Actionable Pharmacogenomics

DAVID KISOR, PHARMD, FCP, RPH
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Disclosures

DFK and DRB are both co-authors of the RxGenomix-American Pharmacists Association Pharmacogenomics Certificate Training Program.

No other significant financial relationships have influenced this presentation.
Learning Objectives

1. Identify the source of pharmacogenomic evidence-based drug selection/drug dosing guidelines.

2. Identify specific sections of guidelines that provide clear gene and drug information with actionable recommendations.

3. Describe a clear approach to keeping up with actionable, evidence-based pharmacogenomic information.
Pharmacogenomics (PGx)

The study of how a patient’s genetics may influence their response to medications

Codeine has been prescribed to pediatric patients for many decades as both an analgesic and an antitussive agent. Codeine is a prodrug with little inherent pharmacologic activity and must be metabolized in the liver into morphine, which is responsible for codeine’s analgesic effects. However, there is substantial genetic variability in the activity of the responsible hepatic enzyme, CYP2D6, and, as a consequence, individual patient response to codeine varies from no effect to high sensitivity. Drug surveillance has

# Codeine: Time to Say “No”?

Joseph D. Tobias, MD, Thomas P. Green, MD, Charles J. Coté, MD, SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE, COMMITTEE ON DRUGS

<table>
<thead>
<tr>
<th>Likely phenotype&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>(~1–2% of patients)</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>(~77–92% of patients)</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>(~2–11% of patients)</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>(~5–10% of patients)</td>
</tr>
</tbody>
</table>

### PGx: Drug Inefficacy • Adverse Drug Reactions • Safety

<table>
<thead>
<tr>
<th>Gene</th>
<th>Metabolism Phenotype</th>
<th>Drug (Standard Dose)</th>
<th>Potential Response</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>Normal (NM)</td>
<td>Clopidogrel</td>
<td>Desired antiplatelet effect</td>
<td>Efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td># of prescriptions 2015: 21,312,667+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate (IM)</td>
<td>Clopidogrel</td>
<td>Stent thrombosis - death</td>
<td>Inefficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td># of prescriptions 2015: 21,312,667+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>NM</td>
<td>Warfarin</td>
<td>Desired anticoagulation</td>
<td>Efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td># of prescriptions 2015: 20,760,075+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor (PM)</td>
<td>Warfarin</td>
<td>Bleeding - death</td>
<td>Adverse Drug Reaction</td>
</tr>
</tbody>
</table>

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<thead>
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<tr>
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<td>NM</td>
<td>Codeine</td>
<td>Desired analgesic effect</td>
<td>Efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td># of prescriptions 2013: 11,225,000++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td></td>
<td>Codeine</td>
<td>Pain</td>
<td>Inefficacy</td>
</tr>
<tr>
<td>Ultrarapid (UM)</td>
<td>Codeine</td>
<td>Morphine overdose - death</td>
<td>Adverse Drug Reaction</td>
<td></td>
</tr>
</tbody>
</table>

Think-Pair-Share

Turn to the person next to you and share:
- Your practice site
- Your experience with pharmacogenomics
- Your confidence (1-5) in defining pharmacogenomics
Pharmacogenetics (PGt)... Pharmacogenomics (PGx)

How genes affect a person’s response to drugs

Pharmacogenetics - Term first coined in 1959

On a practical basis, may involve pharmacokinetics (e.g., CYP enzyme activity)

Pharmacogenetics (PGt) vs. pharmacogenomics (PGx) vs. “drug-gene interactions”...and drug-drug-gene interactions

Clopidogrel interaction

Clopidogrel and genetics *(drug/gene interaction)*

- Clopidogrel is a prodrug, activated by CYP2C19
- A person’s genetics demonstrate activity functioning CYP2C19
- The CYP2C19 reduced activity status may reduce activation of clopidogrel
Clopidogrel interaction

Clopidogrel and genetics *(drug/gene interaction)*

- Clopidogrel is a prodrug, activated by CYP2C19
- A person’s genetics demonstrate activity functioning CYP2C19
- The CYP2C19 reduced activity status may reduce activation of clopidogrel

- Genetic-related reduced activation of clopidogrel may be “worsened” by the drug–drug interaction (drug-drug-gene interaction; i.e., phenoconversion):
  - intermediate metabolizer → poor metabolizer
Drug/Gene Interactions

Could different people respond differently to clopidogrel?
   ◦ Only reduced function?
   ◦ Could someone have increased function?
   ◦ Could someone have zero function?

