Pharmacogenetics: what is your intent?

Human genetic discovery

Drug Safety

Public Policy

Explain variation in phenotype

Clinical trial inclusion/exclusion

Clinical practice
Translational science: The steps to success

Step I: Discovery
Step II: Validation
Step III: Integration into practice
Step IV: Integration into policy
Lots of ways to ask ‘when?’

• Is pharmacogenetics useful?
• Should a test be ordered?
• What does ‘enough data’ look like?
• Is anything ever ‘ready for prime time’?

• If a patient arrives with PGx data, is it actionable?
Goal: Facilitate implementation of pharmacogenetic tests into patient care by clinicians now.
CPIC: Clinical Pharmacogenetics Implementation Consortium

Clinicians, scientists, 3rd party payers, regulators
60 members
33 institutions
Observers: NIH and FDA
8 countries
What is CPIC’s deal?

• CPIC prioritizes gene-drug pairs based upon community input, and has sponsored surveys of the CPIC membership and the ASCPT membership. CPIC accepts input at any time (and a frequent contributor is FDA).

• The purpose of CPIC is to “translate genetic information into clinical actions” and to make recommendations for actionable pharmacogenetic variants (more research needed)
  • those variants that are measurable, interpretable, and it’s clear what to do with the genetic information. That is a core part of the structure of each guideline: to list all possible variants, predict phenotypes, and recommend what to do with that information….that’s a Table in each guideline.

• This is not similar to the EGAPP exercise because not all of the published information is weighted equally – just as pharmacogenetics practioners do in practice. Therefore, the strength of the evidence is evaluated in each guideline.

DISCLOSURE
• By definition, the authors support pharmacogenetics. They want to implement pharmacogenetics now. It is left to the professional organizations (e.g., ASCO, AHA), health systems, individual clinicians to decide whether to take up the information.
A bit more about CPIC

• CPIC assumes that testing is done in situations that enable placing the information into the medical record (could be limited point-of-care testing or comprehensive array testing and only some information is being transferred to the EMR). This means CLIA-cert. environment.

• CPIC is starting with “baby steps” that are not controversial, with clearly “clinically actionable” variants and drugs, with guidelines that are all peer-reviewed and updateable.

• PharmGKB reflects the CPIC guidelines, as well as the guidelines of other established groups, in the Clinical Implementation section.

• The new Genetic Testing Registry (GTR) plans to list CPIC guidelines in the consensus statements section of the GTR display. Details have already been negotiated with PubMed.
Criteria for prioritization of gene/drug pairs

