Pharmacogenomics: Providing Personalized Medicine

April 28, 2020

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Stanford University
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Learning Objectives

At the end of this educational activity, participants should be able to:

- Explain the basic science of liver enzymes and their genetic variations.
- Name the various liver enzymes most frequently tested in relation to psychiatric drugs.
- Describe the clinical indications for using pharmacogenomics.
- Discuss resources for interpreting pharmacogenomic test results.
- List the limitations of current pharmacogenomics tests.
Pharmacogenetics is Defined

“The role of genetics in drug responses.”

F. Vogel, 1959
Genotype <-> Phenotype associations

Relate genetic information (genotype):
1. ATCGCCGGATACCTAGAGAC...
2. ATCGCCGGAGACCTAGAGAC...

to observable traits (phenotypes), e.g.
1. Responds well to cholesterol medication
2. Develops hepatotoxicity

Genome Variation

- About 10 million single nucleotide polymorphisms (SNPs) identified in human population (~4 million present in any individual)
- Many small insertions/deletions in genes
- Many “copy number variants” with multiple copies of genes
- Almost anything else you can think of occurs…
Purine analogs

- 6-mercaptopurine, 6-thioguanine, azathioprine
- Used to treat lymphoblastic leukemia, autoimmune disease, inflammatory bowel disease, after transplant
- Interferes with nucleic acid synthesis
- Therapeutic index limited by myelosuppression
**Metabolism of 6-MP**
Weinshilboum (Mayo Clinic) 2001

Levels of TPMT can drastically affect levels of thioguanines

- More TPMT = less thioguanines
- Associated with risk of severe marrow toxicity
- Shows considerable variability in population
Variation in TPMT Activity
Weinshilboum (Mayo Clinic) 2001

6-MP and TPMT Story Summary

- Observation of clinical variability (toxicity)
- Observation of cellular variability (TPMT activity, TGN concentrations)
- Observation of genetic variability (genome variations in TPMT gene)
The logic of pharmacogenetics

1. Identify variation in drug response
2. Associate it with genetic variation
3. Evaluate clinical significance
4. Develop screening tests
5. Individualize drug therapy

What is the clinical promise?

• Focused treatment by pre-identifying genetic backgrounds likely to respond
• Reduce adverse events by predicting who is at risk
• A way to save drugs in the pipeline that are very effective only in subpopulations
• Better understanding of drug interactions
Defining P-etics vs. P-omics

- **Pharmacogenetics** = study of individual gene-drug interactions, usually the gene that has the dominant effect on a drug response. (SIMPLE relationship)
- **Pharmacogenomics** = study of the full set of PK/PD genes, often using high-throughput data (sequencing, expression, proteomics) (COMPLEX interactions)

Example: Codeine & CYP2D6

- Codeine is a commonly used opioid – must be metabolized into morphine for activity
- CYP2D6 is the protein that performs this metabolism
- 7% of caucasians have a variant version of CYP2D6 with no activity -> codeine does not work
Candidate Genes Involved in Metabolism of Codeine and Morphine

The O-dealkylation of Codeine by CYP2D6
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Cytochrome P450 2D6

- Absent in 7% of Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes the primary metabolism of
  - propafenone
  - Codeine
  - β-blockers
  - tricyclic antidepressants
- Inhibited by
  - fluoxetine
  - haloperidol
  - paroxetine
  - quinidine

CYP2D6 Alleles

- >100 alleles reported
- Many alleles function not known
- ~50 alleles have no activity
- ~10 alleles have decreased activity
- The *2 variant can have 1, 2, 3, 4, 5 or 13 copies resulting in increased activity

http://www.cypalleles.ki.se/cyp2d6.htm
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Allelic Frequencies of CYP2D6

CYP2D6 and Simvastatin

- Simvastatin = HMG CoA reductase, used to decrease LDL, increase HDL cholesterol.
- Dose of simvastatin required to get cholesterol-lowering effect is related to 2D6 mutations and duplications.
- Another report demonstrates that “statins” are metabolized differently.
  Biopharm Drug Dispos. 2000 Dec;21(9):353-64.
Copy number polymorphisms = CNPs

- Increasing evidence for variation in the number of copies of a gene in humans
- Won’t necessarily be picked up with normal genotyping technology (e.g. sequencing)
- Associated with cancers, genetic diseases, and now with drug response variation
- Methods for quantifying transcript level, to detect CNPs are coming down in costs

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Pharmacogenetic Laboratory Test Report

