel exonic variants were revealed that reached a frequency of over 1 %. These data emphasize the potential of whole-genome sequencing to capture several novel and potentially important ADMET-associated variants in patients.

6.2.5 Copy Number Variant

In addition to identifying sequence changes in the genetic code, current genomic research also focuses on structural changes in genetic representation of genes (duplications, deletions) such as copy number variations (CNVs) [5, 6]. When CNVs are at least 1 kb in length, vary from the reference genome, and are identified

in a population at a frequency of at least 1 %, they are called copy number polymorphisms (CNPs) [5, 33]. CNVs are common in the human population, affect about 15 % of the genome, and are likely to result in the change of expression levels of genes in or close to the effected regions [34]. With specific regard to psychiatric illness, CNVs have been shown to contribute to conditions such as Alzheimer's disease, schizophrenia, and autism [35–37].

CYP2D6 is a highly polymorphic gene that encodes an enzyme responsible for metabolizing 25 % of currently used drugs [38]. Included in this list of substrates are SSRIs, tricyclic antidepressants, and some antipsychotics. To date there are 75 individual variant *CYP2D6* alleles documented in the Human Cytochrome P450 Allele Nomenclature Database (http://www.cypalleles.ki.se), which include those with normal, reduced, and nonfunctional enzymatic activity levels resulting from different combinations of SNPs. In addition to SNPs, CNVs of *CYP2D6* wild-type and variant alleles have been observed resulting in increased expression levels of this enzyme in vivo [39]. Carriers of multiple functional alleles of *CYP2D6* can result in rapid metabolization of substrates, and standard dosing recommendations for *CYP2D6*-metabolized medications may not suffice.

6.3 Objective 3: Pharmacogenomics Resources

There are a multitude of online resources available regarding the research and clinical implementation of pharmacogenetics.

6.3.1 HapMap Project

The HapMap Project (www.hapmap.org) is an international collaboration of scientists and different funding agencies that have developed a haplotype map of the human genome. This resource is designed to describe common patterns of DNA sequence variations, where they occur on the chromosome, and how they are distributed in different populations. These data are devised to be a resource for researchers to identify genes affecting disease, drug response, and environmental health.

6.3.2 The 1000 Genomes Project

The goal of The 1000 Genomes Project (www.1000genomes.org/) is to discover and locate genetic variants that have frequencies of at least 1 % in various populations. Although the title stipulates 1000 genomes, the project intends to combine the light sequencing (4× coverage) data from a total of 2500 genomes to provide an accurate picture of estimated variants and genotypes that were not sequenced directly. This

project was designed with the intent that individual researchers will utilize the 1000 Genomes dataset to expand their personal data to include millions of additional variants beyond those genotyped directly by the investigator. This process is entirely computational and requires no genotyping cost. The additional genotype data allows investigators to localize phenotype-associated loci and target associated genes more precisely.

6.3.3 The Psychiatric GWAS Consortium (PGC)

The PGC (http://www.med.unc.edu/pgc) is the largest psychiatric consortium that serves as a repository for the genome-wide genetic data for over 170,000 subjects submitted by over 500 investigators from at least 80 institutions. As discussed earlier, GWAS data analysis requires large sample sizes to identify robust genetic associations, and obtaining this data for investigators can be a challenge. The PCG repository of genetic data can be used by individual investigators to conduct mega-analysis of gene associations of psychiatric disorders. Initially, analysis was focused on autism, attention-deficit hyperactivity disorder, bipolar disorder, major depressive disorder, and schizophrenia but has expanded to encompass other disorders in addition to CNV analysis.

PGC is also involved in the Psych Chip project where they are conducting new genotyping of large numbers of new cases and controls. To accomplish this, the Infinium® PsychArray BeadChip from Illumina (http://products.illumina.com/) was developed in collaboration with the PCG in order to evaluate genetic variants associated with common psychiatric disorders. The PsychArray BeadChip, or the Psych Chip, is a SNP array that contains 250,000 exome variants selected by the PGC, high-density sequencing coverage of loci associated with psychiatric illness, and genome-wide common variants that allow comparison to other GWAS studies.

6.3.4 PharmGKB

PharmGKB (www.pharmgkb.org) is a knowledge base and resource center that contains and disseminates clinical information about pharmacogenomics and drug response. In 2009, a collaboration between PharmGKB and Pharmacogenomics Research Network (PRN) created the Clinical Pharmacogenetics Implementation Consortium (CPIC). The purpose of CPIC is to develop clinical guidelines from the interpretation of rigorous laboratory genetic testing into applicable instructions for clinicians to implement pharmacogenetic information into practice. Guidelines can either focus on specific genes or drugs and encompass directions on how to assign phenotypes to genotypes in addition to drug-specific prescribing recommendations. CPIC guidelines are published in peer-reviewed journals and are periodically updated with supplemental data; these guidelines and additional resources are located on the CPIC webpage (http://www.pharmgkb.org/page/cpic).