How would we know?

Clopidogrel and genetics

When did we first learn about a CYP2C19 genotype and clopidogrel?

Why didn’t the FDA say something?

How many people might this affect?

Genotype and phenotype

Genotype: Genetic coding

Examples:
- *2 - rs4244285 c.681G>A; Splicing defect
- *17 - rs12248560 c.-806C>T; Increased expression

Phenotype: Expression of genetic coding

Examples:
- Normal metabolizer (NM)
- Poor metabolizer (PM)

CYP2C19 SNPs/Phenotypes

Relatively common gene forms:
- *1 (standard function)
- *2, *3 (loss of function; no function)
- *17 (gain of function)

CYP2C19 SNPs/Phenotypes

One allele from mom, one allele from dad

Combinations of alleles must be considered
  - *17/*17 = ultrarapid metabolizer/UM
  - *1/*1 = normal (extensive) metabolizer/NM (EM)
  - *1/*2 = intermediate metabolizer/IM
  - *2/*2 = poor metabolizer/PM
  - *2/*17 = intermediate metabolizer/IM

How would I explain PGx to a patient? To a colleague?

Turn to the person next to you, and in 30 seconds or less, explain what pharmacogenomics means to you.

Then, ask them to explain back their definition of pharmacogenomics.
What does PGx look like in practice?
Considering antiplatelet therapy with clopidogrel for ACS/PCI

CYP2C19 genotype results

- UM (*1/*17, *17/*17)
  - Standard dosing of clopidogrel
- EM (*1/*1)
- IM (*1/*2, *1/*3, *2/*17)
  - Consider alternative antiplatelet agent (e.g., prasugrel, ticagrelor)
- PM (*2/*2, *2/*3, *3/*3)

Where is this actually happening?

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Author Manuscript
Pharmacogenomics. Author manuscript; available in PMC 2014 May 01.

Published in final edited form as:

University of Florida and Shands Hospital Personalized Medicine Program: clinical implementation of pharmacogenetics

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3Department of Medicine, University of Florida, FL, USA
4Department of Pathology, Immunology & Laboratory Medicine, University of Florida, FL, USA

Where is this actually happening?

What about in the drug store?
Integrating Pharmacogenomics into Pharmacy Practice via Medication Therapy Management

A whitepaper developed by the American Pharmacists Association.

How long before I see this in my pharmacy?

Physicians ordering pharmacogenomic testing?
Direct to consumer pharmacogenomic testing?
Pharmacogenomic information on my smartphone?
But how do I know what to recommend?

### Level Definitions for CPIC Genes/Drugs

<table>
<thead>
<tr>
<th>CPIC LEVEL</th>
<th>CLINICAL CONTEXT</th>
<th>LEVEL OF EVIDENCE</th>
<th>STRENGTH OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Genetic information should be used to change prescribing of affected drug</td>
<td>Preponderance of evidence is high or moderate in favor of changing prescribing</td>
<td>At least one moderate or strong action (change in prescribing) recommended.</td>
</tr>
</tbody>
</table>

| B          | Genetic information could be used to change prescribing of the affected drug because alternative therapies/dosing are extremely likely to be as effective and as safe as non-genetically based dosing | Preponderance of evidence is weak with little conflicting data | At least one optional action (change in prescribing) is recommended. |

[https://cpicpgx.org](https://cpicpgx.org)
Tour of a CPIC guideline

Which tables do I look for?

