Pharmacogenomics in Current Practice

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Objectives

• Review the concept of pharmacogenetics and pharmacogenomics
• Discuss how genetics affect the activity of drug metabolizing enzymes
• Discuss examples of how pharmacogenetics and pharmacogenomics will lead to individualization of drug therapy
• Identify resources for obtaining current and updated pharmacogenomics information
Clinical Problem

“The vast majority of drugs – more than 90% - only work in 30 or 50 per cent of the people...Drugs out there on the market work, but they don’t work in everybody” Allen Roses, vice president at GlaxoSmithKline
What if there were a way...

• ...to know if a depressed patient would respond to an antidepressant—before it was prescribed?
• ...to predict if a patient will have analgesia with morphine or codeine?

In recent years, advances in genetic testing have made such drug-response predictions possible for patients with certain gene variants.

A new initiative ON PRECISION MEDICINE

• “Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”
  — President Barack Obama, State of the Union Address, January 20, 2015
• $130 million to NIH for development of a voluntary national research
• $70 million to the National Cancer Institute (NCI)
• $10 million to FDA to acquire additional expertise and advance the development of high quality, curated databases to support the regulatory structure needed to advance innovation in precision medicine and protect public health.
• $5 million to Office of the National Coordinator for Health Information Technology (ONC) to support the development of interoperability standards and requirements that address privacy and enable secure exchange of data across systems.

https://obamawhitehouse.archives.gov/node/333101
Accessed November 27, 2017
Pharmacogenetics vs. Pharmacogenomics

- **Genetics:** study of genetic causes of *individual variations* in drug response. Limited to the effects of one or a few genes.

- **Genomics:** study of the *genome-wide role of human variation in drug response*. Includes:
  - pharmacogenetic effects
  - the application of genomic technologies in drug discovery, disposition, and function

American Association of Pharmaceutical Scientists (AAPS) Pharmacogenomics Focus Group

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Reasons for Variability in Drug Response
Goal of Pharmacogenomics

- Optimize drug therapy
  - Maximize effectiveness
  - Minimize toxicity
  - Minimize pharmacokinetic and pharmacodynamic variability of drug therapy
  - Avoid unnecessary treatment

“The right drug, right dose, to the right person”

Question #1

What is pharmacogenomics?
A. Branch of pharmacology that studies genes in drug safety
B. Branch of pharmacology that studies genes in drug efficacy
C. Branch of pharmacology that allows drug dosing and selection based on genetic makeup of the individual
D. All of the above
Pharmacogenomic Nomenclature

• **Polymorphism**: variation in DNA sequence
  – Base change frequency > 1% of population
  – Single Nucleotide Polymorphism (SNP or “snips”)
  – Changes in more than 1 nucleotide
  – Entire gene insertion, deletion, or extra copies of a gene

• **Mutation**: base change frequency < 1% of population


Understanding the effect of genetic polymorphism

- Identify the polymorphism
- What can be affected by the polymorphism?
  - Drug metabolizing enzyme
  - Drug transporter
  - Drug target
  - Disease
  - Or no functional effect
- Who is impacted?
  - Individual vs population
- How does it affect a drug?
  - Pharmacokinetic or pharmacodynamic effect
    - Dosing, efficacy, toxicity
    - No effect on a drug
- How does it affect a disease?
  - Increase or decrease susceptibility
  - Utility as screening or diagnostic tool

Allele – a variant or wild type form of a gene at a particular location on a chromosome

Allele nomenclature example: VKORC1 1173 C > T
(Does not distinguish if this is a wild type or variant)

**Allele/SNP Nomenclature**

- **Gene**
- **Nucleotide position within sequence of gene**
- **Original “Wild-type” nucleotide**
- **Variant nucleotide**

Examples of allele nomenclature:
- CYP2C19*1 (CYP2C19)
- CYP2C19*2 (CYP2C19 681 G > A)
- CYP2C19*3 (CYP2C19 636 G > A)

The * (star) and number after the gene designate the allele


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“Star” Nomenclature (describes alleles)

- **Example 1: CYP2C19** (function varies based on the allele)
  - *1 = always indicate wild type allele (normal) enzymatic activity
  - *2 = NO enzyme activity
  - *3 = NO enzyme activity

- **Example 2 for another enzyme: CYP2D6**
  - *1 = always indicate wild type allele (normal) enzymatic activity
  - *2 = Decreased enzyme activity
  - *3 = Decreased enzyme activity

**Keypoint:** Function of each gene varies based on the allele.
- Allele nomenclature may look exactly the same for different genes; but may have different functional outcomes, depending on specific gene/protein