<table>
<thead>
<tr>
<th>Test</th>
<th>Phenotype</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6</td>
<td>Intermediate Metabolizer</td>
<td>*1/*4</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Normal Metabolizer</td>
<td>*1/*1</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Poor Metabolizer</td>
<td>*2/*2</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Normal Metabolizer</td>
<td>*1/*1</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Intermediate Metabolizer</td>
<td>*1/*3</td>
</tr>
<tr>
<td>VKORC1</td>
<td>High Sensitivity</td>
<td>c.-1639G&gt;A AA</td>
</tr>
<tr>
<td>HLA-B*57:01</td>
<td>Negative</td>
<td>*57:01-rs2998027=G TT</td>
</tr>
<tr>
<td>SLC01B1</td>
<td>Normal Function</td>
<td>*1/*14</td>
</tr>
<tr>
<td>TPMT</td>
<td>Normal Metabolizer</td>
<td>*1/*1</td>
</tr>
<tr>
<td>DPD (DPD)</td>
<td>Normal Metabolizer</td>
<td>*1/*1</td>
</tr>
<tr>
<td>IFNL3 (IL28B)</td>
<td>Favorable Response</td>
<td>rs1297986=CT CC</td>
</tr>
<tr>
<td>NAT2</td>
<td>Slow Acetylator</td>
<td>*982GC</td>
</tr>
<tr>
<td>F2 (Factor II)</td>
<td>Positive Heterozygous</td>
<td>c.970&gt;A GA</td>
</tr>
<tr>
<td>F5 (Factor V)</td>
<td>Negative</td>
<td>c.1610G&gt;A GG</td>
</tr>
<tr>
<td>MTHFR</td>
<td>Intermediate Activity</td>
<td>c.665C&gt;T CT</td>
</tr>
</tbody>
</table>

PharmGKB – http://www.pharmgkb.org/
Clinical Implementation of Pharmacogenomics: A Focus on Guidelines

American Heart Association November 4, 2012

www.pharmgkb.org
CPIC: clinical pharmacogenetics implementation consortium

- CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.

- Key Assumption:
  - Clinical high-throughput and pre-emptive genotyping will become more widespread.
  - Clinicians will be faced with having patients’ genotypes available even if they did not order test with drug in mind.

http://cpicpgx.org/
Key Points about a CPIC guideline

- Based on assumption that the test results are in hand and NOT to discuss the merits of doing the test
- Standardized formats
- Grading of evidence and of recommendations
- Peer reviewed
- Freely available
- Updated
- Authorship with COI policy
- Closely follow IOM practices

CPIC guideline genes and drugs, highlights

- **TPMT**
  - MP, TG, azathioprine
- **CYP2D6**
  - Codeine, tramadol, hydrocodone, oxycodone, TCAs
- **CYP2C19**
  - TCAs, clopidogrel, voriconazole
- **VKORC1**
  - warfarin
- **CYP2C9**
  - Warfarin, phenytoin
- **HLA-B**
  - Allopurinol, CBZ, abacavir, phenytoin
- **CFTR**
  - ivacaftor
- **DPYD**
  - 5FU, capecitabine, tegafur
- **G6PD**
  - rasburicase
- **UGT1A1**
  - irinotecan
- **SLCO1B1**
  - simvastatin
- **IFNL3 (IL28B)**
  - interferon
- **CYP3A5**
  - tacrolimus

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Guidelines

CPIC guidelines are designed to help clinicians understand how available genetic test results should be used to optimize drug therapy, rather than whether tests should be ordered. A key assumption underpinning the CPIC guidelines is that clinical high through and pre-emptive (pre-prescription) genotyping will become more widespread, and that clinicians will be faced with having patient genotypes available even if they have not explicitly ordered a test with a specific drug in mind. CPIC guidelines provide patients with individualized treatment recommendations, but they cannot be implemented without robust evidence and clinical judgment.

Each CPIC guideline adheres to a standard format, and includes a standard system for grading levels of evidence linking genotypes to phenotypes, how to assign phenotypes to clinical genotypes, prescribing recommendations based on genotype/phenotype, and a standard system for assigning strength to each prescribing recommendation. The CPIC guidelines were developed by a panel of experts in genomics and were updated in June 2014.

View CPIC’s process for prioritizing CPIC guidelines

Clinical Pharmacogenetics Implementation Consortium Guidelines for Human Leukocyte Antigen-B Genotype and Allopurinol Dosing

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C19 Genotypes and Dosing of Thioridazine

Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B Genotype and Carbamazepine Dosing

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for IFNL3 (IL28B) Genotype and Peg-Interferon-α-Based Regimens

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Linking genotype to phenotype

Table 1: Assignment of likely thiopurine methyltransferase phenotypes based on genotypes

<table>
<thead>
<tr>
<th>Genotypes</th>
<th>Examples of diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td><code>(1,2)TPMT*1/*1</code></td>
</tr>
<tr>
<td>High</td>
<td><code>(1,2)TPMT*2/*2</code></td>
</tr>
<tr>
<td>Intermediate</td>
<td><code>(1,2)TPMT*2/*1</code></td>
</tr>
</tbody>
</table>

Table 2: Recommended dosing of thiopurines by thiopurine methyltransferase phenotype

<table>
<thead>
<tr>
<th>MP/Azathioprine</th>
<th>TGN After MP/Azathioprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

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Supplemental Table S5. Evidence linking genotype with phenotype

