Genomic and Precision Medicine

Week 6: Clinical applications of genomics — Pharmacogenomics

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The Lecture

- **MODULE 1**: Background
  - Genetic factors influence pharmacokinetics
  - Genetic factors influencing pharmacodynamics

- **MODULE 2**: What pharmacogenomic tests are available?

- **MODULE 3**: Is my patient a candidate for pharmacogenomic testing?

- **MODULE 4**: Where to get testing done and how to interpret the results
MODULE 1: Background — Genetic factors affecting pharmacokinetics and pharmacodynamics
Drug Efficacy

- Drug response rates range from ~25-80%
- Characterized by inter-individual variability

Adverse Drug Reactions

- ADR: unintended and noxious
- ADRs, although individually rare, are collectively common

Pharmacogenomics

- Using a patient’s genomic information to improve the efficacy and/or reduce the side effects of drugs
Pharmacokinetics

- How the drug concentration changes as it moves through the body

  How drug gets into body:
  - Orally
  - Intravenously
  - Inhaled

  How drug is biotransformed:
  - Enzymes (e.g. CYP450s)

  How drug gets into tissues and fluids:
  - Circulatory system
  - Transporters (e.g. SLCO1B1)

  How drug is excreted from body:
  - Urine (renal/kidney)
  - Feces
  - Breath
Many drugs are metabolized by the polymorphic Cytochrome P450 enzymes

Proportion of all drugs metabolized by different CYP450s

<table>
<thead>
<tr>
<th>Enzyme activity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM (Ultrarapid metabolizer)</td>
<td>11%</td>
</tr>
<tr>
<td>EM (Extensive (normal) metabolizer)</td>
<td>19%</td>
</tr>
<tr>
<td>IM (Intermediate metabolizer)</td>
<td>8%</td>
</tr>
<tr>
<td>PM (Poor metabolizer)</td>
<td>3%</td>
</tr>
</tbody>
</table>

CYP3A4/5 (36%), CYP2D6 (19%), CYP2C8/9 (16%), CYP1A2 (11%), CYP2C19 (8%), CYP2B6 (3%), CYP2A6 (3%)
Variable activity of CYP2D6 by ethnicity

Activity of CYP450 enzymes varies by race

PMs are mainly found in European populations

UMs are mainly found in North Africa

Dozens of genetic variants can lead to reduced or complete loss of gene function.

<table>
<thead>
<tr>
<th>Underlying genetics</th>
<th>Polymorphic effect of CYP2D6 variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>UM</td>
<td>Extra copy(s) of gene</td>
</tr>
<tr>
<td>EM</td>
<td>Normal functioning genes (most people)</td>
</tr>
<tr>
<td>IM</td>
<td>One non-functioning and one reduced functioning allele</td>
</tr>
<tr>
<td>PM</td>
<td>Two non-functioning alleles</td>
</tr>
</tbody>
</table>

- Reduced function: e.g. non-synonymous
- Loss of function: e.g. gene deletion or frameshift

http://www.cypalleles.ki.se
Pharmacogenomics — Codeine metabolism

**Normal metabolism**
- Codeine (pro-drug) → CYP2D6 → Morphine → Active metabolite → TARGET → signaling

**CYP2D6 poor metabolizers don’t have enough active drug**
- Codeine (pro-drug) → CYP2D6 → Poor metabolizer → Active metabolite

**Patient requires higher dose to achieve efficacy**
Pharmacogenomics — Warfarin metabolism

**Normal metabolism**

- Active compound
- CYP2C9
- Inert metabolite
- Elimination
- Warfarin
- Therapeutic amount

**CYP2C9 poor metabolizers have too much drug (toxicity)**

- Inert metabolite
- Warfarin
- Poor metabolizer
- Toxic amount
- Elimination

**Target**

- Patient requires lower dose to prevent toxic side effects
- Altered clotting
- Target
How the drug exerts its effect on the body (potency)
Pharmacodynamics — Warfarin target

VKORC1, target of coumarin derivatives (e.g. Warfarin)

Variant upstream of VKORC1 leads to reduced expression

Variant upstream of VKORC1 leads to reduced expression.

