Utilizing genomic data in clinical systems

Robert Freimuth, PhD

ISMB - AKES
July 9, 2016
Percentage of the patient population for which a particular drug in a class is ineffective, on average

<table>
<thead>
<tr>
<th>Class</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-depressants SSRIs</td>
<td>38%</td>
</tr>
<tr>
<td>Asthma drugs</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes drugs</td>
<td>43%</td>
</tr>
<tr>
<td>Arthritis drugs</td>
<td>50%</td>
</tr>
<tr>
<td>Alzheimer’s drugs</td>
<td>70%</td>
</tr>
<tr>
<td>Cancer drugs</td>
<td>75%</td>
</tr>
</tbody>
</table>

Adverse Drug Reactions (ADRs)

- Cost to treat inpatient ADRs: $1.6 - 5.6 billion annually
- ~7 M ED visits related to ADRs annually

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-depressants</td>
<td>38%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>40%</td>
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<td>Diabetes Drugs</td>
<td></td>
</tr>
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<td>75%</td>
</tr>
<tr>
<td>Cancer Drugs</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacogenomics (PGx)

- PGx: How genetic variations affect drug response

PK
- Absorption
- Distribution
- Metabolism
- Excretion

PD
- Biochemical Effects
- Physiological Effects
- Mechanism of Action

- Early example of genomic medicine
  - 1953: slow/rapid acetylation of isoniazid
  - 1959: Vogel coins "pharmacogenetics"
  - 1980: Weinshilboum/Sladek – TPMT polymorphism
  - 2001: draft human genome sequence
Right Drug, Right Dose, Right Time – Using Genomic Data to Individualize Treatment (The RIGHT Protocol)

- 1013 Mayo Clinic Biobank participants
- 84-gene next generation sequencing
- Interpreted and reported 5 genes:
  - **SLCO1B1** – Statins
  - **CYP2C19** – Clopidogrel (Plavix)
  - **CYP2C9** – Warfarin (Coumadin)
  - **VKORC1** – Warfarin (Coumadin)
  - **CYP2D6** – Codeine, tramadol, SSRIs
- 30 – 80% carry actionable PGx variant(s) in a given gene
- 99% of the RIGHT patients carried an actionable PGx variant in 1+ genes


Slide adapted from Sue Bielinski, PhD
Information Overload!
PGx Implementations: Enterprise CDS Rules

- **HLA-B*1502**
  - Carbamazepine

- **HLA-B*5701**
  - Abacavir

- **HLA-B*5801**
  - Allopurinol

- **CYP2C9/VKORC1**
  - Warfarin

- **CYP2C19**
  - Clopidogrel
  - Citalopram
  - Escitalopram

- **CYP2D6**
  - Codeine/Tramadol
  - Tamoxifen
  - Paroxetine
  - Fluoxetine
  - Fluvoxamine
  - Venlafaxine

- **SLCO1B1**
  - Simvastatin

- **TPMT Genotype**
  - Mercaptopurine
  - Thioguanine
  - Azathioprine

- **TPMT Phenotype**
  - Mercaptopurine
  - Thioguanine
  - Azathioprine

9 Genes + 18 Drugs: 2076 interventions (Jan-May 2016)
Pharmacogenomics Alert: Cytochrome P450 Enzyme(s)

Metabolizer CYP2D6 Ultra Rapid

Recommendation

Based on this patient's CYP450 enzyme phenotype(s) and unissued medication order(s):

*Acetaminophen-Codeine Tab PO* and *Metabolizer CYP2D6 Ultra Rapid*: Avoid codeine due to potential for toxicity. May consider avoiding tramadol.; see [AskMayoExpert (Codeine)](mailto:AskMayoExpert@mayo.edu) for details.

