The Impact of Pharmacogenomics in Personalized Medicine

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INTRODUCTION

• Healthcare provider equate ‘pharmacogenomics’ as ‘personalized-medicine’.

• The key to personalized medicine is Pharmacogenomics (PGs)- a discipline spanning classical pharmacology and human genetics.

• The term ‘genetic-variability’ is not strange anymore to the healthcare professionals including pharmacists, physicians and health sciences researchers due to explosion of knowledge and technological advancement in the field of
Introduction (cont.)

Molecular biology, genetics, and inception of the World Human Genome Project.

- Many of genetic variations are being examined in terms of their role as predisposing factors for diseases, their influence on drug metabolisms thereby altered therapeutic response.
Specific *genetic traits* may account for a substantial amount of *variation in drug metabolism*, while may explain many *adverse reactions* that would otherwise be characterized as “*idiosyncratic***”.

The goal of PGs is to *optimize drug efficacy, limit drug toxicity, reduce overall costs*, and thereby *improve the quality of care*.

The *lack of appropriate education* on genomics is considered a major barrier to the implementation of pharmacogenomics in clinical practice.
It is evident in the literature that PGs can improve the therapeutic outcomes in patients with the use of genetic information. However, *worldwide, very few pharmacists and other healthcare professionals use PGs in their daily clinical practice.*

Historically, there has been a back of education focusing PGs in pharmacy curriculum.
The purpose of this informative presentation is to identify and introduce fundamental concepts in genetics and genomics as they relate to understanding and teaching of Pharmacogenomics (PGs) and to emphasize its role in pharmacy curriculum.
Further, by using a patient case, this presentation will highlight significance and use of PGs in clinical practice and its importance in improving therapeutic outcomes and quality of care.
Personalized Medicine

- Medicine is personal:
  - We are all different.
  - Some of our differences translate into how we react to drugs as individuals.
  - This is why personalized medicine is important to everyone.
- Why does someone need twice the standard dose to be effective?
- Why does this drug work for you but not me?
- Why do I have side-effects and you don’t?
- Why do some people get cancer and others don’t?
- Why is anecdotal information irrelevant to your own health and treatment?
The Goal of Personalized Medicine

- The **Right** Dose of
- The **Right** Drug for
- The **Right** Indication for
- The **Right** Patient at
- The **Right** Time.
Pharmacogenomics

- What do we mean by ‘individualized /personalized therapy or medicine’?
- What do we mean by “Pharmacogenetics & Pharmacogenomics”?
- Why should we study Molecular Biology and Human Genetics (human genomics)?
Definitions

- **Pharmacogenetics** (PGt) refers to the study of *a gene* involved in response to a drug, whereas
- *Pharmacogenomics* (PGx) refers to the study of *all genes in the genome* involved in response to a drug.
Historical Perspective

- Charles Darwin and Gregor Mendel
- Vogel, first coined the term “pharmacogenetics” (1959)
Historical Perspective

- **Kalow (1962)**: first book: *Pharmacogenetics: Heredity and the Response to Drugs*
Pharmacogenetics (PGt)

- Pharmacogenetics (PGt): is the aspect of personalized medicine whereby patient-specific genomic biomarkers are used to choose the optimal drug and/or dose for the patient, with the goal of assuring drug efficacy in the patient while minimizing or avoiding the risk of an adverse drug reaction.

- What are “bio-markers” and where to search the details?
A molecular marker is a segment of DNA found at a specific site along a chromosome and has properties that enable it to be uniquely recognized using molecular tools such as PCR and gel electrophoresis, and other array techniques.

As with alleles, the molecular markers may be polymorphic that is within a population, they may vary from individual to individual.
The Food and Drug Administration (FDA) provides a “Table of Valid Biomarkers” that presents approved drugs with pharmacogenomics information in specified sections of the package labeling.

See examples in next two slides—these are known as: 

1\textsuperscript{st} adaptation (Table: A-1), and 2\textsuperscript{nd} adaptation (Table: A-2).

The table can be found at www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucmo83378.htm.