**Genotype Nomenclature**
(Refers to the 2 alleles inherited for a specific gene)

- **Example for CYP2C19**
  - An individual may carry 2 copies of *2 allele (CYP2C19*2/*2)
- **Genotypes may impact drug metabolism**
  - CYP2C19*1/*1 = wild type enzyme activity
  - CYP2C19*1/*2 or *1/*3 – reduced enzyme activity
  - CYP2C19*2/*2 or *2/*3 or *3/*3 = no enzyme activity


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**Polymorphism Types**

- **Single Nucleotide Polymorphism (SNP)**
  - A single base substitution occurring within a gene
  - Several million identified
  - May or may not alter protein synthesis
- **Coding SNP**
  - Synonymous
  - Non-synonymous
  - Premature stop codon
- **Other types of polymorphism (hundreds or thousands of nucleotides may be involved)**
  - Gene deletion
  - Copy number variant

Single nucleotide polymorphisms (SNPs) are the most common type of genome variation. SNPs occur throughout the genome but here is a diagram showing just one SNP.

The two alleles of this SNP are referred to as

C

and

T

As everyone inherits a copy of this region of the sequence from each parent, a person can have one of three patterns of this SNP: CC, CT or TT.

Several million identified SNPs may or may not alter protein synthesis.

Coding Region SNPs

- **Synonymous**
- **Non-Synonymous**
  - **Missense** – amino acid change
  - **Nonsense** – changes amino acid to stop codon.
Synonymous Codon SNP

- **Example:** P-glycoprotein (P-gp)
  - ABCB1 3435 C > T
  - The resultant amino acid (isoleucine) is unchanged from the reference DNA sequence
  - **Functional Effect:** ? Effect on P-gp function or expression
  - **Affected Drugs:** Efavirenz, cyclosporine


Non-Synonymous Codon SNP

- **Example:** Thiopurine methyltransferase (TPMT)
  - TPMT 615 G > A
    - Alanine changes to threonine
  - TPMT 874 A > G
    - Tyrosine changes to Cysteine
  - **Functional Effect:** ↓ TPMT enzyme activity
  - **Affected Drugs:** azathiopurine, 6-mercaptopurine
  - May not be able to give the same dose to patients with this polymorphism

Premature Stop Codon SNP

- Example: CYP2C19*3
  - Nucleotide change G > A
  - The reference amino acid tryptophan is not coded
  - Results in termination of protein synthesis
  - **Functional effect:** CYP2C19*3 results in no enzyme activity
  - **Affected Drugs:** proton pump inhibitors (omeprazole, lansoprazole)

Gene Deletion

- **Example:** CYP2D6*5
  - Not a single nucleotide polymorphism
  - Thousands of nucleotide base pairs that comprise CYP2D6 gene are deleted
  - **Functional Effect:** loss of function for CYP2D6
  - **Poor metabolizer phenotype**
  - **Affected Drugs:** SSRIs, codeine, tamoxifen, β-blockers

Copy Number Variant

• **Example:** CYP2D6*XN
  - Extra copies of CYP2D6 gene are present
  - **Functional Effect:** Ultra rapid metabolizer (UM) phenotype
  - **Affected Drugs:** SSRIs, codeine, tamoxifen, β-blockers


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### CYP2D6 Diploype Determines Drug Metabolism

<table>
<thead>
<tr>
<th>Likely phenotype</th>
<th>Activity score</th>
<th>Genotypes</th>
<th>Examples of diploypes</th>
<th>Predicted phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid</td>
<td>&gt;2.0</td>
<td>more than two copies of functional alleles</td>
<td>*1/*1x2, *1/*2x2</td>
<td>Increased enzyme activity, increased formation of metabolites</td>
</tr>
<tr>
<td>Metabolizer</td>
<td></td>
<td>one full function allele plus either one nonfunctional or one reduced function allele</td>
<td>*1/*1, *1/*2, *1/*10, *10/*10, *1/*15, *10/*15</td>
<td>Normal enzyme activity</td>
</tr>
<tr>
<td>Extensive</td>
<td>1.0-2.0</td>
<td>two full or reduced function alleles or one full function allele plus either one nonfunctional or one reduced function allele</td>
<td>*1/*1, *1/*2, *1/*10, *10/*10, *1/*15, *10/*15</td>
<td>Reduced formation of metabolites</td>
</tr>
<tr>
<td>Intermediate</td>
<td>0.5</td>
<td>one reduced and one nonfunctional allele</td>
<td>*1/*4, *1/*10, *1/*15</td>
<td>Low or absent enzyme activity, decreased formation of metabolite</td>
</tr>
</tbody>
</table>

Predicted metabolizer phenotype is used to determine starting drug dosages.