*If this alert is an error or you have questions send an email to micspgx@mayo.edu*
PGx CDS: Genetic Test Results in the EHR

- Narrative text
- Some results are discrete, not all are normalized
- Results are static
CYP2C19 Genotype, B

CYP2C19 Phenotype
Poor metabolizer

CYP2C19 Star Alleles
2/2

CYP2C19 Interpretation
This individual is likely a poor CYP2C19 metabolizer. Caution should be exercised when treating with drugs metabolized by CYP2C19 as follows:

If this patient is taking a prodrug that is activated by CYP2C19, such as clopidogrel, reduced activation of the drug is expected which may result in decreased efficacy of the drug.

If this patient is taking a drug that is inactivated by CYP2C19, such as citalopram, reduced inactivation is expected which may result in higher blood levels of the drug and potential side effects.

Consideration should be given to using drugs not metabolized by CYP2C19.
PGx CDS: Drug Order Triggers Intervention

CDS Rule:
- Drug list
- Genomic interpretations
- Clinical recommendation
Requirements for Scalable Genomic CDS

• Computable data and knowledge
• Standardized data representation
  • Patient genetic data and interpretations (phenotype)
• Dynamic knowledge management (new and evolving)
  • Genetic interpretations, clinical actionability
  • Gene-drug interactions, clinical recommendations
"By adopting and leveraging next-generation sequencing, clinical laboratories are now performing an ever-increasing catalogue of genetic testing spanning genotyping, single genes, gene panels, exomes, genomes, transcriptomes, and epigenetic assays for genetic disorders. By virtue of increased complexity, this shift in genetic testing has been accompanied by new challenges in sequence interpretation. In this context the ACMG convened a workgroup in 2013 comprising representatives from the ACMG, the Association for Molecular Pathology (AMP), and the College of American Pathologists to revisit and revise the standards and guidelines for the interpretation of sequence variants."
### 2015 ACMG Guidelines: Structured Variant Data

#### Variant Nomenclature (Definition)

<table>
<thead>
<tr>
<th>Gene Transcript</th>
<th>Location</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Classification</th>
<th>Disease</th>
<th>Inheritance</th>
<th>Parental Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>YY</td>
<td>Exon X/Intron X/Promoter/UTR</td>
<td>c.XXX (p.XXX)</td>
<td>(Apparently) homozygous/Heterozygous/Hemizygous/Heteroplasmic/Homoplasmic/Mosaic/Somatic</td>
<td>Pathogenic/Likely pathogenic/Uncertain significance</td>
<td>Disease Z</td>
<td>Autosomal recessive/Autosomal dominant/X-linked/Mitochondrial</td>
<td>Paternal/Maternal/De novo/Unknown</td>
</tr>
</tbody>
</table>

#### Patient Results

PMID 25741868, Supplemental Data
### 2015 ACMG Guidelines: Structured Variant Data

#### Disease Context

<table>
<thead>
<tr>
<th>Gene Transcript</th>
<th>Location</th>
<th>Variant</th>
<th>Zygosity</th>
<th>Classification</th>
<th>Disease</th>
<th>Inheritance</th>
<th>Parental Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>YY  NM_12345.6</td>
<td>Exon X/ Intron X/ Promoter/ UTR</td>
<td>c.XXX (p.XXX)</td>
<td>(Apparently) homozygous/ Heterozygous/ Hemizygous/ Heteroplasmic/ Homoplasmic/ Mosaic/ Somatic</td>
<td>Pathogenic / Likely pathogenic / Uncertain significance</td>
<td>Disease Z</td>
<td>Autosomal recessive/ Autosomal dominant/ X-linked/ Mitochondrial</td>
<td>Paternal/ Maternal/ De novo/ Unknown</td>
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</tbody>
</table>

PMID 25741868, Supplemental Data
### 2015 ACMG Guidelines: Structured Variant Data