<table>
<thead>
<tr>
<th>Type of experimental model (in vitro, in vivo preclinical, or clinical)</th>
<th>Major findings</th>
<th>References</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro MP’s metabolism to methylmercapturine absent in human orthocytes, lymphocytes, liver, and kidneys from TPMT homozygous deficient individuals</td>
<td>(28, 113-115)</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>In vitro TG’s metabolism to methylthioguanine</td>
<td>(114)</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>In vitro Heterologous expression of TPMT antibodies mercapturine, mercapturine to methylthioguanine, and TGP to methylthioguanine</td>
<td>(119, 120)</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Preclinical TPMT knock-out mice have more morbidity and mortality from thioguanine and mercapturine than wild type mice, heterozygotes were at intermediate risk</td>
<td>(121)</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Clinical TPMT wildtype patients with ALL have higher risk of hematologic relapse than those with at least one variant TPMT allele, particularly in regimens that are primarily antimetabolite-based: wildtype patients with B-ALL have higher risk of treatment failure</td>
<td>(122-124)</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.


UnitedHealthcare® Commercial Medical Policy

PHARMACOGENETIC TESTING

Policy Number: 2019T0587E Effective Date: October 1, 2019

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Related Commercial Policies
- Cardiovascular Disease Risk Tests
- Chemosensitivity and Chemoresistance Assays in Cancer
- Pharmacogenetic Testing
- Genetic Testing
- Laboratory Tests and Services

Community Plan Policy

Medicare Advantage Coverage Summaries

COVERAGE RATIONALE

The use of pharmacogenetic Multi-Gene Panels to guide therapy decisions is proven and medically necessary for antidepressants and antipsychotics medication when ALL of the following criteria are met:
- The individual has a diagnosis of major depressive disorder or anxiety; and
- The individual has failed at least one prior medication to treat their condition; and
- The Multi-Gene Panel has no more than 15 relevant genes (refer to Table 1)

The use of pharmacogenetic Multi-Gene Panels for genetic polymorphisms for any other indication, including but not limited to pain management, cardiovascular drugs, anthracyclines, or polypharmacy, is unproven and not medically necessary for evaluating drug-metabolizer status due to insufficient evidence of efficacy.
### Table 1. Antidepressant, Antipsychotic Drugs and Associated Genes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Genes</th>
<th>Select Associated References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>CYP2C19, CYP2D6, COMT, TXNRD2</td>
<td>CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)</td>
</tr>
</tbody>
</table>
| Citalopram | CYP2C19, SLC6A4, GRIK4, HTR2A, FKBP5, COMT, TXNRD2 | • CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)  
  • Polymorphisms in GRIK4, HTR2A, and FKBP5 Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010) |
| Escitalopram| CYP2C19, SLC6A4, COMT, TXNRD2       | • CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)  
  • Interaction between serotonin transporter gene variants and life events predicts response to antidepressants in the GENDEP project (Keers et al., 2011) |
| Fluoxetine | FKBP5, COMT, TXNRD2                 | Polymorphisms in GRIK4, HTR2A, and FKBP5 Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010) |
| Paroxetine | CYP2D6, HTR1A, FKBP5, COMT, TXNRD2  | • CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015)  
  • Polymorphisms in GRIK4, HTR2A, and FKBP5 Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010) |
| Fluvoxamine| CYP2D6, COMT, TXNRD2                | CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015) |
| Venlafaxine| CYP2D6, FKBP5                      | Polymorphisms in GRIK4, HTR2A, and FKBP5 Show Interactive Effects in Predicting Remission to Antidepressant Treatment (Horstmann et al., 2010) |
| Amitriptyline| CYP2C19, 2D6                    | CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017) |
| Nortriptyline| CYP2D6                        | CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Tricyclic Antidepressants (Hicks et al., 2017) |
| Clomipramine| CYP2C19, 2D6                     | CPIC Guideline for CYP2D6 and CYP2C19 Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors (Hicks et al., 2015) |

https://cignaforcnp.cigna.com/public/content/pdf/coveragePolicies/medical/mm_0500_coveragepositioncriteria_pharmacogenetic_testing.pdf

Medical Coverage Policy

Effective Date: 11/15/2019
Next Review Date: 1/15/2020
Coverage Policy Number: 0500

Pharmacogenetic Testing

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**Related Coverage Resources**

- Genetics
- Genetic Testing Collateral: Genetic Tests and Biomarkers File
- Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators
- Lomatidine Mesylate, Mipomersen Sodium
- PCSK9 Inhibitors
- Serological Testing for Inflammatory Bowel Disease

**INSTRUCTIONS FOR USE**

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. For example, a customer’s particular benefit plan document (e.g., Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document) may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan...
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PharmGKB – http://www.pharmgkb.org/

CPIC guidelines linked to “Practice Guideline” filter on PubMed
Conclusions

1. Pharmacogenomics combines molecular understanding of drug response and human genetic variation to optimize drug use.
2. Currently rolling out in clinical use, mostly based on genotyping → sequencing coming
3. Need good information systems to support clinical use by clinicians (physicians and pharmacists)

Thank you!

Russ.altman@Stanford.edu

https://www.pharmgkb.org/