More sensitive to inhibition by Warfarin; lower dose required.

https://www.pharmgkb.org/pathway/PA145011114
Off target effects — Abacavir hypersensitivity

Drug affects target, but also interacts with unintended target

Abacavir binds to host HLA-B in patients with the HLA-B*5701 genotype

- HIV reverse transcriptase
- HIV replication

Hypersensitivity reaction, potentially life-threatening

Patients should avoid drug

- Host HLA-B (*5701)

No reaction

- Host HLA-B (*other)

Patient is fine
Gene/c variation in cytochrome P450 genes can impact a drug’s:

A. Efficacy
B. Toxicity
C. Both
C. BOTH

We saw examples of CYP450 polymorphisms affecting efficacy (codeine) and toxicity (warfarin)
MODULE 2: What pharmacogenic tests are available?
Pharmacogenomic Biomarkers in Drug Labeling

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>HUGO Symbol</th>
<th>Referenced Subgroup</th>
<th>Labeling Sections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Infectious Diseases</td>
<td>HLA-B</td>
<td>HLA-B*5701 allele carriers</td>
<td>Boxed Warning, Contraindications, Warnings and Precautions, Patient Counseling Information</td>
</tr>
<tr>
<td>Ado-Trastuzumab</td>
<td>Oncology</td>
<td>ERBB2</td>
<td>HER2 protein overexpression or gene amplification positive</td>
<td>Indications and Usage, Warnings and Precautions, Adverse Reactions, Clinical Pharmacology, Clinical Studies</td>
</tr>
</tbody>
</table>

- 2006 – PGx in drug label
- 158 drug-biomarker pairs
- 12% of 385 drugs approved 1998-2012
- Not all PGx markers in drug label are clinically valid
- Commercial test may not even be available

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
FDA table of pharmacogenomic biomarkers in drug labeling

- Most in therapeutic area of oncology (tumor markers)

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
Over half of non-cancer biomarkers are in three CYP450 enzymes

- CYP2C9
- CYP2C19
- CYP2D6

Safety-related

Tumor markers 34%

CYP450s 34%

Other 29%

HLA 3%

Variation in HLA genes increasingly associated with severe adverse events

http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm
PharmGKB – PGx biomarker levels

Testing required
• Label states or implies that some sort of gene, protein or chromosomal testing ‘should be performed’ before using drug. This includes labels that state that the variant is an indication for the drug.

Testing recommended
• Label states or implies that some sort of gene, protein or chromosomal testing is recommended or ‘should be considered’ before using drug.

Actionable
• Label contains information about changes in efficacy, dosage or toxicity due to such variants, but does not discuss genetic testing

Informational
• Label mentions a gene or protein is involved in the metabolism or pharmacodynamics of the drug, but there is no information to suggest that variation in these genes/proteins leads to different response

Adapted from PharmGKB website: http://www.pharmgkb.org/page/drugLabelLegend
Small number of non-cancer biomarkers are ‘required’ or ‘recommended’

**REQUIRED**
- HLA - Carbamazapine
- CFTR – Ivacaftor
- CYP2D6 – Tetrabenazine
- OTC, POLG – Valproic acid
- CYP2D6 – Pimozide

**RECOMMENDED**
- HLA – Abacavir
- TPMT – Azathioprine
- CYP2C19 – Clopidogrel
- CYP2D6 – Dextromethorphan/quinidine
**Highlights from the drug label**

### HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Indocin safely and effectively. See full prescribing information for Indocin.

**INDOCIN (cholinesterase) CAPSULES**
Initiated U.S. Approval: 2000

#### WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS
See full prescribing information for complete boxed warning.
Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Indocin immediately if any of the following occur:
- Neutropenia/agranulocytosis (5.1)
- Thrombotic thrombocytopenic purpura (5.1)
- Aplastic anemia (5.1)

#### RECENT MAJOR CHANGES
- Indications and Usage, Coronary Stenting (1.2)
- Dosage and Administration, Coronary Stenting (2.2)

#### INDICATIONS AND USAGE
Indocin is an adenosine diphosphate (ADP) antagonist platelet aggregational inhibitor indicated for:
- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary artery thrombosis, when used with aspirin (1.2)

Important limitations:
- For stroke, Indocin should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

#### DOSAGE AND ADMINISTRATION
- **Stroke:** 50 mg once daily with food (2.1)
- **Coronary Stenting:** 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in nonischemic patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.5, 12.3)

#### DOSAGE FORMS AND STRENGTHS
Capsules: 50 mg (3)

#### CONTRAINDICATIONS
- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemorrhagic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