#### Need standard terminology and criteria for variant classification

<table>
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<th>Classification</th>
<th>Disease</th>
<th>Inheritance</th>
<th>Parental Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>YY</td>
<td>Exon X/Intron X/</td>
<td>c.XXX</td>
<td>(Apparently) homozygous/</td>
<td>Pathogenic / Likely</td>
<td>Disease Z</td>
<td>Autosomal recessive/</td>
<td>Paternal/</td>
</tr>
<tr>
<td>NM_12345.6</td>
<td>Promoter/UTR</td>
<td>(p.XXX)</td>
<td>Heterozygous/ Hemizygous/</td>
<td>pathogenic / Uncertain</td>
<td></td>
<td>Autosomal dominant/</td>
<td>Maternal/</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Heteroplasmic/ Homoplasmic/</td>
<td>significance</td>
<td></td>
<td>X-linked/ Mitochondrial</td>
<td>De novo/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mosaic/ Somatic</td>
<td></td>
<td></td>
<td></td>
<td>Unknown</td>
</tr>
</tbody>
</table>
2015 ACMG Guidelines: Variant Classification

- Survey to establish consensus on terminology
  - Focus: Mendelian and mitochondrial variants
    - Not somatic, PGx, multigenic non-Mendelian
  - Discussion forums at ACMG meetings
  - Input from specialized variant classification systems
    - Breast and colon cancer, cystic fibrosis

- Standardized terms for variant classification:
  - Pathogenic, Likely pathogenic
  - Uncertain significance
  - Likely benign, Benign
2015 ACMG Guidelines: Variant Classification

- **Types of evidence**
  - Population data
  - Computational and predictive data
  - Functional data
  - Segregation data
  - De novo data
  - Allelic data
  - Other supporting data

- **Sources of data**
  - Patient clinical record
  - Pedigree analysis
  - Public databases
  - Literature review
  - Predictive software tools
  - Genotype-phenotype correlations (internal)
2015 ACMG Guidelines: Evidence Framework

Categories and Weight of Evidence

Types of Evidence

Criteria

PMID 25741868
### Table 3 Criteria for classifying pathogenic variants

<table>
<thead>
<tr>
<th>Evidence of pathogenicity</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very strong</td>
<td>PVS1 null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease</td>
</tr>
<tr>
<td></td>
<td>Caveats:</td>
</tr>
<tr>
<td></td>
<td>• Beware of genes where LOF is not a known disease mechanism (e.g., GFAP, MYH7)</td>
</tr>
<tr>
<td></td>
<td>• Use caution interpreting LOF variants at the extreme 3’ end of a gene</td>
</tr>
<tr>
<td></td>
<td>• Use caution with splice variants that are predicted to lead to exon skipping but leave the remainder of the protein intact</td>
</tr>
<tr>
<td></td>
<td>• Use caution in the presence of multiple transcripts</td>
</tr>
<tr>
<td>Strong</td>
<td>PS1 Same amino acid change as a previously established pathogenic variant regardless of nucleotide change</td>
</tr>
<tr>
<td></td>
<td>Example: Val→Leu caused by either G&gt;C or G&gt;T in the same codon</td>
</tr>
<tr>
<td></td>
<td>Caveat: Beware of changes that impact splicing rather than at the amino acid/protein level</td>
</tr>
<tr>
<td></td>
<td>PS2 De novo (both maternity and paternity confirmed) in a patient with the disease and no family history</td>
</tr>
<tr>
<td></td>
<td>Note: Confirmation of paternity only is insufficient. Egg donation, surrogate motherhood, errors in embryo transfer, and so on, can contribute to nonmaternity.</td>
</tr>
<tr>
<td></td>
<td>PS3 Well-established in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product</td>
</tr>
<tr>
<td></td>
<td>Note: Functional studies that have been validated and shown to be reproducible and robust in a clinical diagnostic laboratory setting are considered the most well established.</td>
</tr>
<tr>
<td></td>
<td>PS4 The prevalence of the variant in affected individuals is significantly increased compared with the prevalence in controls</td>
</tr>
</tbody>
</table>

PMID 25741868
Table 5: Rules for combining criteria to classify sequence variants