Few examples are given in next slide.
### 1st adaptation (Table: A-1), Table: A-1/ related to PK (Pharmacokinetics) &/or PD (Pharmacodynamics)

<table>
<thead>
<tr>
<th>PK/PD</th>
<th>Biomarker</th>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Package Label Section(s)</th>
</tr>
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<tbody>
<tr>
<td>PD</td>
<td>ALK&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Crizotinib</td>
<td>Oncology</td>
<td>Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
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<tr>
<td>PD</td>
<td>ApoE2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pravastatin</td>
<td>Metabolic and Endocrinology</td>
<td>Clinical Studies, Use in Specific Populations</td>
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<td>PD</td>
<td>BRAF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Vemurafenib</td>
<td>Oncology</td>
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<tr>
<td>PD</td>
<td>CCR5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Maraviroc</td>
<td>Antivirals</td>
<td>Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information</td>
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<td>CD30&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>PD</td>
<td>CFTR&lt;sup&gt;h&lt;/sup&gt; (G551D)</td>
<td>Ivaclafor</td>
<td>Pulmonary</td>
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<td>Chromosome 5q&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Lenalidomide</td>
<td>Hematology</td>
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<td>C-Kit&lt;sup&gt;j&lt;/sup&gt;</td>
<td>Imatinib</td>
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<td>PK</td>
<td>CYP1A2&lt;sup&gt;k&lt;/sup&gt;</td>
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<td>Gastroenterology</td>
<td>Clinical Pharmacology</td>
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<td>Musculoskeletal</td>
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</table>
Table A-2

Drugs Listed by Therapeutic Area

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Drug</th>
<th>Biomarker</th>
<th>Package Label Section(s)</th>
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<tr>
<td>Analgesics</td>
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<td>Analgesics</td>
<td>Codeine</td>
<td>CYP2D6</td>
<td>Warnings and Precautions, Use in Specific Populations, Clinical Pharmacology</td>
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<td>Analgesics</td>
<td>Tramadol and acetaminophen</td>
<td>CYP2D6</td>
<td>Clinical Pharmacology</td>
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<td>Antiarrhythmics</td>
<td>Quinidine</td>
<td>CYP2D6</td>
<td>Precautions</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Voriconazole</td>
<td>CYP2C19(^1)</td>
<td>Clinical Pharmacology, Drug Interactions</td>
</tr>
<tr>
<td>Antifungals</td>
<td>Terbinafine</td>
<td>CYP2D6</td>
<td>Drug Interactions</td>
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<tr>
<td>Anti-infectives</td>
<td>Chloroquine</td>
<td>G6PD</td>
<td>Precautions</td>
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<td>Anti-infectives</td>
<td>Rifampin, isoniazid, and pyrazinamide</td>
<td>NAT1; NAT2</td>
<td>Adverse Reactions, Clinical Pharmacology</td>
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<tr>
<td>Antivirals</td>
<td>Maraviroc</td>
<td>CCR5(^d)</td>
<td>Indications and Usage, Warnings and Precautions, Clinical Pharmacology, Clinical Studies, Patient Counseling Information</td>
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<td>Antivirals</td>
<td>Abacavir</td>
<td>HLA-B*5701</td>
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<td>IL28B</td>
<td>Clinical Pharmacology</td>
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<td>Peginterferon alfa-2b</td>
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<td>Boxed Warning, Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology</td>
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<td>Use in Specific Populations, Clinical Pharmacology, Clinical Studies</td>
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<td>Cardiovascular</td>
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<td>Precautions, Clinical Pharmacology</td>
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<td>Cardiovascular</td>
<td>Propafenone</td>
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<td>Clinical Pharmacology</td>
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</table>
Genetic Variation

**Types of variants**:

1. SNPs (Single Nucleotide Polymorphism)
2. Coding, non-coding & cis/trans regulatory variants
3. Insertion / deletions, Indels
4. Copy number variants SNPs,
5. Haplotypes and Tag SNPs
CNVs, can be detected via microarray technology, however, it may not detect CNVs of particular genes important for drug metabolism and disposition including members of the CYP (Cytochrome P450), UGT (Uridine Glucuronosyltransferase), GST (Glutathione-S-transferases), and SULT (Sulphotransferases) gene families.