#### WARNINGS AND PRECAUTIONS
- Neutropenia (2.4%) incidence; may occur suddenly, typically resolves within 1-2 weeks of discontinuation, thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukopenia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

#### ADVERSE REACTIONS
Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

#### DRUG INTERACTIONS
- Anticoagulants: Discontinue prior to switching to Indocin (3.5, 7.1)
- Phenylbutazone: Elevated phenylbutazone levels have been reported. Monitor levels (7.5)

#### USE IN SPECIFIC POPULATIONS
- Hepatic impairment: Dose may need adjustment.
- Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.5, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/200X
Placement of pharmacogenomic information in the drug label is inconsistent

<table>
<thead>
<tr>
<th>Label Section</th>
<th>Number of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pharmacology</td>
<td>79</td>
</tr>
<tr>
<td>Indications &amp; Usage</td>
<td>39</td>
</tr>
<tr>
<td>Clinical Studies</td>
<td>38</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>34</td>
</tr>
<tr>
<td>Warnings and Precautions</td>
<td>34</td>
</tr>
<tr>
<td>Dosage &amp; Administration</td>
<td>23</td>
</tr>
<tr>
<td>Adverse Reactions</td>
<td>19</td>
</tr>
<tr>
<td>Precautions</td>
<td>15</td>
</tr>
<tr>
<td>Warnings</td>
<td>14</td>
</tr>
<tr>
<td>Boxed Warning</td>
<td>8</td>
</tr>
</tbody>
</table>
Required tests — usually in Boxed Warning or Indications section......

**Boxed Warning**
Biomakers predictive of serious adverse events
- e.g. Carbamazapine

This is a Boxed Warning indicating serious dermatologic reactions and HLA-B*1502 allele. Biomarkers predictive of serious adverse events, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with Carbamazapine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Carbamazapine. Patients testing positive for the allele should not be treated with Carbamazapine unless the benefit clearly outweighs the risk (see Warnings and Precautions/Laboratory Tests).

**Indications**
Targeted therapies, efficacious for specific biomarker-defined patient population
- e.g. Ivacaftor

1 INDICATIONS AND USAGE

KALYDECO is classified as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the G551D mutation.

**Limitations of Use**

KALYDECO is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene and has not been studied in other populations of patients with CF.
... but not always

- Required tests not always found in boxed warning or indications section of label

- Sometimes found in Warnings, Dosing and Administration, Precautions, etc.

**Tetrabenazine**

Excerpts from the tetrabenazine drug label:

**DOSAGE AND ADMINISTRATION.**

Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM).

The maximum daily dose in PMs is 50 mg with a maximum single dose of 25 mg.

The maximum daily dose in EMs and intermediate metabolizers (IMs) 100 mg with a maximum single dose of 37.5 mg.
Recommended tests - can also be found in Boxed Warnings section

Clopidigrel Boxed Warning – efficacy

**WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

Abacavir Boxed Warning – SAE

**WARNING: HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS, AND SEVERE HEPATOMEGALY**

See full prescribing information for complete boxed warning.

- Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir sulfate. (5.1)
- Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)
- Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)
- Discontinue abacavir sulfate as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue abacavir sulfate if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)
- Following a hypersensitivity reaction to abacavir, NEVER restart abacavir sulfate or any other abacavir-containing product. (5.1)
- Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues. (5.2)

Clinician discretion whether to test or not
Not all PGx markers are in drug label

**Simvastatin** – SLCO1B1 typing for myopathy

**Allopurinol** – HLA-B typing for severe cutaneous adverse reactions (drug hypersensitivity syndrome, Stevens-Johnson syndrome and toxic epidermal necrolysis)
POC medical apps
POC Medical Apps mirror FDA label

**carbamazepine**

**Entire Monograph**

**Black Box Warnings**

- **Appropriate Use**
  - Prescribers should be familiar with complete prescribing information before use, particularly regarding use with other drugs, especially those with toxic potential.

- **Serious Dermatologic Reactions and HLA-B*1502 Allele**
  - Serious, sometimes fatal dermatologic reactions reported, including toxic epidermal necrolysis and Stevens-Johnson syndrome risk.
  - Risk is greater in some Asian countries; strain exposed.