6.4 Objective 4: Current Clinical Applications of Pharmacogenomics and Reimbursement

As discussed in objective 3, there are multiple resources that provide dosing recommendations for psychiatric medications based on genetic profile, but there is very little guidance on when to order a genetic test. The following examples will address this knowledge gap by illustrating how providers are currently employing pharmacogenomics in a clinical setting. Additional considerations, such as the quality control regulation of laboratories that offer genetic testing, and the issue of insurance reimbursement will also be discussed.

At this time, the mood stabilizer carbamazepine is the only medication used in psychiatric medicine that includes a labeling recommendation to obtain genetic testing prior to use in individuals of Asian ancestry [40]. This recommendation was added to the product packaging label based on research showing that patients of East Asian descent were at an increased risk of developing a serious, potentially life-threatening rash when taking carbamazepine [41]. At least 5 % of this risk was attributed to carrying a particular variant of the human leukocyte antigen allele: HLA-B*1502 [42]. This allele is present at a much greater frequency in East Asians (10–15 %), as compared to those of Japanese or Korean (<1 %) descent [43]. This situation provides a fairly straightforward example of when SNPs distant from the site of a medication's mechanism of action significantly impact a drug's side effect profile.

Outside of this recommendation for carbamazepine, how do healthcare providers know when to order genetic testing to guide drug therapy? Many would consider the following two situations: (1) for patients being treated with medication for a new indication in order to avoid multiple medication trials and (2) for patients who are refractory to treatment with a particular medication for the dual purpose of determining the cause of suboptimal treatment response and assisting with the selection of a different medication. A common focus of genetic tests offered by commercial laboratories to improve medication use is the analysis of drug metabolizing enzyme activity, most often enzymes within the cytochrome P450 family.

As part of the genetic testing process, samples (usually blood or saliva) are sent to laboratories where the DNA is sequenced and analyzed for the presence of multiple SNPs and CNVs that have been associated with variable drug response in pharmacogenomics studies. The results of these assays are then interpreted to classify the genotyped individual as a poor, intermediate, extensive, or ultrarapid metabolizer of medications metabolized by the tested enzyme. In this classification system, extensive metabolizers are considered to have an average level of metabolizing capacity, while poor and intermediate metabolizers have a lower metabolic capacity. Poor or intermediate metabolizers typically have higher plasma concentrations of substrate medications, experience more side effects, and require lower-than-normal doses. Alternatively, ultrarapid metabolizers have higher-than-normal enzyme activity resulting in reduced efficacy; these patients may require higher-than-average doses of drugs metabolized by the tested enzyme.

After classifying the metabolizing status of each tested enzyme, a report will typically be sent to the ordering healthcare professional that describes the dosing recommendations made by organizations such as CPIC or the Dutch Pharmacogenetics Working Group [44, 45]. Consider the following example situation: you just diagnosed a 45-year-old woman with depression. This is her first diagnosed episode, and her comorbid conditions include migraines and chronic back pain. She tells you that her sister has had depression for the past several years and that she is still struggling to find a medication that works well for her. She is worried this will happen to her so you broach the topic of pharmacogenomics and she agrees to genetic testing.

The test results return and you note that her CYP2D6 status is classified as extensive (or normal), but that her CYP2C19 status is classified as poor. Your first impression was to select nortriptyline to simultaneously target her migraine, mood, and pain symptoms, but you know that this medication is metabolized in part by CYP2C19. You refer to the report and read that CPIC recommends considering a 50 % reduction in the recommended starting nortriptyline dose in patients with this genetic profile and to utilize therapeutic drug monitoring to guide dose adjustments [46]. In this situation, pharmacogenomic testing alerted a practitioner to initiate and titrate treatment more cautiously than standard recommendations dictate. Additionally, the provider is now aware that medications the patient may take in the future which are metabolized by CYP2C19, such as diazepam, may be present in higher-than-average plasma concentrations, and lower starting doses may be prudent.

Like TDM for lithium, genetic testing can be a helpful tool to improve medication use when it is implemented correctly. Unlike lithium TDM, genetic tests do not need to be repeated unless new variants are found to impact the response of medications your patient is currently receiving or plans to receive in the future. Another dissimilarity between pharmacogenomics tests and the majority of labs used in healthcare decisions (such as lipid and blood glucose screening) is that the provider has to select the lab that will perform the pharmacogenomic testing. In most cases, clinicians cannot simply write an order for pharmacogenomics testing and instruct the patient to visit the genetic test retailer nearest them.

