

# Pharmacovigilance Nugget

## Pharmacogenomics: A Pathway to Personalized Treatment and Therapy

The term pharmacogenomics refers to the study of variations of DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) characteristics as related to drug response. PGx can help us to identify individuals at risk of adverse drug reactions (ADRs); to treat these individuals with a personalized therapy to avoid ADRs; or to reduce the burden of side effects in these individuals. Personalized therapies are, in addition to other factors, driven by genetic polymorphisms<sup>1</sup>.

Genetic polymorphism is a difference in DNA sequence among individuals, groups, or populations. For example, humans develop many different polymorphisms of CYP1A1, one of many cytochrome P450 enzymes of the liver. Although the enzymes have basically the same sequence and structure, polymorphisms in this enzyme can influence how humans metabolize drugs. We can use our knowledge of genetic variations to devise a personalized therapy.

Examples of genetic polymorphisms associated with ADRs are shown in **Table 1**.

### PHARMACOGENOMICS

Pharmacogenomics (PGx) focuses on how genes and biomarkers can affect how an individual respond to drugs.

The goal of PGx is to develop effective, safe medications and doses that can be tailored to an individual's genetic makeup.

**Table 1: Some Genetic Polymorphisms Associated with ADR**

Genetic polymorphism	Drug class	Examples of drug(s)	Reported ADRs
<b>TPMT</b> (Thiopurine Methyltransferase)	<ul style="list-style-type: none"> <li>Antimetabolite</li> <li>Chemotherapeutic</li> </ul>	<ul style="list-style-type: none"> <li>Mercaptopurine</li> <li>Azathiopurine</li> </ul>	Myelotoxicity, leukopenia, death
<b>NAT2</b> (N-acetyltransferase 2)	<ul style="list-style-type: none"> <li>Antimycobacterial</li> <li>Vasodilator (antihypertensive)</li> </ul>	<ul style="list-style-type: none"> <li>Isoniazid</li> <li>Hydralazine</li> </ul>	Peripheral neuropathy Drug-induced lupus, hypotension
<b>CYP2D6</b>	<ul style="list-style-type: none"> <li>Opioid</li> <li>Tricyclic antidepressant</li> </ul>	<ul style="list-style-type: none"> <li>Codeine</li> <li>Desipramine</li> </ul>	Severe abdominal pain or no pain relief Cardiotoxicity, sudden death
<b>CYP2C9</b>	<ul style="list-style-type: none"> <li>Anticoagulant</li> </ul>	<ul style="list-style-type: none"> <li>Warfarin</li> </ul>	Bleeding

<sup>1</sup> Polymorphism: A combination of the Greek words *poly* (meaning multiple) and *morph* (meaning form), polymorphism is a term used in genetics to describe multiple forms of a single gene that exists in an individual or among a group of individuals.

Potential PGx differences in efficacy and/or safety can arise from genetic variants that are not yet as well characterized as metabolism or transporter genes. General DNA sample collection for exploratory analyses and characterization of genetic factors is particularly important for drugs with high inter-subject variability in pharmacokinetics (PK) or pharmacodynamics (PD). Thus it is strongly encouraged to consider routine DNA sampling.

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*“The goal of PGx is to develop effective, safe medications and doses that can be tailored to an individual's genetic makeup<sup>2</sup>”*

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## Pharmacogenomic Testing

### Advantages to PGx testing

Genomic data has emerged as a key component of precision medicine, offering a way for healthcare professionals to determine the most effective therapies for individuals based on their DNA. These are some of the advantages of PGx testing:

- Determining an individual's drug metabolizing capacity
- Enabling better selection or stratifications of individuals with known risk factors
- Increasing individual compliance
- Increasing positive outcome rate of treatment (and thus clinical studies)
- Targeted therapies
- Reducing risk for adverse reactions
- Reducing time and cost of conducting clinical studies

As more organizations begin to pursue the benefits of personalized therapies (**Figure 1**), health insurance may cover these tests and treatments more widely. The cost of sequencing a human genome has decreased significantly. Companies such as 23andMe offer genetic testing and analysis to the public for less than \$99 or 69€. These direct to consumer services enable individuals to provide their healthcare provider (HCP) with genetic information that may change not only the patient-HCP relationship, but also the course of their treatment.