What other resources are available? Appendices? YouTube videos?
### Warfarin

**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></td>
<td>*1/*1</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.

Pharmacogenetics for Safe Codeine Use in Sickle Cell Disease

Roseann S. Gammal, PharmD,§ Kristine R. Crews, PharmD,§ Cyrine E. Haidar, PharmD,§ James M. Hoffman, PharmD,§ MS,§ Donald K. Baker, PharmD, MBA,§ Patricia J. Barker, PharmD,§ Jeremie H. Estepp, MD,§ Deqing Pei, MS,§ Ulrich Broeckel, MD,§ Winfred Wang, MD,§ Mitchell J. Weiss, MD, PhD,§ Mary V. Relling, PharmD,§ Jane Hankins, MD,§ MS

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for codeine metabolism</th>
<th>Recommendations for codeine therapy</th>
<th>Classification of recommendation for codeine therapy</th>
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</tr>
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<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine following codeine administration, leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential for toxicity.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing.</td>
<td>Strong</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing.</td>
<td>Moderate</td>
<td>Monitor tramadol use for response.</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief</td>
<td>Avoid codeine use due to lack of efficacy.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.</td>
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Rating scheme is described in Supplementary Data online. There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol use postsurgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable. Some other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultrarapid metabolizers.

Where would I find information on other drug-gene pairs?

- Clinical Pharmacogenetics Implementation Consortium (CPIC): cpicpgx.org

- The Pharmacogenomics Knowledgebase: pharmgkb.org


https://pdfs.semanticscholar.org/ac68/28c6ed1ba9e97c3c0ad5e4fa3f637b084a2e.pdf

- FDA Table of pharmacogenetic biomarkers in drug labeling: https://www.fda.gov/Drugs/ScienceResearch/ucm572698.htm
CPIC guideline genes (n=16) and drugs, January 2018

- **TPMT**
  - MP, TG, azathioprine

- **CYP2D6**
  - Codeine, tramadol, hydrocodone, oxycodone, TCAs, SSRIs, ondansetron, tropisetron, atomoxetine (in progress)

- **CYP2C19**
  - TCAs, clopidogrel, voriconazole, SSRIs, PPIs (in progress)

- **VKORC1**
  - Warfarin

- **CYP2C9**
  - Warfarin, phenytoin, celecoxib (in progress)

- **CYP4F2**
  - Warfarin

- **HLA**
  - Allopurinol, CBZ, abacavir, phenytoin

- **CFTR**
  - Ivacaftor

- **DPYD**
  - 5FU, capecitabine, tegafur

- **G6PD**
  - Rasburicase

- **UGT1A1**
  - Atazanavir

- **SLCO1B1**
  - Simvastatin

- **IFNL3 (IL28B)**
  - Interferon

- **CYP3A5**
  - Tacrolimus

- **CYP2B6**
  - Efavirinz (in progress)

- **RYR1**
  - Inhaled anesthetics (in progress)

[https://cpicpgx.org/guidelines/](https://cpicpgx.org/guidelines/)
Identifying Evidence-based Drug-Gene Pairs

Query the CPIC drug-gene database for evidence level A and B drug-gene pairs (https://cpicpgx.org/genes-drugs/).

Genes–Drugs

CPIC assigns CPIC levels to genes/drugs with (1) PharmGKB Clinical Annotation Levels of Evidence of 1A, 1B, 2A and 2B, or (2) a PharmGKB PGx level for FDA-approved drug labels of “actionable pgx”, “genetic testing recommended”, or “genetic testing required”, or (3) based on nomination to CPIC for consideration.

- View CPIC’s process for assigning CPIC levels
- View CPIC’s levels for genes/drugs
- View CPIC’s process for prioritizing CPIC guidelines

CPIC invites feedback on existing and planned gene/drug guidelines.