- **Aplastic Anemia/Agranulocytosis**
  - Risk 8x greater than that of general public, but low overall risk in unselected general population, transient or persistent, death, platelet, or WBC counts not uncommon.

- **Diminished Efficacy in Poor Metabolizers**
  - Clopidogrel efficacy dependent on conversion to active metabolite by CYP450 enzymes, principally CYP2C19; less active metabolite formed and smaller anti-platelet effect observed in CYP2C19 poor metabolizers on recommended clopidogrel doses; poor metabolizers w/ ACS or undergoing PCI had higher cardiovascular event rates than in pts w/ normal CYP2C19 fxn; CYP2C19 genotype tests are available and may assist in tx strategy; consider alternative dosing strategies or other anti-platelet tx in CYP2C19 poor metabolizers.

**clopidogrel**

**Entire Monograph**

**Black Box Warnings**

- **Diminished Efficacy in Poor Metabolizers**
  - Clopidogrel efficacy dependent on conversion to active metabolite by CYP450 enzymes, principally CYP2C19; less active metabolite formed and smaller anti-platelet effect observed in CYP2C19 poor metabolizers on recommended clopidogrel doses; poor metabolizers w/ ACS or undergoing PCI had higher cardiovascular event rates than in pts w/ normal CYP2C19 fxn; CYP2C19 genotype tests are available and may assist in tx strategy; consider alternative dosing strategies or other anti-platelet tx in CYP2C19 poor metabolizers.
Presence of pharmacogenomic marker information in an FDA drug label implies that the marker is clinically validated

A. True
B. False
B. False

Pharmacogenomic markers in the drug label can appear for informational purposes only, without clinical validation.
What the FDA label does NOT tell you

- How clinically valid or useful the PGx biomarker is
- Whether your patient is a candidate for testing
- Whether a test for the biomarker is even available
- How to interpret results of testing
MODULE 3: Is my patient a candidate for pharmacogenomic testing?
Consider pharmacogenomic testing if...

- It is required for efficacy
- It can help avoid a severe adverse reaction
- It can help dose a drug with a narrow therapeutic index
CFTR genotype-dependent efficacy of Ivacaftor

Health individual

Normal ion transport

CFTR – chloride channel

Epithelial cell

>1000 mutations lead to Cystic Fibrosis, each affecting CFTR protein in different ways

Δ508F affects folding; channel doesn’t reach surface (85% of patients)

W1282X results in truncated protein

G551D affects function (gating) of channel (4% of patients)

Drug effective only in patients with G551D mutation

Just approved for 8 more mutations!
Consider pharmacogenomic testing if...

- It is required for efficacy
- It can help avoid a severe adverse reaction
- It can help dose a drug with a narrow therapeutic index
**Consequence of ADR?**

**Importance of testing**

- **Low**
  - Depression (Tetrabenazine)

- **High**
  - Myopathy (Simvastatin)
  - Liver failure/death (Valproic Acid)

Additional consequences:
- Stevens-Johnson’s syndrome
- Myelosuppression
- Toxic epidermic necrolysis
- Long QT syndrome
Consider pharmacogenomic testing...

It is required for efficacy. It can help avoid a severe adverse reaction. It can help dose a drug with a narrow therapeutic index.
Correction for multiple testing

Therapeutic index

Drug dose

Therapeutic effect

No effect

TI

Desired effect

Toxic effect

Anti-thrombotic

Blood clots

Brain hemorrhage

Pharmacogenomics may help with dosing
Are alternative therapies available?

- Clopidogrel vs ticagrelor
- Simvastatin vs atorvastatin

**Consider using alternative therapy**


Is the ADR dose-dependent?

Rhabdomyolysis among ~6000 patients taking simvastatin in the SEARCH trial

Conservative dosing may mitigate risk of ADR
Before ordering a test, have a sense of the clinical validity and utility

• Where to find information on clinical validity and utility
  • PLoS Currents: Evidence on Genomic Tests
  • Professional guidelines, literature

• Evaluating PPV and NPV of test
• Considering other factors
• Is the test appropriate in all ethnicities?
Eight non-cancer* PGx reviews available

clopidogrel  interferon-alpha  interferon-alpha
warfarin    simvastatin    simvastatin
thiopurines tamoxifen     tamoxifen
abacavir    statins       statins

*Non-tumor-based
**Clinical Validity**: Test accuracy and reliability in predicting abacavir hypersensitivity (predictive value).