E.g., this chart is relevant to the metabolism of codeine to morphine by CYP2D6:

- **Ultrarapid metabolizers** avoid codeine use due to potentially toxic morphine levels.
- **Poor metabolizers** avoid codeine use due to lack of efficacy.
- **Extensive & Intermediate metabolizers** use age- & weight-specific dosing
  - Intermediate metabolizers may not respond as well as extensive metabolizers.
Polymorphism Types Summary

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  – Premature stop codon

• Other types of polymorphism (hundreds or thousands of nucleotides may be involved)
  – Gene deletion
  – Copy number variant

Patient Case

• 35 year old Asian female complains of dyspepsia & epigastric pain. Denies N/V and blood in stools. Urea breath test is positive. She is diagnosed with *H. Pylori* peptic ulcer disease

• PMH: No other significant PMH. NKDA

• Medications: Begins 10-day course of omeprazole, amoxicillin, & clarithromycin
Systematic Application of Pharmacogenomic Polymorphisms

- Identify the polymorphism and what it may affect
  - CYP2C19 enzyme
  - The variant CYP2C19*3 or *2 allele results in no activity

- Identify the individual affected
  - Rate of rapid metabolizers:
    - 56-81% in European and North Americans
    - 27-38% in Asian population
    - Increased activity of the enzyme
  - Rate of slow metabolizers:
    - 2.3-8.5% in Europeans
    - 8-23% in Chinese and Japanese population
    - Frequency of the CYP2C19*3 allele are higher in Asians
    - Decreased activity of the enzyme

Systematic Application of Pharmacogenomic Polymorphisms

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  - Rate of rapid metabolizers are
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  - Frequency of the CYP2C19*3 allele are higher in Asians

- Relevance to a drug
  - Omeprazole plasma concentrations & exposure are higher in individuals with the CYP2C19*3 allele compared to those with CYP2C19*1 allele

<table>
<thead>
<tr>
<th>CYP2C19 Genotype and Omeprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
</tr>
<tr>
<td>CYP2C19*1/*1</td>
</tr>
<tr>
<td>CYP2C19*1/*2</td>
</tr>
<tr>
<td>CYP2C19*1/*3</td>
</tr>
<tr>
<td>CYP2C19*2/*2</td>
</tr>
<tr>
<td>CYP2C19*2/*3</td>
</tr>
<tr>
<td>CYP2C19*3/*3</td>
</tr>
</tbody>
</table>

Futura et al. Clinical Pharmacology and Therapeutics 1999; 64(5):552-61
Systematic Application of Pharmacogenomic Polymorphisms

- **Identify polymorphism and what it may affect**
  - CYP2C19 enzyme
  - The variant CYP2C19*3 or *2 allele results in no activity
- **Identify the individual affected**
  - Rate of rapid metabolizers are
    - 56-81% in European and North Americans
    - 27-38% in Asian population
- **Relevance to a drug**
  - Omeprazole plasma concentrations & exposure are higher in individuals with the CYP2C19*3 allele compared to those with CYP2C19*1 allele
- **Relevance to a disease**
  - *H. pylori* cure rates vary based on CYP2C19 genotype in patients who are on omeprazole-containing regimens
  - **Patients with wild-type have decreased cure rate compared to patients with *3 or *2 variants of CYP2C19**


Strategies in the clinical practice in patients who are nonresponsive to initial proton pump inhibitor therapy.

Therapeutic Area: Oncology

Figure 1. Percentage of FDA pharmacogenomic biomarkers in drug labeling within each therapeutic area. Biomarkers include markers that may be germline or somatic gene variants, functional deficiencies, expression changes, or chromosomal abnormalities.