Quantitative PCR employing fluorescent probes is more appropriate technique to determine CNVs.
Other methods and platforms include pyrosequencing, multiplex PCR analysis and LabChip microfluidic technology. Most methods are capable of discriminating between 0, 1, 2, and 3 copies.

(Methods, mostly images: from slide #27 to #48)
Roche Chip for Cytochrome P450 Genes: CYPC19 and CYP2D6

Xie and Frueh, Pharmacogenomics steps toward Personalized Medicine, Personalized Medicine 2005, 2, 325-337
Microarray Analysis: methods cont.

**FIGURE 15.14** Preparation and use of microarrays to study gene expression. RNAs are isolated from control and experimental tissues, for example, normal cells and cancer cells, and used to prepare cDNAs labeled with different fluorescent dyes. Equal amounts of the cDNA samples are mixed and hybridized to microarrays containing probes complementary to the cDNAs of the genes of interest. After hybridization, the microarrays are analyzed using sophisticated laser scanners and computer software that remove background noise and quantify the signals from the two fluorescent cDNA populations.
Rstriction Fragment Length Polymorphism (RFLP) analysis/methods cont.

C. Prenatal diagnosis

Families with a history of severe genetic disease, such as an affected previous child or near relative, may wish to determine the presence of the disorder in a developing fetus. Prenatal diagnosis, in association with genetic counseling, allows for an informed reproductive choice if the fetus is affected.

1. Methods available: The available diagnostic methods vary in sensitivity and specificity. Visualization of the fetus, for example, by ultrasound or fiberoptic devices (fetoscopy), is useful only if the genetic abnormality results in gross anatomic defects, for example, neural tube defects. The chemical composition of the amniotic fluid can also provide diagnostic clues. For example, the presence of high levels of α-fetoprotein is associated with neural tube defects. Fetal cells obtained from amniotic fluid or from biopsy of the chorionic villi can be used for karyotyping, which assesses the morphology of metaphase chromosomes. New staining and cell sorting techniques have permitted the rapid identification of trisomies and translocations that produce extra chromosome or chromosomes of abnormal lengths. However, molecular analyses of fetal DNA promises to provide the most detailed genetic picture.

2. Sources of DNA: DNA may be obtained from white blood cells, amniotic fluid, or chorionic villi (Figure 33.15). For amniotic fluid, in the past, it was necessary to culture the cells in order to have sufficient DNA for analysis. This took 2–3 weeks to grow a sufficient number of cells. The development of the polymerase chain reaction (see below) has dramatically shortened the time needed for a DNA analysis.
From *Roche Molecular Diagnostics*: uses **microarray technology** to test for sequence variations in the CYP2D6 and CYP2C19 genes.

- Approved by US Food and Drug Administration
- In this test, PCR amplicons are generated, fragmented, labeled, hybridized to the microarray, and the bound products stained. Finally, the array is scanned, data analyzed, and the genotype and predicted phenotype determined using AmpliChip CYP450 test algorithm.
Early **SNP array** allowed testing for thousands of SNPs. Today, arrays can interrogate up to **millions of genetic markers** including **SNPs and copy number variations (CNVs)** throughout the genome.

- Two marker leaders are **Affymetrix** and **Illumina**, who use different technologies, **GeneChip** and **BeadChip**, respectively.

- GWAS are used for designing of any study that seeks **to determine associations** between
Results of GWAS studies are often displayed in so-called **Manhattan plots**, which summarize the association of each tested genetic variation with the measured trait (Fig. 3-4, slide # 46)
**Fig. 3-4:** Manhattan Plot / (methods: last slide)

**FIGURE 3-4** Representation of a Manhattan plot of a genome-wide association study (GWAS). In this example, a number of sequence variations were associated with a trait of interest as indicated by peaks that reach $P$-values $<10^{-7}$ (dotted line). (Reproduced with permission from Petukhova L, Duvic M, Hordinsky M, et. al. Genome-wide association study in *Alopecia areata* implicates both innate and adaptive immunity. *Nature*. 2010;466:113-117.)
Pharmacogenetics (PGt)

- Qn. :- Successful implementation (practice) of pharmacogenetics in the clinic/hospital depends upon -

(try to complete the sentence)

- Ans. on next slide
1. *a priori* knowledge about a *specific allele* in the genome, and

2. its *linkage*: (a) *to altered pharmacokinetics (PK)*, data on prior discoveries and clinical findings, and

3. (b) *to pharmacodynamics (PD)* (compared to the statistical norm in the population)
4. the ability to *accurately test a patient* for the *presence of a specific allele* in his/her genome,

5. the ability to *offer* the patient *more effective alternatives* than would be typically offered to a patient in the statistical norm of the population.
6. **predicting** how the patient *will respond* to the drug.