- The prevalence of the *HLA-B*^5701^ allele is highest in Caucasian populations (5-8%) [3][18][19][20]. In African-American, Asian, and Hispanic populations, the prevalence is 0.26-3.6% [19][20][21][22]. In a review of the adult and adolescent antiretroviral guidelines and the abacavir prescribing information [12][16], the prevalence of the *HLA-B*^5701^ allele between ethnic populations has no impact on clinical recommendations.

- In studies conducted in North America, Europe, and Australia where patients were diagnosed with an abacavir hypersensitivity reaction based on symptom presentation, *HLA-B*^5701^ test sensitivity was 46-78% [22][23][24]. In contrast, *HLA-B*^5701^ test sensitivity was 94-100% in patients with an immunologically confirmed (via skin patch testing) abacavir hypersensitivity reaction [25][26][27]. There is suggestion that the discrepancy of lower estimates of test sensitivity was the inclusion of non-abacavir related hypersensitivity reactions [28].

- *HLA-B*^5701^ test specificity, regardless of whether the abacavir hypersensitivity reaction is based on symptom presentation or immunologic confirmation, is 90-100% [22][23][24][25][26][27].

- Pooled data from 3 study populations reported a positive predictive value and negative predictive value of 82% (95% Confidence Interval [CI] 71-90%) and 85% (95% CI 81-88%), respectively [22][23][24].

- A report by Hughes et al. suggested a “high genetic penetrance of *HLA-B*^5701^ in predisposing [patients] to abacavir hypersensitivity” [24].
Professional guidelines, literature
Before ordering a test, have a sense of the clinical validity and utility

- Where to find information on clinical validity and utility
  - PLoS Currents: Evidence on Genomic Tests
  - Professional guidelines, literature

- Evaluating PPV and NPV of test

- Considering other factors

- Is the test appropriate in all ethnicities?
Evaluating PPV and NPV

<table>
<thead>
<tr>
<th></th>
<th>HLA-B*5801 – Allopurinol – related SCAR</th>
<th>IFNL3 – PegIFNα efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>0.4% (ADR)</td>
<td>50% (efficacy)</td>
</tr>
<tr>
<td>PPV</td>
<td>2.6%</td>
<td>90.7%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>58.8%</td>
</tr>
</tbody>
</table>

Rare outcomes can never lead to high PPV, no matter how good the sensitivity/specificity of the test.

- **Rule out ADR**
  - 100% of SCAR patients have *5801
  - 20% of pop. carries *5801, most will not have SCAR

- **Identify likely responders**
  - Variant – high likelihood of responding
  - improved adherence to drug?
Before ordering a test, have a sense of the clinical validity and utility

- Where to find information on clinical validity and utility
  - PLoS Currents: Evidence on Genomic Tests
  - Professional guidelines, literature
- Evaluating PPV and NPV of test
- Considering other factors
- Is the test appropriate in all ethnicities?
Factors affecting inter-individual variability in drug response

Factors affecting Warfarin dosing

- Genetics
- Sex
- Age
- Race
- Concomitant drugs
- Underlying disease

Consider other ways to measure a patient’s response

Consider other factors simultaneously
Before ordering a test, have a sense of the clinical validity and utility

- Where to find information on clinical validity and utility
  - PLoS Currents: Evidence on Genomic Tests
  - Professional guidelines, literature
- Evaluating PPV and NPV of test
- Considering other factors
- **Is the test appropriate in all ethnicities?**
Approximate prevalence of the human leukocyte antigen (HLA) alleles HLA-B*1502 (Carbamazepine) and HLA-B*5801 (Allopurinol) in various geographic regions of the world.
Other practical considerations

- Turn around time
- Economics – is it covered by insurance
Turn-around time

Standard

Point of care

Pre-emptive
Other practical considerations

- Turn around time
- Economics – is it covered by insurance
Medicare coverage decisions

In order to be eligible, all services must be medically necessary and otherwise defined in the member's benefits contract

- TPMT for treatment of IBD with thiopurines — yes
- VKORC1 and CYP2C9 for Warfarin treatment — NO
Insurace coverage (U.S.)