Download Table (CSV)
Advanced training programs

**PGx Certificate Programs**

Shenandoah University

NACDS/University of Pittsburgh

UC Denver
- [http://www.cvent.com/events/pharmacogenomics-certificate-program-for-practicing-pharmacists/event-summary-aa27ce1e628e4ec1ae93b95ba4cc2a5e.aspx](http://www.cvent.com/events/pharmacogenomics-certificate-program-for-practicing-pharmacists/event-summary-aa27ce1e628e4ec1ae93b95ba4cc2a5e.aspx)

University of Florida
- [http://precisionmed.pharmacy.ufl.edu/overview/ce/](http://precisionmed.pharmacy.ufl.edu/overview/ce/)

APhA/RxGenomix/Manchester University

**Master of Science in Pharmacogenomics**

Manchester University
- [http://www.Manchester.edu/pgx](http://www.Manchester.edu/pgx)
Now, time to practice!

Using the laboratory report provided, work with a partner to answer the questions on the following slides.
Case 1

Your patient is undergoing treatment for cancer and is prescribed a product containing codeine as part of her pain management therapy. Pharmacogenomic (PGx) testing was previously performed with the results being available for interpretation by the pharmacist.

What would your recommendation be relative to the PGx testing results provided?
Table 2  Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

<table>
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<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.(^b,^c)</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing.</td>
<td>Strong</td>
<td>—</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.</td>
<td>Moderate</td>
<td>Monitor tramadol use for response.</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief</td>
<td>Avoid codeine use due to lack of efficacy.</td>
<td>Strong</td>
<td>Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.(^b,^c)</td>
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\(^a\)Rating scheme is described in Supplementary Data online.\(^b\)There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol use post-surgery. Use of other analgesics in CYP2D6 poor and ultrarapid metabolizers may therefore be preferable.\(^c\)Some other opioid analgesics, such as hydrocodone and oxycodone, are metabolized by CYP2D6. To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in CYP2D6 poor and ultrarapid metabolizers.
Case 2

BT is a 58-year-old Caucasian male who has just undergone percutaneous coronary intervention with coronary artery stent placement. BT has a history of diabetes and hypertension. BT is placed on dual-antiplatelet therapy, including aspirin and prasugrel. Pharmacogenetic (PGx) testing was performed and the results report is available. The primary care prescriber wishes to change prasugrel to clopidogrel and you are consulted on this case.

What is your recommendation for BT?
Case 2

Review the pharmacogenetics test report for BT and make your recommendation.
### Summary Table 1

**Table 1** Assignment of likely CYP2C19 phenotypes based on genotypes

<table>
<thead>
<tr>
<th>Likely phenotype</th>
<th>Genotypes</th>
<th>Examples of diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrapid metabolizer: normal or increased activity (~5–30% of patients)</td>
<td>An individual carrying two increased activity alleles (*17) or one functional allele (*1) plus one increased-activity allele (*17)</td>
<td>*1/*17, *17/*17</td>
</tr>
<tr>
<td>Extensive metabolizer: homozygous wild-type or normal activity (~35–50% of patients)</td>
<td>An individual carrying two functional (*1) alleles</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Intermediate metabolizer: heterozygote or intermediate activity (~18–45% of patients)</td>
<td>An individual carrying one functional allele (*1) plus one loss-of-function allele (*2–*8) or one loss-of-function allele (*2–*8) plus one increased-activity allele (*17)</td>
<td>*1/*2, *1/*3, *2/*17</td>
</tr>
<tr>
<td>Poor metabolizer: homozygous variant, mutant, low, or deficient activity (~2–15% of patients)</td>
<td>An individual carrying two loss-of-function alleles (*2–*8)</td>
<td>*2/*2, *2/*3, *3/*3</td>
</tr>
</tbody>
</table>
## Summary Table 2

### Table 2  Antiplatelet therapy recommendations based on CYP2C19 status when considering clopidogrel for ACS/PCI patients