- Professional organizations (e.g. American Society for Clinical Pharmacology and Therapeutics, American Society for Clinical Oncology, American Heart Association, PGRN’s CPIC, etc.) recommending that genetic testing accompany that drug use in peer-reviewed guidelines
- FDA labeling recommending use of genetic testing for the affected drug
- Evidence that CMS and/or third party payors reimburse for genetic testing for that drug’s use
- Lawsuits penalizing clinicians who fail to use the pharmacogenetic test
- Availability of stand-alone CLIA-approved tests for individual loci
- Clinical trials demonstrating drug effects linked to functional pharmacogenetic loci
- Narrow therapeutic index for the affected drug
- Preclinical studies demonstrating drug effects linked to functional pharmacogenetic loci
- In vitro or in vivo evidence that drug A is handled identically to drug B, with strong pharmacogenetic evidence linking the variation to drug B
Highest ranked gene/drug pairs for clinical implementation based on survey of ASCPT members
<table>
<thead>
<tr>
<th>Gene Drug Pairs</th>
<th>Status</th>
<th>Author Contact</th>
<th>Others Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT - thiopurines</td>
<td>published</td>
<td>Relling</td>
<td>EE Gardner, WJ Sandborn, K Schmiegelow, C-H Pui, SW Yee6, CM Stein, M Whirl-Carrillo, WE Evans and TE Klein</td>
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<tr>
<td>CYP2C19 - clopidogrel</td>
<td>published</td>
<td>Shuldiner</td>
<td>Stuart Scott</td>
</tr>
<tr>
<td>CYP2C9, VKORC1 - warfarin</td>
<td>published</td>
<td>Julie Johnson</td>
<td>Li Gong, Michelle Whirl-Carrillo, Jeffrey L. Anderson, Stephen E. Kimmel, Ming Ta Michael Lee, Munir Pirmohamed, Stuart A. Scott, C. Michael Stein, Mia Wadelius, Teri E. Klein, Brian Gage, and Russ B. Altman</td>
</tr>
<tr>
<td>CYP2D6 - codeine</td>
<td>in press</td>
<td>Kris Crews</td>
<td>Todd Skaar, Andrea Gaedigk, Padmaja Mummaneni, Henry Dunnenberger, Teri Klein, HJ Guchelaar</td>
</tr>
<tr>
<td>DPYD - 5FU/capecitabine</td>
<td>initiated</td>
<td>Howard McLeod</td>
<td>Caroline Thorn</td>
</tr>
<tr>
<td>HLA-B - abacavir</td>
<td>under way</td>
<td>Deanna Kroetz</td>
<td>Teri Klein</td>
</tr>
<tr>
<td>HLA-B - carbamazepine</td>
<td>under way</td>
<td>Susan Leckband</td>
<td>Michelle Whirl-Carrillo, Munir Pirmohamed</td>
</tr>
<tr>
<td>HLA-B - phenytoin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B - allopurinol</td>
<td>under way</td>
<td>Ming-Ta Michael Lee</td>
<td>Teri Klein, Caroline Thorn, Werner Pichler, Wichitra Tassaneeyakul, Taisei Mushiroda, John T. Callaghan, Michael Hershfield, Chang-Youh Tsai, Chen-Yang Shen</td>
</tr>
<tr>
<td>CYP2D6 - antidepressants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G6PD - rasburicase, Septra</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>UGT1A1 - irinotecan</td>
<td></td>
<td></td>
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<tr>
<td>IL28B - pegIntron</td>
<td></td>
<td>Andrew Muir</td>
<td>David Goldstein, Teri Klein</td>
</tr>
<tr>
<td>SLCO1B1 - simvastatin</td>
<td>initiated</td>
<td>Russ Wilke</td>
<td></td>
</tr>
<tr>
<td>CYP2D6, CYP2C19 - TCAs</td>
<td></td>
<td>Jesse Swen, Kevin Hicks</td>
<td>Caryn Lerman, Susan Leckband, David Mrazek</td>
</tr>
<tr>
<td>CYP2D6 - SSRIs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Uniform Elements of CPIC Guidelines (Main)

• Introduction
• Focused Literature Review
• Gene:
  – Background
  – Genetic Test Interpretation
    • Table 1. Assignment of likely _____ [gene] phenotypes based on *genotypes*
  – Available Genetic Test Options
  – Incidental findings
  – Other considerations
Uniform Elements of CPIC Guidelines (Main)

• **Drug(s):**
  – Background
  – linking genetic variability to variability in drug-related phenotypes
  – **Dosage Recommendations**
    • Table 2. Recommended Dosing of ____ [drug/s] by ____ [gene] phenotype
    • Strength of recommendations grading system
  – **Recommendations for Incidental Findings**
  – **Other considerations**
  – **Potential Benefits and Risks for the Patient**
  – **Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests**
Uniform Elements of CPIC Guidelines (Supplement)

- Literature Review details
- Genetic Test Interpretation
- Available Genetic Test Options
- Supplemental Table. Genotypes that constitute the * alleles for ______
- Supplemental Table. Association between allelic variants and _____ [gene function]
- Supplemental Table. Frequencies of alleles in major race/ethnic groups
- Supplemental Table. Evidence linking genotype with phenotype
  - Levels of Evidence grading system
Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling¹, EE Gardner¹, WJ Sandborn², K Schmiegelow³,⁴, C-H Pui⁵, SW Yee⁶, CM Stein⁷, M Carrillo⁸, WE Evans¹ and TE Klein⁸
Key criteria to develop a CPIC Table 2: Gene/drug dosing recommendations

• What genotypes have such severe functional effects that a clinician would really act upon them?
  – E.g. homozygous defective vs everything else
  – E.g. ultrarapid vs everything else
  – E.g. homozygous wild-type vs heterozygote vs everything else

• What drugs are so clearly affected that a clinician would be wrong not to act on the result if it were available?
## Table 2: dosing recommendations