<table>
<thead>
<tr>
<th>Pathogenic</th>
<th>Likely pathogenic</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) 1 Very strong (PVS1) AND</td>
<td>(i) 1 Very strong (PVS1) AND 1 moderate (PM1–PM6) OR</td>
<td>(i) 1 Stand-alone (BA1) OR</td>
</tr>
<tr>
<td>(a) ≥1 Strong (PS1–PS4) OR</td>
<td>(ii) 1 Strong (PS1–PS4) AND 1–2 moderate (PM1–PM6) OR</td>
<td>(ii) ≥2 Strong (BS1–BS4)</td>
</tr>
<tr>
<td>(b) ≥2 Moderate (PM1–PM6) OR</td>
<td>(iii) 1 Strong (PS1–PS4) AND 2 supporting (PP1–PP5) OR</td>
<td></td>
</tr>
<tr>
<td>(c) 1 Moderate (PM1–PM6) and 1 supporting (PP1–PP5) OR</td>
<td>(iv) ≥3 Moderate (PM1–PM6) OR</td>
<td></td>
</tr>
<tr>
<td>(d) ≥2 Supporting (PP1–PP5)</td>
<td>(v) 2 Moderate (PM1–PM6) AND ≥2 supporting (PP1–PP5) OR</td>
<td></td>
</tr>
<tr>
<td>(e) ≥2 Strong (PS1–PS4) OR</td>
<td>(vi) 1 Moderate (PM1–PM6) AND ≥4 supporting (PP1–PP5) OR</td>
<td></td>
</tr>
<tr>
<td>(ii) 1 Strong (PS1–PS4) AND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(iii) 1 Strong (PS1–PS4) AND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) ≥3 Moderate (PM1–PM6) OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) 2 Moderate (PM1–PM6) AND ≥2 Supporting (PP1–PP5) OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(c) 1 Moderate (PM1–PM6) AND ≥4 Supporting (PP1–PP5) OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Likely benign)</td>
<td>(Likely benign)</td>
<td></td>
</tr>
<tr>
<td>(i) 1 Strong (BS1–BS4) and 1 supporting (BP1–BP7) OR</td>
<td>(i) Other criteria shown above are not met OR</td>
<td></td>
</tr>
<tr>
<td>(ii) ≥2 Supporting (BP1–BP7)</td>
<td>(ii) the criteria for benign and pathogenic are contradictory</td>
<td></td>
</tr>
</tbody>
</table>
"Because of the great potential to aid clinical laboratory practice, efforts are underway for clinical variant databases to be expanded and standardized. Standardization will provide easier access to updated information as well as facilitate submission from the clinical laboratory. For example, the ClinVar database allows for the deposition of variants with clinical observations and assertions, with review status tracked to enable a more transparent view of the levels of quality of the curation."

PMID 25741868
TPMT*3A - Haplotype

Variation ID: 12722
Review status: (0/4) no assertion criteria provided

Interpretation

Clinical significance: Pathogenic
Last evaluated: Jun 28, 2005
Number of submission(s): 1
Condition(s): Thiopurine methyltransferase deficiency [MedGen - Orphanet - OMIM]
See supporting ClinVar records

Allele(s)

NM_000367.3(TPMT):c.460G>A (p.Ala154Thr)
Allele ID: 27761
Variant type: single nucleotide variant
Cytogenetic location: 6p22.3

Assertions for related alleles

NM_000367.3(TPMT):c.460G>A (p.Ala154Thr) [ClinVar]
Clinical significance: Pathogenic
Review status: (0/4)
Number of submission(s): 1
Condition(s): Thiopurine methyltransferase deficiency [MedGen - Orphanet - OMIM]
See supporting ClinVar records

NM_000367.3(TPMT):c.719A>G (p.Tyr240Cys) [ClinVar]
Clinical significance: Pathogenic
Review status: (0/4)
Number of submission(s): 1
Condition(s): Thiopurine methyltransferase deficiency [MedGen - Orphanet - OMIM]
See supporting ClinVar records

