

# Personalized Medicine, Pharmacogenomics, and the Practice of Psychiatry: On the Threshold of Predictive Therapeutics in Psychopharmacology?

By Stephen M. Stahl, MD, PhD

## NEW TREND IN PSYCHOPHARMACOLOGY

Personalizing medicine by understanding the unique properties of each patient's genome has the potential of predicting what drug to prescribe for that individual. This approach has already proven useful for several drugs in medicine and promises to become a strategy for selection of therapeutics in psychiatry soon. Understanding some of the key concepts, strategies, and advances in the field of pharmacogenomics can set the stage for adapting emerging findings to the practice of psychopharmacology.

## WHAT IS PHARMACOGENETICS, OR IS IT PHARMACOGENOMICS?

Some key terms in this field are defined in Table 1.<sup>1,2</sup> DNA polymorphisms are the unique changes in DNA sequence that are considered to be the mediators of variations in drug response to treatment, susceptibility to disease, and other differences among individuals. Single nucleotide polymorphisms (SNPs) are the most common type of DNA variation, and are intensely investigated as causes of variations in drug responsiveness among individuals (Table 1).<sup>1-3</sup>

**TABLE 1.**  
**Key Terms<sup>1,2</sup>**

<i>Term</i>	<i>Definition</i>
DNA	Nucleic acids that store genetic "blueprints;" there are 3 billion pairs of nucleotide bases in the human genome
Gene	Region of DNA sequence; regulates and/or translates into function; heritable; estimated $\geq 10,000$ genes on 23 pairs of chromosomes in humans
Allele	One of the variant forms of a gene (at a particular position or locus)
Genotype	The genetic makeup of an individual; the set of alleles for a given trait
Genome	The set of genotypes for all genes of an individual; genome is >99% identical between individuals
DNA polymorphism	A common variation in the DNA sequence among individuals; some variations are responsible for individual characteristics, such as susceptibility to disease and response to drug treatment
SNP	Most common type of DNA variation; occurs every 100–300 nucleotides

SNP=single nucleotide polymorphism.

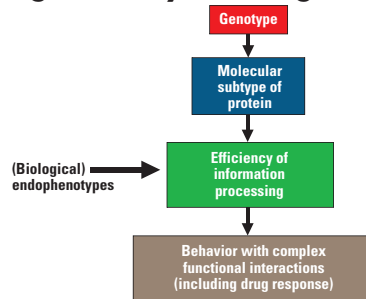
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**FIGURE 1.<sup>3</sup>**  
**Pharmacogenetics: how relevant are your genes to your drug response?**



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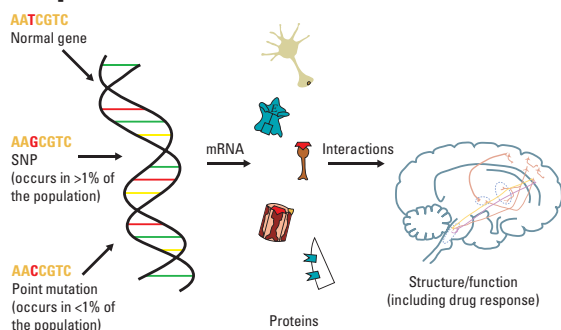
**TABLE 2.**  
**Key Strategies**

Pharmacogenetics	Linking one (or several) predetermined SNPs to a given function, especially to drug response (likelihood that a drug has efficacy or that a drug has side effects)
Pharmacogenomics	Analyzing whole genomes for functional correlations (especially to drug response); genome-wide association

SNP=single nucleotide polymorphism.

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**FIGURE 2.**  
**Where does a SNP fit into drug response?**



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Figure 1 attempts to show the link between a gene and drug response.<sup>3</sup> Therefore, the specific type of gene that an individual expresses will dictate the molecular subtype of protein that gene expresses. Depending upon subtle molecular variations in that protein (eg, for an enzyme, receptor, or growth factor), this hypothetically alters the efficiency of information processing in brain circuits and, thus, dictates differences in behaviors mediated by those circuits.<sup>3</sup> Changing neurotransmission at these circuits with drugs acting by specific mechanisms may have different functional interactions within these circuits; this can theoretically determine whether the drug alters information

**TABLE 3.**  
**Examples of Pharmacogenomics in Medicine**

**Warfarin**

- Warfarin's mechanism of anticoagulant action is inhibition of the enzyme that recycles vitamin K (VKORC1)
- 60% of anticoagulant drug response to warfarin depends upon which genetic variant a patient has for VKORC1 and also for CYP 2C9
- FDA highlights the use of tests for these genetic variants to predict reasonable (and thus safe as well as effective) doses of warfarin for individual patients

**Pertuzumab (Herceptin)**

- Pertuzumab is the humanized monoclonal antibody to the human epidermal growth factor receptor or HER2 and its mechanism of anti-cancer action is to bind to HER2/neu receptor to reduce tumor growth
- HER2 overexpression predicts poor disease outcome for breast cancer and pertuzumab reduces relapse and mortality in HER2 positive tumors but no benefits for HER2 positive tumors
- FDA recommends drug use only for patients whose tumors are HER2 positive (30% to 40% of all breast cancers) to avoid unnecessary exposure to cardiac toxicity and unnecessary expense in patients destined not to respond

**Imatinib (Gleevec)**

- Imatinib targets gene expressed in a subset of patients with CML positive for the Philadelphia chromosome by turning off the cancer-causing protein signal (BCR-ABL) in these patients
- FDA recommends drug use only for these patients to avoid risk of cardiac toxicities and unnecessary expense in patients destined not to respond

VKORC1=Vitamin K epoxide reductase complex 1; CYP=cytochrome P450; FDA=Food and Drug Administration; HER2=human epidermal growth factor receptor; HER2/neu=erbB2 (v-erb-b2 erythroblastic leukemia viral oncogene homolog 2); CML=chronic myelogenous leukemia; BCR-ABL=Philadelphia chromosome.