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<sup>2</sup> U.S. National Library of Medicine / Genetics Home Reference

**Figure 1 Benefits of Personalized Therapies**




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*“Personalized medicine is our chance to revolutionize health care, but it will require a team effort by innovators, entrepreneurs, regulators, payers, and policymakers.”<sup>3</sup>*

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However, it is worth determining first:

- Will genotyping tailor drug treatment for individuals?
- Is there a risk that the patient’s condition could deteriorate while awaiting the results?
- Consider ethical issues surrounding patient decisions to know information.
- Does the HCP have the tools/knowledge to evaluate an overwhelming amount of data to apply precision medicine strategies to patient care?

At this time, all approved biomarkers are genomic, but soon there will be markers of methylation, transcriptomics, proteomics, etc. The challenge will be to integrate them into clinical practice. HCPs will need to be trained and to have access to tools that integrate clinical, PK, PD, biomarker, and other data; only then will they be able to decide on the best treatment option. Genetic counsellors help translate *data* into *understanding* for HCPs and patients.

## **Integration of Pharmacogenomics into Pharmacovigilance**

The activities in **Figure 2** are PGx considerations that must be applied throughout the product life cycle.

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<sup>3</sup> Brook Byers Partner, Kleiner Perkins Caufield & Byers

**Figure 2. Considering PGx**



As an example, PGx might be applied for risk management in these situations:

- Identify populations that should receive lower or higher doses of a drug, or longer titration intervals, based on genetic effects on drug exposure, dose-response, early effectiveness, and/or common adverse reactions.
- Identify responder populations based on phenotypic, receptor, or genetic characteristics
- Identify high-risk groups liable to experience adverse reactions

The practice of evaluating biomarkers as part of the study design might benefit clinical trials in these ways:

- Optimizing PV by identifying the percentage of individuals at risk of ARDs and tailoring informed consent forms, protocol, and investigator brochures.
- Recommending therapeutic dosage regimens of specific drugs for specific populations during clinical trials and in post-marketing settings
- Improving clinical trials and post-marketing treatment by stratifying group populations based on genetic differences in ethnic and cultural identities and their susceptibility for drug activity

When possible, the Reference Safety Information (RSI) of a product should provide information on important inter-individual variability in drug pharmacokinetics or response, and on the extent to which such variability can have a genetic basis. Should the product's indication or dosage adjustments depend on a particular genotype, the expression of a gene, or a particular phenotype, it should be stated in the product labeling. Individuals with a specific genotype or phenotype might not respond to the treatment or be at risk of a pronounced PD effect or adverse reaction. When known, such

situations should be clearly described. If interactions with other products depend on polymorphisms of metabolising enzymes or certain genotypes, this should also be stated.

As a result of these changes, drug product labeling has increasingly included preapproval information on the likelihood of treatment response based on genetic/genomic status or the need to genotype before a specified dose can be prescribed. Drug product labeling has also been revised after approval to include PGx information that can alter the benefit/risk ratio or allow adjustment of dosing.

## In Closing

The prospect of using the genome as an important factor in drug development is a reality. For the adoption of genomic biomarker testing into clinical practice and public health to be successful, we must demonstrate the clinical validity and utility of an identified biomarker and the corresponding test. With advances in artificial intelligence and machine learning, applications help us assess the complexity and volume of the data to be evaluated, so that researchers can better interpret and act on genomic data gained through genome sequencing<sup>4</sup>.

Furthermore, the ability to use genetic diagnostics, to identify, for instance, rare subsets of adverse events, is a key element in driving this transformation in medical care and drug development; it permits, among other important points, the extrapolation of early signals on drug-related events from one population to another. The participation of health professionals in genotyping their individual patients might allow co-reporting of both PGx and PV data.

Despite several challenges that still must be addressed (such as training time and interpretability of results), the great potential of PGx in reducing the occurrence of ADRs justifies the ongoing effort to develop new PV strategies to further personalize drug treatment, to refine the current clinical trial and post-marketing drug safety surveillance, and to safeguard patient health.

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<sup>4</sup> Genome sequencing: is a method of detecting mutations, such as Single Nucleotide Polymorphisms (SNPs) and Copy Number Variations (CNVs)

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