Table 1

<table>
<thead>
<tr>
<th>Pharmacogenomic marker Drug (s)</th>
<th>Genome Outcome</th>
<th>Multi-tumor marker*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABL</td>
<td>Bematinib, dasatinib, matinib, nilotinib, ponatinib</td>
<td>Somatic, Efficacy</td>
</tr>
<tr>
<td>ALK</td>
<td>Crizotinib</td>
<td>Somatic Efficacy</td>
</tr>
<tr>
<td>BRAF</td>
<td>Vemurafenib</td>
<td>Somatic Efficacy</td>
</tr>
<tr>
<td>EGFR</td>
<td>Axitinib, cetuximab, erlotinib, panitumumab, vandetanib</td>
<td>Somatic Efficacy</td>
</tr>
<tr>
<td>FckR</td>
<td>Cetuximab, erlotinib, trastuzumab</td>
<td>Somatic Efficacy</td>
</tr>
<tr>
<td>HER2</td>
<td>Lapatinib, pertuzumab, trastuzumab, trastuzumab-entanabile</td>
<td>Somatic Efficacy</td>
</tr>
<tr>
<td>KRAS</td>
<td>Cetuximab, panitumumab</td>
<td>Somatic Efficacy</td>
</tr>
<tr>
<td>KIT</td>
<td>Imatinib</td>
<td>Somatic Efficacy</td>
</tr>
<tr>
<td>MET</td>
<td>Trametinib</td>
<td>Somatic Efficacy</td>
</tr>
</tbody>
</table>

*Commercially available multi-tumor tumor panel.

Arap Laboratories (http://lsl.angellab.com/Tests/Pub/20172931)

AuroraGen (http://auragen.com/products-and-services/germanci-services/next-generation-sequencing-services/)

Foundation Medicine (http://www.foundationmedicine.com)
<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA biomarker</th>
<th>Gene(s) variant/tumor mutation</th>
<th>Variation type</th>
<th>FDA recommendation</th>
<th>POIs incorporation time</th>
<th>Example of commercially available test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buoden</td>
<td>FMR1/ALB1</td>
<td>T</td>
<td>Translocation</td>
<td>Proposed</td>
<td>January 2003</td>
<td>Vysis LSI BORALI ES Dual Color Translocation Probe</td>
</tr>
<tr>
<td>Captopril</td>
<td>DPD</td>
<td>G</td>
<td>Enzyme activity</td>
<td>Mandatory</td>
<td>March 2003</td>
<td>MYCOTAK™ TheraCue™-5-FU</td>
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<tr>
<td>Cetuximab</td>
<td>EGFR T</td>
<td>Overexpression</td>
<td>Recommended</td>
<td>February 2004</td>
<td>ObscoCytokromEGFR pharmOri™ test³</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Therascreen ARAS RGQ FOLFIRI-KR²</td>
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<tr>
<td>Capatin</td>
<td>TPMT G</td>
<td>SNP</td>
<td>Recommended</td>
<td>December 2011</td>
<td>Permemetas TPMT Genetics</td>
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<tr>
<td>Crealoside</td>
<td>EMIL/AU5</td>
<td>T</td>
<td>Translocation</td>
<td>Recommended</td>
<td>August 2011</td>
<td>Vysis ALK Break Apart FISH Probe-KR²</td>
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<td>Cisplatin</td>
<td>Ph-Chr T</td>
<td>Translocation</td>
<td>Recommended</td>
<td>June 2006</td>
<td>Molecyst™ EGR-AR1, T15T16 Mutation Test</td>
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<td>Docetaxel</td>
<td>dETS2 T</td>
<td>Overexpression</td>
<td>Recommended</td>
<td>February 1999</td>
<td>AbxMAP-CCD5 by immunohistochemistry test</td>
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<td>Efralol</td>
<td>EGFR T</td>
<td>Overexpression</td>
<td>Proposed</td>
<td>November 2004</td>
<td>See FGFR above</td>
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</tr>
</tbody>
</table>