Tracks changes in clinical interpretation over time

### Germline

<table>
<thead>
<tr>
<th>Clinical significance (Last evaluated)</th>
<th>Review status (Assertion method)</th>
<th>Collection method</th>
<th>Condition(s) (Mode of inheritance)</th>
<th>Origin</th>
<th>Citations</th>
<th>Submitter - Study name (Last submitted)</th>
<th>Submission accession</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic (Jan 28, 2005)</td>
<td>no assertion criteria provided</td>
<td>literature only</td>
<td>Thiorpurine methyltransferase deficiency</td>
<td>germline</td>
<td>PubMed (9) [See all records that cite these PMIDs]</td>
<td>OMIM (Dec 30, 2010)</td>
<td>SCV000033806.1</td>
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</tbody>
</table>

# ClinVar

## Submission overview

<table>
<thead>
<tr>
<th>Category of analysis</th>
<th>Current total (Jul 05, 2016)</th>
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</thead>
<tbody>
<tr>
<td>Records submitted</td>
<td>204470</td>
</tr>
<tr>
<td>Records with assertion criteria</td>
<td>114722</td>
</tr>
<tr>
<td>Records with an interpretation</td>
<td>184273</td>
</tr>
<tr>
<td>Total genes represented</td>
<td>27202</td>
</tr>
<tr>
<td>Unique variation records</td>
<td>155661</td>
</tr>
<tr>
<td>Unique variation records with interpretations</td>
<td></td>
</tr>
<tr>
<td>Unique variation records with assertion criteria</td>
<td>142527</td>
</tr>
<tr>
<td>Unique variation records with practice guidelines (4 stars)</td>
<td>90786</td>
</tr>
<tr>
<td>Unique variation records from expert panels (3 stars)</td>
<td>4000</td>
</tr>
<tr>
<td>Unique variation records with assertion criteria, multiple submitters, and no conflicts (2 stars)</td>
<td>11355</td>
</tr>
<tr>
<td>Unique variation records with assertion criteria (1 star)</td>
<td>71574</td>
</tr>
<tr>
<td>Unique variation records with conflicting interpretations</td>
<td>4053</td>
</tr>
<tr>
<td>Genes with variants specific to one gene</td>
<td>4805</td>
</tr>
<tr>
<td>Genes with variants specific to one protein-coding gene</td>
<td>4715</td>
</tr>
<tr>
<td>Genes included in a variant spanning more than one gene</td>
<td>27094</td>
</tr>
<tr>
<td>Variants affecting overlapping genes</td>
<td>8983</td>
</tr>
<tr>
<td>Total submitters</td>
<td>538</td>
</tr>
</tbody>
</table>

Welcome to ClinGen
Building a Genomic Knowledge Base to Improve Patient Care Learn more »

Seeking info about a gene or disease? Type it... Go!
ClinGen's search feature will return relevant information from both ClinGen Curated Resources and reputable external sources.

Sharing Data. Building Knowledge. Improving Care. ClinGen is dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research. Learn more about our organization and our ongoing efforts below.

https://www.clinicalgenome.org/
ClinGen’s Critical Questions

- Is this gene associated with a disease?  
  *Clinical Validity*
- Is this variant causative?  
  *Pathogenicity*
- Is this information actionable?  
  *Clinical Utility*

Building a Genomic Knowledge Base  
*ClinVar & Other Resources*

Improved Patient Care  
Through Genomic Medicine
ClinVar & Variant Nomenclature

607008.0001
985A>G
985A>G (K304E)
985A>G (K329E)
A985G
ACADM, LYS304GLU
K304E
K304E (985 A->G)
K304E (K329E)
K304E only
K329E
K329E(985A>G)
LYS304GLU
c.985A>G
c.985A>G (p.K304E)
c.985A>G (p.Lys304Glu)
c985A>G
p.K304E
p.Lys329Glu
include: K304E (985A>G)
Mutation c.985A>G (p.K304E)
previously known as p.Lys329Glu
Analysis of ACADM 985A>G mutation

Multiplicity in assemblies, transcripts, legacy conventions for numbering systems, abbreviations for amino acids, formats

NC_000001.11:g.75761161A>G
NC_000001.10:g.76226846A>G
NG_007045.1:g.41804A>G
NM_000016.4:c.985A>G
NP_000007.1:p.Lys329Glu
NM_000016.5(ACADM):c.985A>G
(p.Lys329Glu)
## Test Results