- Many private insurance companies follow Medicare decisions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Aetna</th>
<th>Indep BCBS</th>
<th>Cigna</th>
<th>Humana</th>
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</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>CYP2C19</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Warfarin</td>
<td>CYP2C9/VKORC1</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</tr>
<tr>
<td>Thiopurines</td>
<td>TPMT</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Abacavir</td>
<td>HLA-B</td>
<td>Yes</td>
<td>-</td>
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<tr>
<td>Carbamazepine</td>
<td>HLA-B</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

Coverage policies for pharmacogenomic tests by insurer (Aug 2012)

Pharmacogenomic tests are most appropriate for drugs with:

A. a wide therapeutic index  
B. dose-dependent ADRs  
C. genotype-dependent efficacy
C. genotype-dependent efficacy

A. a wide therapeutic index

B. dose-dependent ADRs
MODULE 4: Where to get testing done and how to interpret the results?
Selecting a lab and test

- Where to find a CLIA-certified testing lab
  - PharmGKB and GTR

- Testing method and limitations
  - Single gene vs gene panel
  - Targeted analysis vs mutation screening
  - Deletion/duplication analysis
PharmGKB

- Manually curated pharmacogenomics knowledge base including information from drug label, clinical testing labs and dosing guidelines (http://www.pharmgkb.org)
PharmGKB — genetic tests

Lists testing labs and test manufacturers

GTR
Search for CYP2D6 gene tests
Can filter on different aspects

Many different vendors

**GeneSight Psychotropic**
Lab: AssureRx Health, Inc, Mason, Ohio, United States
- Conditions: Major depressive disorder, Depression, Major depressive disorder 1
- Test targets: CYP1A2, CYP2B6, CYP2C19
- Total conditions (4)
- Total targets (8)

**Cytochrome P450, 2D6**
Lab: Molecular Genetics Laboratory ARUP Laboratories, Salt Lake City, Utah, United States
- Conditions: Disorder due cytochrome p450 CYP2D6 variant, Methylphenidate response, Tamoxifen response
- Test targets: CYP2D6

**Genetic Pharmacology Testing**
Lab: Molecular Genetics Laboratory Cincinnati Children’s Hospital Medical Center
- Conditions: Disorder due cytochrome p450 CYP2D6 variant, Disorder due cytochrome p450 CYP2C19 variant, Disorder due cytochrome p450 CYP2C9 variant
- Test targets: CYP2C19, CYP2C9, CYP2D6

Private companies
Commercial labs (ARUP, Quest, LabCorp)
Hospital/academic labs
Clinical versus Research test

Run in a CLIA-certified lab

Clinical test, Research test

Showing 1 to 14 of 14 tests for 1 condition in 6 labs

Cytochrome P450, 2D6
Selecting a lab and test

- Where to find a CLIA-certified testing lab
  - PharmGKB and GTR

- **Testing method and limitations**
  - Single gene vs gene panel
  - Targeted analysis vs mutation screening
  - Deletion/duplication analysis
### GTR results for CYP2D6

#### Toxicity to drugs: CYP2D6 gene (alleles *3, *4 and *6) screening

**Lab:** GENETAQ Molecular Genetics Centre and Diagnosis of Rare Diseases, Malaga, Andalucia, Spain

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Test targets</th>
<th>Methods</th>
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<tbody>
<tr>
<td>Disorder due cytochrome p450 CYP2D6 variant</td>
<td>CYP2D6</td>
<td>E Sequence analysis of select exons</td>
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#### Genetic Pharmacology Testing

**Lab:** Molecular Genetics Laboratory, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Test targets</th>
<th>Methods</th>
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<tr>
<td>Disorder due cytochrome p450 CYP2D6 variant</td>
<td>CYP2C19</td>
<td>T Targeted variant analysis</td>
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<td>Disorder due cytochrome p450 CYP2C9 variant</td>
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<td>Disorder due cytochrome p450 CYP2C9 variant</td>
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#### GeneSight Psychotropic

**Lab:** AssureRx Health, Inc, Mason, Ohio, United States

<table>
<thead>
<tr>
<th>Conditions</th>
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<tr>
<td>Major depressive disorder</td>
<td>CYP1A2</td>
<td>D Deletion/duplication analysis</td>
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<tr>
<td>Depression</td>
<td>CYP2B6</td>
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<tr>
<td>Major depressive disorder 1</td>
<td>CYP2C19</td>
<td>T Targeted variant analysis</td>
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<td>Total conditions (4)</td>
<td>Total targets (8)</td>
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Recognize limitations of tests