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
Accessed November 27, 2017

<table>
<thead>
<tr>
<th>Drug</th>
<th>POIs biomarker</th>
<th>Gene(s) variant/tumor mutation</th>
<th>Variation type</th>
<th>FDA recommendation</th>
<th>POIs incorporation time</th>
<th>Example of commercially available test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Chr. Sq</td>
<td>T</td>
<td>Deletion</td>
<td>Mandatory</td>
<td>December 2005</td>
<td>Abxcel™ FISH Chr. Sq probe</td>
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<tr>
<td>Methotrexate</td>
<td>TPA21/F    G</td>
<td>SNP</td>
<td>Mandatory</td>
<td>January 2005</td>
<td>Abxcel™ TPA21/F probe</td>
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<td>Nitroprusside</td>
<td>Ph-Chr T</td>
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<td>October 2007</td>
<td>See Ph-Chr above</td>
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<td>Pemetrexed</td>
<td>EGFR T</td>
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<td>Recommended</td>
<td>September 2006</td>
<td>See EGFR above</td>
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<tr>
<td></td>
<td>FGFR3 T</td>
<td>T</td>
<td>Mutation</td>
<td>July 2009</td>
<td>See FGFR above</td>
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<tr>
<td>Pertuzumab</td>
<td>HER2/neu T</td>
<td>Overexpression</td>
<td>Recommended</td>
<td>June 2012</td>
<td>See HER2 above</td>
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<td>Raxibacumab</td>
<td>GFR11 T</td>
<td>SNP</td>
<td>Mandatory</td>
<td>July 2002</td>
<td>RoswellIMW GFR11™ test²</td>
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<tr>
<td>Sorafenib</td>
<td>ER T</td>
<td>Overexpression</td>
<td>Recommended</td>
<td>October 1996</td>
<td>See ER above</td>
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<td>Vemurafenib</td>
<td>FGF2 G</td>
<td>SNP</td>
<td>Proposed</td>
<td>September 2006</td>
<td>Roche® Factor V Limax KR²</td>
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<tr>
<td>Vemurafenib</td>
<td>FGFR3 T</td>
<td>SNP</td>
<td>Proposed</td>
<td>September 2006</td>
<td>Roche® Factor V Limax KR²</td>
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</tr>
<tr>
<td>Translumece</td>
<td>EGFR T</td>
<td>Overexpression</td>
<td>Recommended</td>
<td>June 2003</td>
<td>See TPF7 above</td>
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</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2/neu T</td>
<td>Overexpression</td>
<td>Recommended</td>
<td>September 1998</td>
<td>See HER2 above</td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>EGFR T</td>
<td>Mutation</td>
<td>Recommended</td>
<td>August 2011</td>
<td>Cobas® 4800 BRAF V600E Mutation Test²</td>
<td></td>
</tr>
</tbody>
</table>

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
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Therapeutic Area: Psychiatry

- Primarily affected by Phase I enzymes: CYP2D6 and CYP2C19
  - CYP2D6 > 80% and CYP2C19 < 10%
    - Tricyclic antidepressants:
      - the guidelines recommend a 50% dose reduction of amitriptyline and nortriptyline in persons who are CYP2D6 or CYP2C19 PMs
      - For CYP2D6 ultrarapid metabolizers (UMs), therapy with amitriptyline or nortriptyline should be avoided, or the initial target dose should be increased.
    - SSRIs: FDA label for citalopram recommends a maximum dose of 20 mg/day in known PMs
      - Testing is not routine since it has a wide therapeutic window
      - HLA-B*1502 for carbamazepine and phenytoin
        - Increased risk for Steven’s Johnson Syndrome and Toxic Epidermal Necrolysis (TENS)
        - FDA and The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommend testing in Asian population
          - 10–15% in patients from China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan
          - 2–4% in patients from south Asia and India
          - <0.01% in patients of European, Hispanic, Native American, and African descent
    - Article provides excellent tables with recommendations for dose adjustment for different genetic variants and pharmacogenomic testing resources for variants influencing neuropsychiatric medications


Therapeutic Area: Anticoagulation (warfarin)

- Metabolism affected by CYP2C9 and VKORC1
  - CYP2C9 *2 and *3 variant = ↓ activity by 50-90% = ↑ warfarin concentration
    - Caucasians: 3-20%; Asians & African Americans – 1-4%
  - VKORC1 (vit K epoxide reductase complex subunit 1)
    - VKORC1 1173 C > T (Asians: 82-89%; Caucasians: 14-41%, African Americans: 9%)
    - VKORC1 1639 G > A (Asians: 82%; Caucasians: 14%)
    - 5 common haplotypes categorized into Group A and B
      - Group A (1 and 2) – require lower warfarin dose (Asians:89%, Caucasians:37%; AA:14%)
      - Group B (7,8,9) – require higher warfarin dose (Asians:10%, Caucasians:58%; AA:49%)
    - Genotype AA: Caucasians 18% - require lower warfarin dose
    - Genotype BB: Caucasians 35% - require higher warfarin dose
  - Clinical algorithm for warfarin dosing
    - http://www.warfarindosing.org
Warfarin: package insert

Table 1: Three Ranges of Expected Maintenance COUMADIN Daily Doses Based on CYP2C9 and VKORC1 Genotypes

<table>
<thead>
<tr>
<th>VKORC1</th>
<th>CYP2C9</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>*1/*2</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4 mg</td>
</tr>
</tbody>
</table>

*Ranges are derived from multiple published clinical studies. VKORC1 -1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose.*
Genomic Testing for Warfarin

- May guide warfarin dose and decrease time to stabilization of dose
- Long term impact on safety unknown and utility limited once therapeutic dose is achieved
- Prescribing information contains pharmacogenetic testing information
- Pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness is covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who
  - have not been previously tested for CYP2C9 or VKORC1 alleles; and
  - have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and
  - are enrolled in a prospective, randomized, controlled clinical study when that study meets the following standards...