7. utilization of pharmacogenetics and personalized medicine *must add value to healthcare*, i.e. **cost** associated with must be *ethically and economically justified*.

*Let us see,*”How this science started”.
Cost of Sequencing a Genome

Kisor et al. (2014) Pharmacogenetics, kinetics, and dynamics for personalized medicine, J & B Learning

Figure 11-1: The cost of sequencing a complete (whole) genome has continued to decline, first following Moore’s law (i.e., doubling capacity every 2 years) but then accelerating to a faster-paced reduction with the advent of new technologies starting in about 2008.
Genetic diversity may manifest (a) as changes in the staining pattern of chromosomes, (b) as variation in the copy number of megabase segments of DNA, (c) as nucleotide changes in DNA, (d) as alterations in proteins, or as disease.
The concept of Genetic Polymorphism

- It is estimated that the genomes of any two given individuals differ by approximately one nucleotide in every 1000, or a difference of approximately 3 million base pairs in total.
The frequency of polymorphisms may vary among different racial/ethnic groups.

Some of these gene polymorphisms or variations may only be responsible for small differences among people such as hair and eye color, while some may result in diseases or increase the risk of diseases in people.
When a variant is so common that it is found in more than 1% of chromosomes in the general population, the variant constitutes what is known as a genetic polymorphism.

In contrast, alleles with frequencies of less than 1% are, by convention, called rare variants (=mutations).
SNPs (cont.)

- For example, a particular sequence reads AGGTCAGT for one allele and AGGTCGAGT for another (the SNP is A > G).
- In some cases one nucleotide can have not just one, but two or three allelic variants.
- One specific example is the SNP at position 2677 in the multidrug resistance gene 1 (MDR1 or ABCB1) that is triallelic, meaning that T or A can be found instead of wild-type G (G> T/A)
**PGx Resources**

- **PharmGKB**: Pharmacogenomics Knowledgebase is available at [www.pharmgkb.org](http://www.pharmgkb.org)
- This database organizes, presents, and disseminates information and knowledge concerning *genetic variation as it relates to drug response*
- It includes annotations of relationships between genes, drugs, and disease that are supported by vetted literature
PharmGKB (cont.)

- The site serves as a dissemination portal for the pharmacogenomic-based *drug dosing guidelines* produced by the Clinical Pharmacogenetics Implementation Consortium (CPIC).
- It’s a joint effort between PharmGKB and the Pharmacogenetics Research Network (PGRN)
- CPIC guidelines are also published in the *Journal Clinical Pharmacology and Therapeutics*
- Supported by Health/National Institute of General Medical Services and managed by Stanford University
• **DBSNP**

• **Single Nucleotide Polymorphism database (dbSNP)**: Public domain database

• Provided by the National Center for Biotechnology Information (NCBI) of the U.S. National Library of Medicine
[A] Clinically Relevant PGx:
1. Well known PGx associations
2. Clinically relevant PGx summaries
3. PGx drug dosing guidelines
4. Drug labels with PGx information
5. Genetic tests for PGx
6. Star (*) allele translocations
[B] PGx based Drug Dosing Guidelines
[C] PGx Research:
1. VIP- Very Important PGx gene summaries
2. View PharmGKB pathways
   (a) Alphabetically
   (b) By therapeutic category
3. Annotated SNPs by gene
4. Drugs with genetic information
23 and Me

- Drug response Reports
- 23 members; took survey and details are filled in
The associated SNPs are then considered *to mark a region* of the human genome which influences the risk of disease.