<table>
<thead>
<tr>
<th>Test Description</th>
<th>Flag</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 Genotype, B</td>
<td></td>
<td>Poor metabolizer 2/2</td>
</tr>
<tr>
<td>CYP2C19 Phenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Star Alleles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Interpretation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Interpretation (Phenotype)**

This individual is likely a poor CYP2C19 metabolizer. Caution should be exercised when treating with drugs metabolized by CYP2C19 as follows:

If this patient is taking a prodrug that is activated by CYP2C19, such as clopidogrel, reduced activation of the drug is expected which may result in decreased efficacy of the drug.

If this patient is taking a drug that is inactivated by CYP2C19, such as citalopram, reduced inactivation is expected which may result in higher blood levels of the drug and potential side effects.

**Clinical Recommendation**

Consideration should be given to using drugs not metabolized by CYP2C19.

**ACMG**

**CPIC**
Clinical PGx Implementation Consortium (CPIC)

• Formed in 2009 to provide guidelines that enable the translation of genetic lab results into clinical actions
  • Reviewed every 2 years (max)
• Includes over 130 clinicians and scientists, from 62 institutions and 14 countries
  • Observers from NIH and FDA

“The key underlying assumption for all CPIC guidelines is that clinical high-throughput and pre-emptive genotyping will eventually become common practice and clinicians will increasingly have patients' genotypes available before a prescription is written.”
PGx Guidelines: Translating Data to Action

Data
- Genotype
  - rs1142345: T/T,
  - rs1800460: C/T
- Diploptotype
- Molecular Phenotype
- Clinical Significance
  - TPMT *1/*3B
  - Intermediate Metabolizer
  - Adjust dose when treated with mercaptopurine

Knowledge

Action
PGx Guidelines: Layering Phenotypes

rs1142345: T/T, rs1800460: C/T

TPMT *1/*3B

Intermediate Metabolizer

Adjust dose when treated with mercaptopurine

**Variant-Level**

- T = benign
- C = pathogenic

**Allele-Level**

- *1 = "normal function"
- *3B = "no function"

©2011 MFMER | slide-33
PGx Guidelines: Layering Phenotypes

rs1142345: T/T, rs1800460: C/T

TPMT *1/*3B

Intermediate Metabolizer

Adjust dose when treated with mercaptopurine

Variant-Level

T = benign
C = pathogenic

C = benign
T = pathogenic

Allele-Level

*1 = "normal function"

*3B = "no function"

1 "normal function" allele + 1 "no function" allele
PGx Guidelines: Layering Phenotypes

rs1142345: T/T, rs1800460: C/T

TPMT *1/*3B

Intermediate Metabolizer

Adjust dose when treated with mercaptopurine

Variant-Level

T = benign
C = pathogenic

C = benign
T = pathogenic

Allele-Level

"normal function"

"no function"

1 "normal function" allele + 1 "no function" allele
# PGx Phenotype Codes for Test Results