This leads to the question: how do you select a pharmacogenomics laboratory to sequence your patient's DNA, and who is regulating these tests? The Food and Drug Administration (FDA) has the authority to regulate the clinical validity of pharmacogenomics tests. However, so far the FDA has only exercised this authority over genetic tests sold as kits [47]. Therefore, clinicians may wish to refer to resources such as PharmGKB for current literature and guideline summaries prior to determining how applicable specific test results may be to their patient. The Centers for Medicare and Medicaid Services (CMS) also regulates laboratory testing through the Clinical Laboratory Improvement Amendments (CLIA) [48]. CLIA certification is focused on analytical validity and the overall quality of laboratory practices [49]. Practitioners planning to order genetic tests may wish to consider selecting facilities that have CLIA certification because it ensures that an independent body has approved their employees' training and analytical laboratory quality.

CLIA certification is also necessary for reimbursement from Medicare and Medicaid [48]. Currently there are very few pharmacogenomics tests that are covered by insurance. As noted in a detailed review of pharmacogenomic reimbursement, Milligan stated that private third-party payers tend to take cues from Medicare with respect to what tests should be covered [50]. Pharmacogenomics tests for many medications are not covered because they are considered experimental and lack established clinical value [51]. However, as time progresses the costs of these tests will decrease, and the body of evidence supporting the relationship between genetic variation and drug response will accumulate. It is reasonable to predict that personalized drug prescribing will be a cost effective, reimbursable means of improving drug response in the future.

6.5 Objective 5: Future of Pharmacogenomics

Several issues complicate the widespread adoption of genetic testing in psychiatric pharmacy. As noted in many reviews, there is an absence of large, prospective randomized clinical trials comparing the cost and outcomes of patients treated with or without pharmacogenomics-based medication algorithms in the field of mental health. Some speculate that a large-scale study necessary to prove the cost/benefits analysis of pharmacogenomics within the mental health arena will never be attempted due to unacceptably high costs [52].

In 2009, a retrospective analysis of the STAR*D trial attempted to assess whether the benefits of pharmacogenomics testing outweighed the costs [53]. For this study, the author used genotype data from one SNP in a serotonin gene that was previously associated with citalopram response in combination with a rather complex cost analysis assessment that assumed that patients entered treatment at age 40 and were followed over the course of their lifetime [23, 53]. The authors concluded that the genetic testing for this one SNP was not cost effective [53]. However, the authors did state that incorporating multiple genetic variants into a cost-benefit analysis might improve the predictive power of a pharmacogenomics test and push the cost-benefit analysis in favor of testing [53].

This comment leads to several important considerations regarding the future of pharmacogenomics testing. First, like any new technology, the cost of running sequencing assays is steadily decreasing. Costs are already below $100 for the reagents used to analyze about 500,000 SNPs [52]. Furthermore, it is highly likely that incorporating more loci of genetic variability will improve the predictive power of pharmacogenomics.

No discussion of pharmacogenomics would be complete without addressing the ethical issues associated with collecting and storing DNA. Patient uncertainty regarding the use and confidentiality of collected DNA may become a substantial barrier to the widespread adoption of genetic testing once reimbursement is no longer an issue. In the research setting, patient rights are protected via a detailed informed consent process, which informs individuals that they are surrendering

their DNA for current and future genetic testing. Alternatively, "tiered" approaches to genetic research are being used where patients can consent to have their DNA studied for the current trial in which they are participating but decline consent for future research [54].

When genetic information is used for diagnosis or treatment decisions, there is concern that test results could be used to discriminate against individuals when they seek future employment or health insurance. The United States enacted a law in 2008 to protect individuals from this type of discrimination. It is called the Genetic Information Nondiscrimination Act (GINA). GINA contains two parts that expressly prohibit health insurance providers from using genetic information to make eligibility or coverage decisions. In addition, GINA forbids employers from making employment decisions based on an individual's genetic profile [55]. There are a few uncovered groups in this act, such as those serving in the military or those working for employers with less than 15 employees. Furthermore, GINA does not apply to any other insurance type, such as life or disability insurance.

6.6 Conclusion

As the cost of genetic testing decreases and evidence supporting the utility of pharmacogenomics in drug prescribing continues to grow, it will be increasingly important for clinicians to understand the resources available to them for interpreting the quality and relevance of pharmacogenomic test results. This chapter was designed to provide an introduction to the application of pharmacogenomics in the mental health field. The interested reader is referred to the websites discussed throughout the chapter and those listed here:

1. PharmGKB: www.pharmgkb.org
2. CPIC dosing guidelines: http://www.pharmgkb.org/page/cpic
3. 1000 Genomes: www.1000genomes.org/
4. The Psychiatric GWAS Consortium: http://www.med.unc.edu/pgc
5. HapMap Project: www.hapmap.org
6. Dutch Pharmacogenetics Working Group: http://www.pharmgkb.org/page/dpwg
7. CLIA lab certification: http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/
8. GINA: http://www.genome.gov/24519851

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