<table>
<thead>
<tr>
<th>Phenotype (genotype)</th>
<th>Implications for clopidogrel</th>
<th>Therapeutic recommendations</th>
<th>Classification of recommendations^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer (UM) (*1/*17, *17/*17) and extensive metabolizer (EM) (*1/*1)</td>
<td>Normal (EM) or increased (UM) platelet inhibition; normal (EM) or decreased (UM) residual platelet aggregation^b</td>
<td>Clopidogrel: label-recommended dosage and administration</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate metabolizer (*1/*2, *1/*3, *2/*17)</td>
<td>Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor</td>
<td>Moderate</td>
</tr>
<tr>
<td>Poor metabolizer (*2/*2, *2/*3, *3/*3)</td>
<td>Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor</td>
<td>Strong</td>
</tr>
</tbody>
</table>
Case 3

Samuel is a 30 year old male with hypertension. He is receiving metoprolol succinate 100 mg once daily. Samuel is now started on fluoxetine for treatment of depression. Two days after starting on the fluoxetine, the patient is seen at the emergency room, having suffered a fractured arm after getting “dizzy” and falling. As part of his discharged process, the ER pharmacist is asked to provide medication counseling.

What is your recommendation for Samuel?
Drug-Drug-Gene Interaction

The addition of an inhibitor or inducer of a drug metabolizing enzyme in an individual receiving a drug metabolized by a variant form of that enzyme.

Drug-gene interaction: metoprolol/CYP2D6 *4/*10 - IM
Drug-drug interaction: metoprolol/fluoxetine - Δ to PM

Drug-drug-gene interaction = phenoconversion
# DPWG: CYP2D6-Metoprolol

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Phenotype</th>
<th>EL</th>
<th>CR</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>1,966</td>
<td>PM</td>
<td>4</td>
<td>C</td>
<td>Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 75%</td>
<td>95-110</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)</td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>4</td>
<td>B</td>
<td>4</td>
<td>B</td>
<td>Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 50%</td>
<td>96-100, 102, 107, 108, 110-115</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)</td>
<td></td>
</tr>
<tr>
<td>UM</td>
<td>4</td>
<td>D</td>
<td>4</td>
<td>D</td>
<td>Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE</td>
<td>98, 100-103</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other indications: select alternative drug (e.g., atenolol, bisoprolol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE</td>
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</tr>
</tbody>
</table>

EL = Evidence level; CR = Clinical relevance
4 = Published controlled study of “good quality”; 0 = Data “on file”; - = not reported
C = Clinical effect (long standing, not permanent); B = Clinical effect (short lived ) ; D = Clinical effect (long standing permanent)

### DPWG: CYP2D6-Metoprolol

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Phenotype</th>
<th>EL</th>
<th>CR</th>
<th>Interaction</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>1,966</td>
<td>PM</td>
<td>4</td>
<td>C</td>
<td>Yes Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 75% Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)</td>
<td>95–110</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IM</td>
<td>4</td>
<td>B</td>
<td>Yes Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or reduce dose by 50% Other indications: be alert to ADEs (e.g., bradycardia, cold extremities) or select alternative drug (e.g., atenolol, bisoprolol)</td>
<td>96–100, 102, 107, 108, 110–115</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UM</td>
<td>4</td>
<td>D</td>
<td>Yes Heart failure: select alternative drug (e.g., bisoprolol, carvedilol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE Other indications: select alternative drug (e.g., atenolol, bisoprolol) or titrate dose to a maximum of 250% of the normal dose in response to efficacy and ADE</td>
<td>98, 100–103</td>
</tr>
</tbody>
</table>

EL = Evidence level; CR = Clinical relevance
4 = Published controlled study of “good quality”; 0 = Data “on file”; - = not reported
C = Clinical effect (long standing, not permanent); B = Clinical effect (short lived; D = Clinical effect (long standing permanent)

Actionable Pharmacogenomics

Conclusions

- Scientific basis established decades ago
- Clinical guidelines from a number of organizations
- Pharmacist expertise
- Numerous practice settings
- Will become a standard of care