<table>
<thead>
<tr>
<th>LOINC</th>
<th>LOINC Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>50956-2</td>
<td>HLA-B*57:01</td>
</tr>
<tr>
<td>57979-7</td>
<td>HLA-B*15:02</td>
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<tr>
<td>79711-8</td>
<td>HLA-B*58:01</td>
</tr>
<tr>
<td>79712-6</td>
<td>HLA-A*31:01</td>
</tr>
<tr>
<td>79713-4</td>
<td>TPMT gene product metabolic activity interpretation</td>
</tr>
<tr>
<td>79714-2</td>
<td>CYP2C19 gene product metabolic activity interpretation</td>
</tr>
<tr>
<td>79715-9</td>
<td>CYP2D6 gene product metabolic activity interpretation</td>
</tr>
<tr>
<td>79716-7</td>
<td>CYP2C9 gene product metabolic activity interpretation</td>
</tr>
<tr>
<td>79717-5</td>
<td>CYP3A5 gene product metabolic activity interpretation</td>
</tr>
<tr>
<td>79718-3</td>
<td>UGT1A1 gene product metabolic activity interpretation</td>
</tr>
<tr>
<td>79719-1</td>
<td>DPYD gene product metabolic activity interpretation</td>
</tr>
<tr>
<td>79720-9</td>
<td>CYP2B6 gene product metabolic activity interpretation</td>
</tr>
<tr>
<td>79721-7</td>
<td>CYP4F2 gene product metabolic activity interpretation</td>
</tr>
<tr>
<td>79722-5</td>
<td>SLCO1B1 gene product functional interpretation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Answer ID</th>
<th>Answer (CPIC Phenotype Term)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA6576-8</td>
<td>Positive</td>
</tr>
<tr>
<td>LA6577-6</td>
<td>Negative</td>
</tr>
<tr>
<td>LA10315-2</td>
<td>Ultrarapid metabolizer</td>
</tr>
<tr>
<td>LA25390-8</td>
<td>Rapid metabolizer</td>
</tr>
<tr>
<td>LA25391-6</td>
<td>Normal metabolizer</td>
</tr>
<tr>
<td>LA10317-8</td>
<td>Intermediate metabolizer</td>
</tr>
<tr>
<td>LA9657-3</td>
<td>Poor metabolizer</td>
</tr>
<tr>
<td>LA25392-4</td>
<td>Increased function</td>
</tr>
<tr>
<td>LA25393-2</td>
<td>Normal function</td>
</tr>
<tr>
<td>LA25395-7</td>
<td>Decreased function</td>
</tr>
<tr>
<td>LA25394-0</td>
<td>Poor function</td>
</tr>
</tbody>
</table>
Supplemental Table S4. Drug(s) that pertain to this guideline.

<table>
<thead>
<tr>
<th>Drug or Ingredient</th>
<th>Source</th>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>RxNorm</td>
<td>RxUCUI</td>
<td>190521</td>
</tr>
<tr>
<td>Abacavir</td>
<td>DrugBank</td>
<td>Accession Number</td>
<td>DB01048</td>
</tr>
<tr>
<td>Abacavir</td>
<td>ATC</td>
<td>ATC Code</td>
<td>305AF06</td>
</tr>
<tr>
<td>Abacavir</td>
<td>PharmGKB</td>
<td>PharmGKB ID</td>
<td>PA448004</td>
</tr>
</tbody>
</table>

Supplemental Table S5. Gene(s) that pertain to this guideline

<table>
<thead>
<tr>
<th>Gene Symbol</th>
<th>Source</th>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B</td>
<td>HGNC</td>
<td>Symbol</td>
<td>HLA-B</td>
</tr>
<tr>
<td>HLA-B</td>
<td>HGNC</td>
<td>ID</td>
<td>HGNC:4932</td>
</tr>
<tr>
<td>HLA-B</td>
<td>NCBI</td>
<td>Gene ID</td>
<td>3106</td>
</tr>
<tr>
<td>HLA-B</td>
<td>Ensembl</td>
<td>Ensembl ID</td>
<td>ENSG00000234745</td>
</tr>
<tr>
<td>HLA-B</td>
<td>PharmGKB</td>
<td>PharmGKB ID</td>
<td>PA35056</td>
</tr>
</tbody>
</table>

Supplemental Table S7. Example Implementation of this Guideline: Pharmacogenetic Genotype/Phenotype Summary Entries

<table>
<thead>
<tr>
<th>Test Result for HLA-B*57:01&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Coded Genotype/Phenotype Summary&lt;sup&gt;c&lt;/sup&gt;</th>
<th>EHR Priority Result Notation&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Consultation (Interpretation) Text Provided with Test Result*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>None</td>
<td>Normal/Low Risk&lt;sup&gt;*&lt;/sup&gt;</td>
<td>The HLA-B<em>57:01 allele, associated with abacavir hypersensitivity, was not detected in this patient. The patient may be prescribed abacavir.Please refer to the hospital formulary guidelines for specific dosing information. It should be noted that a negative HLA-B</em>57:01 result does not absolutely rule out the possibility of some form of abacavir hypersensitivity. Administration of abacavir therapy requires close observation including immediate discontinuation of therapy should any signs or symptoms of hypersensitivity develop.</td>
</tr>
<tr>
<td>Positive</td>
<td>HLA-B*57:01/Carrier</td>
<td>Abnormal/Priority High Risk&lt;sup&gt;*&lt;/sup&gt;</td>
<td>The HLA-B<em>57:01 allele, associated with abacavir hypersensitivity, was detected in this patient. HLA-B</em>57:01 positive patients should NOT be prescribed abacavir.</td>
</tr>
</tbody>
</table>