- Known, common alleles (functional or not)
- Known rare alleles

### CYP2D6 Allele Frequencies Across Populations

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<thead>
<tr>
<th>Allele</th>
<th>African</th>
<th>Caucasian</th>
<th>East Asian</th>
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<tbody>
<tr>
<td>*1</td>
<td>39%</td>
<td>54%</td>
<td>34%</td>
</tr>
<tr>
<td>*2</td>
<td>20%</td>
<td>27%</td>
<td>13%</td>
</tr>
<tr>
<td>*3</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*4</td>
<td>3%</td>
<td>19%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*5</td>
<td>6%</td>
<td>3%</td>
<td>6%</td>
</tr>
<tr>
<td>*6</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*7</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*8</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*9</td>
<td>&lt;1%</td>
<td>2%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*10</td>
<td>7%</td>
<td>3%</td>
<td>42%</td>
</tr>
<tr>
<td>*14</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*17</td>
<td>20%</td>
<td>18%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*36</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>*39</td>
<td>39%</td>
<td>54%</td>
<td>34%</td>
</tr>
<tr>
<td>*41</td>
<td>11%</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>*40</td>
<td>2%</td>
<td>3%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>*41</td>
<td>11%</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>*42</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Some only test for most common alleles

Some assay may not be able to detect duplications

Duplications:
- African: 5%
- Caucasian: 4%
- East Asian: <1%
<table>
<thead>
<tr>
<th>Allele</th>
<th>Protein effect</th>
<th>Luminex xTag Y3</th>
<th>Roche Amplichip</th>
<th>Autogenomics INFINITI</th>
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</thead>
<tbody>
<tr>
<td>*1</td>
<td>F</td>
<td>Presumed</td>
<td>Presumed</td>
<td>Presumed</td>
</tr>
<tr>
<td>*2</td>
<td>F</td>
<td>-1584G, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>-1584G, 1039C&gt;T, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>2850G&gt;T</td>
</tr>
<tr>
<td>*3</td>
<td>NF</td>
<td>2549delA</td>
<td>2549delA</td>
<td></td>
</tr>
<tr>
<td>*4</td>
<td>NF</td>
<td>100C&gt;T, 1551G&gt;C, 1846G&gt;A, 4180G&gt;C</td>
<td>100C&gt;T, 1039C&gt;T, 1661G&gt;C, 1846G&gt;A, 2850C&gt;T, 4180G&gt;C</td>
<td>1846G&gt;A</td>
</tr>
<tr>
<td>*5</td>
<td>NF</td>
<td>Deletion</td>
<td>Deletion</td>
<td>Deletion</td>
</tr>
<tr>
<td>*6</td>
<td>NF</td>
<td>1707delT</td>
<td>1707delT, 1976G&gt;A, 4180G&gt;C</td>
<td>1707delT</td>
</tr>
<tr>
<td>*7</td>
<td>NF</td>
<td>2915A&gt;C</td>
<td>2915A&gt;C</td>
<td></td>
</tr>
<tr>
<td>*8</td>
<td>NF</td>
<td>1661G&gt;C, 1758G&gt;T, 2850C&gt;T, 4180G&gt;C</td>
<td>1661G&gt;C, 1758G&gt;T, 2850C&gt;T, 4180G&gt;C</td>
<td>1758G&gt;T</td>
</tr>
<tr>
<td>*9</td>
<td>DF</td>
<td>2613–2615delAGA</td>
<td>2613–2615delAGA</td>
<td>2615_7delAGA</td>
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<tr>
<td>*10</td>
<td>DF</td>
<td>100C&gt;T, 1661G&gt;C, 4180G&gt;C</td>
<td>100C&gt;T, 1039C&gt;T, 1661G&gt;C, 4180G&gt;C</td>
<td>100C&gt;T</td>
</tr>
<tr>
<td>*11</td>
<td>NF</td>
<td>883G&gt;C, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>883G&gt;C, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>Not tested</td>
</tr>
<tr>
<td>*12</td>
<td>NF</td>
<td>124G&gt;A</td>
<td>Not tested</td>
<td>124G&gt;A</td>
</tr>
<tr>
<td>*13</td>
<td>NF</td>
<td>1758G&gt;A</td>
<td>Not tested</td>
<td>1758G&gt;A</td>
</tr>
<tr>
<td>*14</td>
<td>NF</td>
<td>138insT</td>
<td>138insT</td>
<td>Not tested</td>
</tr>
<tr>
<td>*15</td>
<td>NF</td>
<td>1023C&gt;T, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>1023C&gt;T, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>1023C&gt;T</td>
</tr>
<tr>
<td>*16</td>
<td>NF</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not tested</td>
</tr>
<tr>
<td>*17</td>
<td>NF</td>
<td>1659G&gt;A, 1661G&gt;C, 2850C&gt;T, 3183G&gt;A, 4180G&gt;C</td>
<td>1659G&gt;A, 1661G&gt;C, 2850C&gt;T, 3183G&gt;A, 4180G&gt;C</td>
<td>1659G&gt;A</td>
</tr>
<tr>
<td>*18</td>
<td>F</td>
<td>-1584C, 31G&gt;A, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>-1584C, 31G&gt;A, 1661G&gt;C, 2850C&gt;T, 4180G&gt;C</td>
<td>Not tested</td>
</tr>
<tr>
<td>*19</td>
<td>NF</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not tested</td>
</tr>
<tr>
<td>*20</td>
<td>NF</td>
<td>100C&gt;T, 4039C&gt;T, 1661G&gt;C, 4180G&gt;C, gene conversion to CYP2D7 in exon 9</td>
<td>100C&gt;T, 4039C&gt;T, 1661G&gt;C, 4180G&gt;C, gene conversion to CYP2D7 in exon 9</td>
<td>Not tested</td>
</tr>
<tr>
<td>*21</td>
<td>NF</td>
<td>Not tested</td>
<td>Not tested</td>
<td>Not tested</td>
</tr>
</tbody>
</table>