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processing there and, subsequently, whether it works to reduce symptoms.<sup>1-3</sup>

Although some experts use the terms “pharmacogenetics” and “pharmacogenomics” interchangeably, many consider pharmacogenetics to be the study of specific SNPs at specific genes with known functions that could plausibly be linked to drug response, whereas pharmacogenomics scans the whole human genome to find SNPs empirically associated with a drug response, without necessarily knowing the function of the SNP (Table 2).<sup>1,2</sup> Pharmacogenetics tests SNPs identified in advance, such as those linked to various neurotransmitters, receptors, or growth factors, whereas pharmacogenomics scans the entire genome to determine SNPs that are associated

with drug response and often identifies genes whose functions are not known or would not have been predicted in advance to be linked to drug response.

In either case, SNPs (on the left in Figure 2) alter protein synthesis by making subtle molecular changes in the amino acid sequence of these proteins (middle of Figure 2), hypothetically leading to changes within brain circuits that alter function, including causing symptoms of psychiatric disorders.<sup>3</sup> SNPs may also determine whether these circuits will respond to specific drugs by determining the capability of various molecular targets within specific brain circuits to alter the efficiency of information processing and thereby reduce psychiatric symptoms (on the right in Figure 2; Figure 1).

**TABLE 4.**  
**Key Challenges to Pharmacogenomics in Psychiatry**

**Lack of Data**

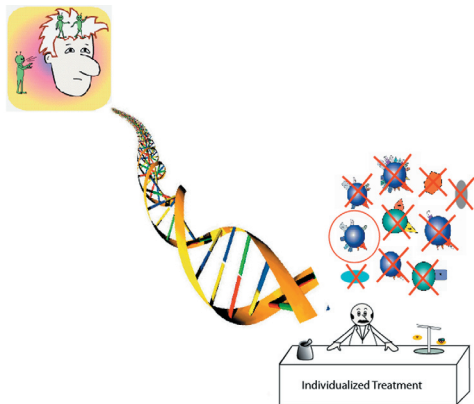
- Need to confirm preliminary results
- Need to evaluate usefulness of implementation in clinical practice settings

**Limited Catalogue of Functional Variants**

- Non-genetic heterogeneity in drug response may confound the role of genetic heterogeneity (eg, age, smoking, compliance)

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**FIGURE 3.**  
**Can pharmacogenetics do this in psychiatry?...**



(...Not yet)

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**CONCLUSION**

**Status of Pharmacogenomics in Medicine Today**

Several examples exist where knowing which genetic variant of specific genes that a

**TABLE 5.**  
**Promising Leads in Psychopharmacology**

<i>Genetic Variant</i>	<i>Functional Drug Response</i>
CYP 2D6	Codeine: ultrarapid metabolizers, rapid conversion to morphine, more side effects Nortriptyline: slow metabolizers, more toxicity at lower doses
Apo-E4	Good predictor of Alzheimer's risk, but no link yet to drug response
5-HT transporter	Might predict antidepressant response?
COMT	Might predict cognitive responses to some drugs?
5-HT <sub>2A</sub> receptor	Might predict adverse effects to some antidepressants?
D <sub>2</sub> receptor	Link to antipsychotic response?
Multigene approach	High potential clinical utility as pharmacogenomic strategy in psychopharmacology; five specific genes preliminarily linked to response to the novel antipsychotic iloperidone <sup>8</sup>

CYP=cytochrome P450; Apo-E4=Apolipoprotein E 4; 5-HT=serotonin; COMT=catechol-O-methyl transferase; D<sub>2</sub>=dopamine.

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patient expresses will dictate either the dose of a drug to be given (eg, warfarin) or whether the drug will work or not (eg, pertuzumab and imatinib chemotherapies) (Table 3).<sup>1,4</sup> What about psychiatry? Can pharmacogenomics lead to individualized treatments for psychiatric disorders (Figure 3)? Some of the key challenges to implementing clinically useful pharmacogenomics in psychiatry today are listed in Table 4 and include the fact that there are generally only preliminary and unconfirmed results for many specific genes with hypothesized links to drug response (Table 5).<sup>5-8</sup> However, the promising leads shown in Table 5, coupled with proven advances in other fields (Table 3) pave the way for psychiatry. Soon there may be clinically applicable pharmacogenomic markers for psychopharmacologic management.

The key question we want answered is: "Does testing for genetic polymorphisms in subjects undergoing psychiatric drug treatment lead to improvement in outcome, or are

testing results useful in medical, personal, or public health decision making?"<sup>1</sup> When that answer is "yes," pharmacogenomics will come of age in psychiatry. Until then, stay tuned and stay informed. **CNS**

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