Supplemental Table S8. Example Implementation of this Guideline: Point of Care Clinical Decision Support

<table>
<thead>
<tr>
<th>Flow Chart Reference Point&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CDS Context, Relative to Genetic Testing</th>
<th>Trigger Condition</th>
<th>CDS Alert Text&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pre-Test</td>
<td>No HLA-B*57:01 result on file</td>
<td>A HLA-B<em>57:01 genotype test is recommended before prescribing abacavir for the FDA’s black box warning regarding the risk of serious hypersensitivity reactions in patients that carry this allele. A HLA-B</em>57:01 genotype test does not appear to have been ordered for this patient. Please do the following to order the HLA-B*57:01 genotype test (insert dialogue boxes here to order clinical HLA-B test).</td>
</tr>
<tr>
<td>2</td>
<td>Post-Test</td>
<td>HLA-B*57:01 Carrier</td>
<td>The HLA-B*57:01 allele has been detected in this patient. This allele is associated with high risk of severe hypersensitivity to abacavir. DO NOT prescribe abacavir for the FDA’s black box warning. Please choose an alternate antiretroviral. For more information, please consult a clinical pharmacist.</td>
</tr>
</tbody>
</table>

<sup>a</sup>See Supplemental Figure S4.
<sup>b</sup>The specific wording of the alert text may differ among sites.

Supplemental Figure S4. HLA-B*57:01 Genotype and Abacavir: Point of Care Clinical Decision Support

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Displaced lines indicate optional steps

Note: Circled numerals refer to Supplementary Table S8

Supplemental Figure S4. HLA-B*57:01 Genotype and Abacavir: Point of Care Clinical Decision Support

Supplemental Table S6. Translation of Genotype Test Result into Interpreted Phenotype<sup>c</sup>

<table>
<thead>
<tr>
<th>Test Result for HLA-B*57:01&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Examples of Diplotypes&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Interpreted Phenotype&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>X/X</td>
<td>Low Risk of abacavir hypersensitivity</td>
</tr>
<tr>
<td>Positive</td>
<td>X/57:01 or 57:01/57:01</td>
<td>High Risk of abacavir hypersensitivity</td>
</tr>
</tbody>
</table>

*This table corresponds to the recommendations in the CPIC guideline manuscript.
Implementation of Large Scale Clinical Genomics

Results

Evidence

Clinical Recommendation(s)
Implementation of Large Scale Clinical Genomics

Results

ACMG Guidelines

Variant Interpretations

CDS Rules

Clinical Recommendation(s)

Evidence

Domain Guidelines (e.g., CPIC PGx)

Allele Functional Status

Protein Phenotype(s)
Standards Needed for Clinical Genomics

- **Data Standards**
  - Genetic data (observed result)
  - Test metadata

- **Process Standards**
  - Variant & haplotype interpretation
  - Genotype-phenotype translation rules

- **Terminology Standards**
  - Coded results and interpretations
  - Molecular phenotype

- **Reporting Standards**
  - Message syntax
Acknowledgements

- ClinGen
- NCBI
- CPIC
- PGRN
- eMERGE
- PharmGKB
- HL7 Clinical Genomics
- AMIA GenTBI WG
- PGRN/PHONT: NIGMS U19 GM61388
- Mayo Clinic Office of Information and Knowledge Management (OIKM)
- Mayo Clinic Center for Individualized Medicine (CIM)
"Here's my DNA sequence."