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for MP and azathioprine pharmacologic measures</th>
<th>Dosing recommendations for MP</th>
<th>Classification of recommendations</th>
<th>Dosing recommendations for azathioprine</th>
<th>Classification of recommendations</th>
<th>Implications for pharmacologic measures after TG</th>
<th>Dosing recommendations for TG</th>
<th>Classification of recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous wild-type or normal, high activity</td>
<td>Lower concentrations of TGN metabolites, higher methylITIMP; this is the &quot;normal&quot; pattern</td>
<td>Start with normal starting dose (e.g., 75 mg/m²/d or 1.5 mg/kg/d) and adjust doses of MP (and of any other myelosuppressive therapy) without any special emphasis on MP compared to other agents. Allow 2 weeks to reach steady state after each dose adjustment.⁴,⁵,⁷,⁹,¹⁰</td>
<td>Strong</td>
<td>Start with normal starting dose (e.g., 2–3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.⁴,⁷,⁹,¹⁰</td>
<td>Strong</td>
<td>Lower concentrations of TGN metabolites, but note that TGN after TG are 5–10x higher than TGN after MP or azathioprine</td>
<td>Start with normal starting dose. Adjust doses of TG and of other myelosuppressive therapy without any special emphasis on TG. Allow 2 weeks to reach steady state after each dose adjustment.⁴,¹⁶</td>
<td>Strong</td>
</tr>
<tr>
<td>Heterozygote or intermediate activity</td>
<td>Moderate to high concentrations of TGN metabolites; low concentrations of methylITIMP</td>
<td>Start with reduced doses (start at 30–70% of full dose; e.g., at 50 mg/m²/d or 0.75 mg/kg/d) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In those who require a dosage reduction based on myelosuppression, the median dose may be −40% lower (44 mg/m²) than that tolerated in wild-type patients (75 mg/m²).⁶,¹² In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing MP over other agents.⁴,⁷,¹³,¹⁵,¹⁷,¹⁹,²⁵,²⁹,³¹,³²</td>
<td>Strong</td>
<td>If disease treatment normally starts at the &quot;full dose&quot;; consider starting at 30–70% of target dose (e.g., 1.1–2.5 mg/kg/d), and titrate based on tolerance. Allow 2–4 weeks to reach steady state after each dose adjustment.⁴,⁷,⁹,¹⁰</td>
<td>Strong</td>
<td>Moderate to high concentrations of TGN metabolites; but note that TGN after TG are 5–10x higher than TGN after MP or azathioprine</td>
<td>Start with reduced doses (reduce by 30–50%) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 2–4 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, and depending on other therapy, emphasis should be on reducing TG over other agents.⁴,¹⁶</td>
<td>Moderate</td>
</tr>
<tr>
<td>Homozygous variant, mutant, low, or deficient activity</td>
<td>Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease; no methylITIMP metabolites</td>
<td>For malignancy, start with drastically reduced doses (reduce daily dose by 10-fold and reduce frequency to thrice weekly instead of daily, e.g., 10 mg/m²² given just 3 days/week) and adjust doses of MP based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing MP over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.⁴,⁵,²⁴,²⁵,²⁹,³¹,³²</td>
<td>Strong</td>
<td>Consider alternative agents. If using azathioprine start with drastically reduced doses (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of azathioprine based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. Azathioprine is the likely cause of myelosuppression.²⁷,²⁹,³¹,³³</td>
<td>Strong</td>
<td>Extremely high concentrations of TGN metabolites; fatal toxicity possible without dose decrease</td>
<td>Start with drastically reduced doses¹⁶ (reduce daily dose by 10-fold and dose thrice weekly instead of daily) and adjust doses of TG based on degree of myelosuppression and disease-specific guidelines. Allow 4–6 weeks to reach steady state after each dose adjustment. In setting of myelosuppression, emphasis should be on reducing TG over other agents. For nonmalignant conditions, consider alternative nonthiopurine immunosuppressant therapy.⁴</td>
<td>Strong</td>
</tr>
</tbody>
</table>

MP, mercaptopurine; TG, thioguanine; TGN, thioguanine nucleotide; TIMP, secondary metabolite of MP.

*Rating scheme is described in Supplementary Data online.
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Azathioprine</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous wild-type or normal, high activity</td>
<td><strong>Dosing recommendations for azathioprine</strong>&lt;br&gt;Start with normal starting dose (e.g., 2–3 mg/kg/d) and adjust doses of azathioprine based on disease-specific guidelines. Allow 2 weeks to reach steady state after each dose adjustment.(^4,27,29)</td>
<td><strong>Classification of recommendations(^a)</strong>&lt;br&gt;Strong</td>
</tr>
<tr>
<td>Heterozygote or intermediate activity</td>
<td><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.(^4,27,29,31)</strong></td>
<td><strong>Strong</strong>&lt;br&gt;Moderate to high concentrations of TGN metabolites; but note that TGN after TG are 5–10× higher than TGN after MP or azathioprine</td>
</tr>
</tbody>
</table>
Dosing recommendations: strength based on back-up evidence