GWA studies investigate the entire genome (non-candidate-driven) in contrast to gene-specific-candidate-driven studies!
These studies compare the DNA of two groups of participants: people with the disease (cases) and similar people without (controls).

Millions of genetic variants are read using **SNP arrays**.

If one type of the variant (one allele) is more frequent in people with the disease, the SNP is said to be “associated” with the disease.
FYI : if you want to know more

- How to use an article about genetic association.
- 3 articles in a series (A,B & C) by
- John Attia et al. (2009) JAMA, Vol. 301, No.1
Pharmacogenetics – guide therapy

All patients with same diagnosis (not all respond to therapy)

Severe overdosing (toxicity)

Sub-therapeutic (inadequate response)

Individualized therapy

Treat with conventional dose

Maximizing Genotype-to-Phenotype Correlations
SNP Nomenclature

- A SNP can be described in a numeric and alphabetic context

- Provides information regarding:
  - Specific gene
  - Location of the SNP with respect to the gene
  - Nucleotides involved
SNP Nomenclature

ABCB1  3435 C > T

- Gene = First few letters/numbers : (ABCB1)
- Location on DNA (SNP location) = Numbers between gene name and the nucleotide : (3435)
- First nucleotide letter = *original* nucleotide (reference nucleotide): C
- Second nucleotide letter = nucleotide *change* (variant nucleotide) : T

An example of a SNP is the VKORC1 1173 C>T. Based on the pharmacogenomic nomenclature of this SNP, what is the gene of interest?

A. 1173  
B. VKORC1  
C. VKORC1 1173  
D. VKORC1 C>T
Alleles

- Allele = one of the *variant forms of a gene* at a particular location on a chromosome

- Humans possess *two alleles*
  - One allele acquired from your biological *mother*
  - The other from your biological *father*

- Different allele subtypes can exist for a gene
Allele Subtypes: Naming Nomenclature of

Cytochrome P450 (CYP) gene CYP2C19

Super family → CYP2C9*2A ← Suballele

Individual member    Allele

Family     Subfamily
Examples of three allele subtypes:
- CYP2C19*1
- CYP2C19*2
- CYP2C19*3

CYP2C19 = gene
*1, *2, *3 = allele subtype
*1 allele = is wild-type (common allele, normal allele)
### Cytochrome P450-2C19 Genotype & Drug Metabolising Status

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<thead>
<tr>
<th>Genotype</th>
<th>Metabolizing Status</th>
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<tbody>
<tr>
<td>*1/*1</td>
<td>Extensive metabolizer</td>
</tr>
<tr>
<td>*1/*17</td>
<td>Extensive metabolizer</td>
</tr>
<tr>
<td>*17/*17</td>
<td>Ultrarapid metabolizer</td>
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<tr>
<td><em>1/</em>(2,3,4,5,6,7,8)</td>
<td>Intermediate Metab...</td>
</tr>
<tr>
<td><em>(2b,3,4,5,6,7,8)/</em>(2,3,4,5,6,7,8)</td>
<td>Poor metabolizer</td>
</tr>
</tbody>
</table>

[EM=enhanced inhibition of platelet aggregation]
Allele Subtypes

- Identifying subtypes is relevant to the functional effect for each gene

- **CYP2C19*1** functional allele
- **CYP2C19*2** loss-of-function alleles
- **CYP2C19*3**
- **CYP2C19*17** increased - activity allele

Homozygous vs. Heterozygous

- An individual genotype identifies both alleles for a specific gene

- If both alleles in an individual are CYP2C19*2, the respective genotype would be homozygous and identified as:
  - CYP2C19*2/*2

- If an individual has one CYP2C19*2 allele and one CYP2C19*3 allele, then the respective genotype would be heterozygous and identified as:
  - CYP2C19*2/*3
Now You Determine Enzyme Activity!

- A physician orders genetic testing for his patient with the following result: CYP2C19*2/*3
- Which of the following is correct regarding enzyme activity?

A. The patient’s genotype is homozygous with normal functional activity
B. The patient’s genotype is heterozygous with normal functional activity
C. The patient’s genotype is homozygous with a loss-of-functional activity
D. The patient’s genotype is heterozygous with a loss-of-functional activity