Question 2

Which polymorphism will most likely influence warfarin dosing?
A. CYP2C9 and VKORC1
B. CYP2C19 and VKORC1
C. CYP2D6 and VKORC9
D. CYP2D6 and VKORC1
**FDA Table of Pharmacogenomic Biomarkers in Drug Labeling**

- 164 drugs (some multiple entries for multi-gene info)
- Last updated August 23, 2016
- **Specific Genotype-Based Drug Dosing:** the pharmacogenetic biomarker listed in the table has variants that affect the given drug’s safety or efficacy, and dosage
  - Example: **aripiprazole** CYP2D6 Poor Metabolizers should take half of the standard dose. (Abilify monograph “Dosage and Administration”)
  - Example: **citalopram** CYP2C19 Poor Metabolizers should not exceed 20 mg/day. (Celexa monograph “Clinical Pharmacology”)

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Accessed November 27, 2017
FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

• **Non-Relevant Genotypes:** some labels have a gene biomarker listed in the FDA table; detail shows that the gene is NOT relevant for that drug
  – Example: **citalopram** steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.
    • Citalopram steady state levels were not significantly different in poor metabolizers and extensive metabolizers of CYP2D6.
  – Example: **prasugrel** has four entries – CYP2C19, CYP2C9, CYP3A5, CYP2B6. The “Use in Specific Populations” section in the Effient (prasugrel) insert says:
    • There was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel’s active metabolite or its inhibition of platelet aggregation.

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

FDA Table of Pharmacogenomic Biomarkers in Drug Labeling

• **Drug Interactions:** some labels include pharmacogenetic information that apply to drug interactions rather than the primary metabolism of the given drug.
  – Example: **escitalopram** CYP2D6 Poor Metabolizers. The escitalopram “Drug Interactions” section mentions the following with regard to an escitalopram – CYP2D6 interaction:
    • In vitro studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers. There are...data suggesting a modest CYP2D6 inhibitory effect for escitalopram...caution is indicated in the co-administration of escitalopram and drugs metabolized by CYP2D6.

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm
Factors to Consider with Pharmacogenomics Testing

- Legal issues
- Cost implications
- Social issues
Challenges of Pharmacogenomics Implementation

- **Education of health care providers**
- **Access**
  - Availability of test
  - Insurance coverage
- **Feasibility**
  - Turn around time
  - Efficiency
- **Cost**
  - Counseling
  - Genetic test

<table>
<thead>
<tr>
<th>Pharmacogenomic Tests</th>
<th>Drug</th>
<th>Test</th>
<th>Self-Pay Cost ($)</th>
<th>Contract Cost</th>
<th>Specimen</th>
<th>Results in days</th>
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<td>HER2IHC/HER2/CEP 17 FISH</td>
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<td>277 731</td>
<td>Formalin-fixed; paraffin-embedded tumor tissue</td>
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<td>Whole blood Buccal swab</td>
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<td></td>
</tr>
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</table>

PharmGenEd™ team personal communication with selected labs. Jan-Feb 2009
Where to find more information on Pharmacogenomics

- National Institute of Health – National Human Genome Research Institute
  www.genome.gov
- US Food and Drug Administration
- Clinical Pharmacogenetics Implementation Consortium (CPIC®)
  https://cpicpgx.org/
- PharmGKB - NIH-funded resource that provides information about how human genetic variation affects response to medications
  www.Pharmgkb.org

Question #3

Which of the following resources is useful for finding how a genetic variation affects response to a specific medication?

A. National Institute of Health – National Human Genome Research Institute
B. PharmGKB
C. FDA Table of Pharmacogenomic Biomarkers in Drug Labeling
D. B and C
Genetic tests

Prescribe with confidence using pharmacogenetics and YouScript®

Personalized Prescribing Report

Patient: John L. Doe
Account: Johnson Primary Care
Referrer: Mary Johnson, MD
Date of Birth: 06/21/1924
Lab #: 300134
Reported: 07/27/2016

CUMULATIVE DRUG-DRUG AND DRUG-GENE INTERACTIONS

Impact Medication Cause(s) Effects & Management

Major codeine CYP2D6 Intermediate Metabolizer Paed ● Codiene active metabolite levels may decrease by 81-100%.
● Decreased effectiveness of codeine.
● Increase codeine dose for pain control as necessary.
● No change in codeine dose for cough is necessary.
● Potential alternatives to codeine for pain include: morphine (MS Contin), hydromorphone (Dilaudid) or oxycodone (Opana).
● Potential alternatives to codeine for cough include: benzonatate (Tussion) or guaifenesin (Robitussin).