- o Missing rare alleles
- o Missing gene duplications
- o Potential for misclassification
Interpreting test results

- CPIC
- PharmGKB dosing guidelines
Clinical Pharmacogenomics Implementation Consortium

Purpose: to provide actionable prescribing decisions when genotype is already available in the clinical environment.

Focus on HOW available genetic test results should be used to optimize drug therapy, rather than WHETHER tests should be ordered.

Eleven non-cancer (tumor-based)* PGx reviews available

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
<th>Drug</th>
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<tbody>
<tr>
<td>clopidogrel</td>
<td>interferon-alpha</td>
<td>Allopurinol</td>
<td></td>
</tr>
<tr>
<td>warfarin</td>
<td>simvastatin</td>
<td>5-fu, capecetabine</td>
<td></td>
</tr>
<tr>
<td>thiopurines</td>
<td>codeine</td>
<td>TCA</td>
<td></td>
</tr>
<tr>
<td>abacavir</td>
<td>carbamazapine</td>
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</tr>
</tbody>
</table>

*CPIC: Implementing PGx
a PharmGKB & PGRN collaboration
Example CPIC guideline

Figure 1 Algorithm for suggested clinical actions based on CYP2C19 genotype when considering treatment with clopidogrel for ACS patients.

Considering antiplatelet therapy with clopidogrel for ACS/PCI

CYP2C19 genotype results

- UM (*1/*17, *17/*17)
- EM (*1/*1)
- IM (*1/*2, *1/*3, *2/*17)
- PM (*2/*2, *2/*3, *3/*3)

Standard dosing of clopidogrel
Consider alternative antiplatelet agent (e.g., prasugrel, ticagrelor)
PharmGKB – dosing/action guideline

CPLIC Dosing Guideline for azathioprine and TPMT

Summary
Consider an alternate agent or extreme dose reduction of azathioprine for patients with low or deficient TPMT activity. Start at 30-70% of target dose for patients with intermediate enzyme activity.

Look up your guideline
Pick TPMT alleles: *1 *3A

Phenotype (Genotype)
Heterozygote or intermediate activity (one functional allele - *1, plus one nonfunctional allele - *2, *3A, *3B, *3C, or *4)

Implications
Moderate to high concentrations of TGN metabolites; low concentrations of methylTIMP

Recommendations (Strength: Strong)
If disease treatment normally starts at the "full dose", consider starting at 30-70% of target dose (e.g., 1-1.5 mg/kg/d), and titrate based on tolerance. Allow 2-4 weeks to reach steady state after each dose adjustment.

Individual testing laboratories should also provide test interpretation and treatment guidance

https://www.pharmgkb.org/gene/PA356