A: Strong recommendation for the statement
B: Moderate recommendation for the statement
C: Optional recommendation for the statement

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P450-2C19 (CYP2C19) genotype and clopidogrel therapy

Stuart A. Scott, Katrin Sangkuhl, Eric E. Gardner, Charles M. Stein, Jean-Sebastien Hulot, Julie A. Johnson, Dan M. Roden, Teri E. Klein, Alan R. Shuldiner
Algorithm for suggested clinical actions based on *CYP2C19* genotype among coronary patients initiating antiplatelet therapy.

 ACS/PCI Patient Population

- Initiate antiplatelet therapy with standard dosing of *clopidogrel*

  - **CYP2C19 testing if genotype is unknown**

    - **UM** (*1/*17, *17/*17)
      - Standard dosing of *clopidogrel*
    - **EM** (*1/*1)
    - **IM** (*1/*2)
      - *Prasugrel* or other alternative therapy
    - **PM** (*2/*2)

Scott et al, CPT, submitted
<table>
<thead>
<tr>
<th>Phenotype (genotype)</th>
<th>Implications for clopidogrel</th>
<th>Therapeutic recommendations</th>
<th>Classification of recommendations</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&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Clopidogrel - label recommended dosage and administration.</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM) (*1/*2)</td>
<td>Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Prasugrel or other alternative therapy (if no contraindication)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Poor Metabolizer (PM) (*2/*2)</td>
<td>Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events</td>
<td>Prasugrel or other alternative therapy (if no contraindication)</td>
<td>Strong</td>
</tr>
</tbody>
</table>

<sup>1</sup> See Supplement, Strength of Therapeutic Recommendations.

<sup>2</sup> The CYP2C19*17 allele may be associated with increased bleeding risks (12).
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MV Relling¹, EE Gardner¹, WJ Sandborn², K Schmiegelow³,⁴, C-H Pui⁵, SW Yee⁶, CM Stein⁷, M Carrillo⁸, WE Evans¹ and TE Klein⁸

Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450-2C19 (CYP2C19) Genotype and Clopidogrel Therapy

SA Scott¹, K Sangkuhl², EE Gardner³, CM Stein⁴,⁵, J-S Hulot⁶,⁷, JA Johnson⁸,⁹,¹⁰, DM Roden¹¹,¹², TE Klein² and AR Shuldiner¹³,¹⁴

Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 Genotypes and Warfarin Dosing

JA Johnson¹, L Gong², M Whirl-Carrillo², BF Gage³, SA Scott⁴, CM Stein⁵, JL Anderson⁶, SE Kimmel⁷,⁸,⁹, MTM Lee¹⁰, M Pirmohamed¹¹, M Wadelius¹², TE Klein² and RB Altman²,¹³

Clin Pharmacol Ther. 2011
A bit more about CPIC

• CPIC assumes that testing is done in situations that enable placing the information into the medical record (could be limited point-of-care testing or comprehensive array testing and only some information is being transferred to the EMR). This means CLIA-cert. environment.

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• The new Genetic Testing Registry (GTR) plans to list CPIC guidelines in the consensus statements section of the GTR display. Details have already been negotiated with PubMed.
| Dosing Guidelines | Acenocoumarol VKORC1 | Dosing Guidelines for amitriptyline | Amitriptyline CYP2D6 | Dosing Guidelines for aripiprazole | Aripiprazole CYP2D6 | Dosing Guidelines for atomoxetine | Atomoxetine CYP2D6 | Dosing Guidelines for azathioprine | Azathioprine TPMT | Dosing Guidelines for capecitabine | Capecitabine DPYD | Dosing Guidelines for carvedilol | Carvedilol CYP2D6 | Dosing Guidelines for citalopram | Citalopram CYP2C19 | Dosing Guidelines for clomipramine | Clomipramine CYP2D6 | Dosing Guidelines for clopidogrel | Clopidogrel CYP2C19 | Dosing Guidelines for clozapine | Clozapine CYP2D6 | Dosing Guidelines for codeine | Codeine CYP2D6 | Dosing Guidelines for doxepin | Doxepin CYP2D6 |
• There is a lot to do, so more active participants desired!

• We like to hear comments (even if they are obvious), for discussion in our iterative process

• In the clinic, a ‘NO’ guideline isn’t helpful