Major Lopressor CYP2D6 Intermediate Metabolizer Paed ● Lopressor levels may increase by >200%.
● Increased risk of dizziness, fatigue, shortness of breath, depression and bradycardia.
● Decrease Lopressor dose by 50% in CYP2D6 Intermediate Metabolizers with heart failure.
● For patients stable on Lopressor, titrate the dose based on symptomatic response.
● Potential alternatives to Lopressor include: atenolol (Tenormin) and bisoprolol (Zebeta).

DRUG-GENE INTERACTIONS

**Impact**
- CYP2C19 Poor Metabolizer
- CYP3A5 Non-Expresser

**Medication**
- Plavix

**Cause(s)**
- CYP2C19 Poor Metabolizer

**Effects & Management**
- Plavix active metabolite levels may decrease by 51-65%.
- Decreased effectiveness of Plavix.
- Increased risk of major adverse cardiovascular events and stent thrombosis.
- Avoid Plavix in CYP2C19 Poor Metabolizer patients.
- These recommendations apply predominantly to ACS patients undergoing PCI.
- Potential alternatives to Plavix include: clopidogrel (Plavix) and prasugrel (Effient).

**Impact**
- Zocor

**Medication**
- CYP3A5 Intermediate Metabolizer

**Cause(s)**
- CYP3A5 Intermediate Metabolizer

**Effects & Management**
- Zocor levels may increase by 25-75%.
- Increased risk of rash, redness, swelling, and pruritus.
- Decreased Zocor dose if necessary.
- Potential alternatives to Zocor include: statins (Vittero), niacin (Revasco) and ezetimibe (Suvia).

**DRUG-DRUG INTERACTIONS**

**Impact**
- Zocor

**Medication**
- Gemfibrozil

**Cause(s)**
- Gemfibrozil

**Effects & Management**
- Coadministration of gemfibrozil and Zocor is contraindicated.
- Zocor active metabolite levels may increase by 5%.
- Increased risk of malabsorption and myopathy.
- Avoid coadministration of gemfibrozil and Zocor if possible.
- Potential alternatives to gemfibrozil include: fenofibrate acid (Trilix) and fenofibrate (Triate).

**ALTERNATE MEDICATIONS BEING CONSIDERED**

**Impact**
- Cellecox

**Medication**
- CYP2C19 Poor Metabolizer

**Cause(s)**
- CYP2C19 Poor Metabolizer

**Effects & Management**
- Cellecox levels may increase by 76-200%.
- Increased risk of dry mouth, esophageal dysmotility, somnolence, GTC prolongation and nausea.
- Initiate Cellecox dose at 50% of normal in CYP2C19 Poor Metabolizers.
- Limit Cellecox dose to 20 mg daily in CYP2C19 Poor Metabolizers.
- Potential alternatives to Cellecox include: vildagliptin (Vildia), metformin (Ryzox) and diuretics (Trilex).

---

**Pharmacogenetic Laboratory Test Report**

**Patient:** John Doe  
**Date of Birth:** 05/02/1924  
**Collected:** 07/22/2015

**Account:** John Doe  
**Lab #:** 300154  
**Received:** 07/27/2015

**Reference:**  
**Sample:** Buccal Swab  
**Reported:** 07/27/2015

**RESULTS**

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<tr>
<th>Test</th>
<th>Phenotype</th>
<th>Genotype</th>
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<td>CYP3A4</td>
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<tr>
<td>CYP3A5</td>
<td>Non-Expresser</td>
<td>3’3’5’3</td>
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</table>

**LABORATORY RESULTS INTERPRETATION**

CYP2D6 Intermediate Metabolizers have decreased CYP2D6 activity. For CYP2D6 inactivated drugs, consider prescribing decreased doses to prevent adverse effects. For produgs that require activation by CYP2D6, consider prescribing increased doses or alternative treatment for optimal therapeutic response.

CYP2C19 Poor Metabolizers have greatly decreased CYP2C19 activity. For CYP2C19 inactivated drugs, consider prescribing decreased doses or alternative treatment to prevent adverse effects. For produgs that require activation by CYP2C19, consider prescribing increased doses or alternative treatment for optimal therapeutic response.

CYP2C9 Normal Metabolizers have normal (extensive) CYP2C9 activity. Prescribe CYP2C9 metabolized drugs at normal doses.

CYP3A4 Normal Metabolizers have normal (extensive) CYP3A4 activity. Prescribe CYP3A4 metabolized drugs at standard doses. Patients may still have significant variation in CYP3A4 activity due to various patient and environmental factors, despite having a CYP3A4 Normal Metabolizer phenotype.

CYP3A5 Non-Expressers (also known as Poor Metabolizers) have greatly decreased CYP3A5 activity. The majority of the population (80-90%) have this genotype, except for people of African origin. Prescribe CYP3A5 metabolized drugs at standard doses.
ADVISORY NOTE TO TREATING PRACTITIONER:

The YouScript software and Personalized Prescribing Report are clinical decision support tools intended to add to the information healthcare practitioners have available when evaluating and prescribing medications. The recommendations provided may be based on limited patient information and do not supersede sound clinical judgement. The healthcare practitioner has responsibility for all treatment decisions independent of the available genetic test results and any information provided by YouScript software, reports or consultations.

Reviewed By: Sample, PharmD and Example, MD
(877) 786-4302 | Genexel Corporation | 2101 Western Ave. Ste. 100, Seattle, WA 98121

MEDICATION HISTORY:

Current Medications:
- aspirin low dose, gemfibrozil, HCTZ, Lopressor, Paxil, Plavix, Prinivil, Tylenol 3, Zocor

Alternate Medications:
- Celebrex

Failed Medications:
- Zofran

Interaction Impact Legend:
- Contraindicated: This drug has an interaction that is contraindicated in the product insert due to the potential for a severe or life threatening reaction. This combination should not be administered together.
- Major: This drug has an interaction that may result in severe clinical effects or large changes in drug levels. The risks of the interaction generally outweigh the benefits of prescribing the drug.
- Moderate: This drug has an interaction that may result in substantial clinical effects or moderate changes in drug levels. Changes in therapy, such as making dose adjustments or prescribing alternatives, may be warranted.
- Minor: This drug has an interaction that may result in minor clinical effects or small changes in drug levels. The benefits of prescribing the drug generally outweigh the risks of the interaction. Major changes in therapy are not expected, although minor dose adjustments may be appropriate.
- Minimal: This drug may be associated with clinically insignificant and/or favorable interactions. No change in therapy is necessary.

LABORATORY OF PERSONALIZED HEALTH
Division of Genomics Inc.
97 Jefferson Street, Hartford, CT 06106
Tel: (860) 565-4074 Fax: (860) 565-4064
www.genomics.net/LPH

HLOmet WARFARIN
CYP2C9 AND VKORC1 DNA TYPING REPORT

Patient Name: ___________  Patient ID: ___________  LPH ID: ___________
Patient Date of Birth: ___________  Date of specimen receipt into laboratory: ___________
Name of Physician/Authorized person requesting test: ___________

<table>
<thead>
<tr>
<th>CYP2C9 ALLELES</th>
<th>CARRIER STATUS</th>
<th>METABOLIZER STATUS</th>
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<tbody>
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<tr>
<td>&quot;G&quot;</td>
<td>Carrier</td>
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<tr>
<td>&quot;A&quot;</td>
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<td>Poor</td>
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<tr>
<td>&quot;E&quot;</td>
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<table>
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<td>&quot;A&quot;</td>
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<tr>
<td>&quot;E&quot;</td>
<td>Double Carrier</td>
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- Specimen did not meet LPH acceptability

Comments and recommendations:

Refer to the LPH website at www.genomics.net/LPH for additional clinical and scientific background information.

Test Report Date: ___________
Signed: ____________________________
Lab Director: ____________________________
Question #4

A patient’s pharmacogenetic laboratory test report shows that he is a CYP2D6 poor metabolizer. He is prescribed Tylenol with codeine for an ankle sprain.

What is the effect of CYP2D6 poor metabolizer phenotype with codeine?
A. Patient may experience increased side effect
B. Patient may experience decreased efficacy
C. Patient may have increased exposure to the metabolite
D. A and C
Take home points

• Pharmacogenomics is the study of how genetic makeup affects clinical outcomes of drug therapies.

• Currently, there are only a number of medications that require genotype testing prior to initiation of therapy. However, additional clinical applications may be around the corner.

• Identification of opportunities to perform genetic testing and application of results is key.

• Genetic testing is readily available but costly among other barriers.