Getting Personal: The Impact of Pharmacogenomics on Patient Care

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Disclosures

• Dr. Aquilante has no conflicts to disclose
• Dr. Arwood has no conflicts to disclose
CPE Information

- Target Audience: Pharmacists
- ACPE#: 0202-0000-19-047-L04-P
- Activity Type: Knowledge-based
Learning Objectives

At the completion of this knowledge-based activity, participants will be able to:

1) Describe the evidence supporting the use of pharmacogenomic information in clinical pharmacy practice.
2) Discuss barriers to implementing pharmacogenomic testing in clinical pharmacy practice.
3) Explain effective strategies to overcome barriers to implementing pharmacogenomic testing.
4) Identify novel implementation strategies that bridge pharmacogenomic research and clinical practice, and discuss the ethical implications of pharmacogenomic testing.
1. Which of the following groups publishes peer-reviewed, evidence-based clinical guidelines for specific gene-drug pairs?
   A. Food and Drug Administration (FDA)
   B. Clinical Pharmacogenetics Implementation Consortium (CPIC)
   C. Centers for Disease Control (CDC)
   D. National Institutes of Health Pharmacogenetics Research Network (NIH-PGRN)
2. Which of the following represents a barrier to implementing pharmacogenomics with respect to result integration in the electronic health record?

A. Prescribers would like tools to identify which patients to test
B. Prescribers report lack of comfort in using pharmacogenetic test results
C. Prescribers cannot recall every tested patient and results may get buried
D. Prescribers desire randomized controlled evidence in many scenarios
3. Which of the following is the best potential solution to overcome prescriber knowledge gaps?
   A. Create a section in the chart specifically for genetic test results
   B. Educate patients to manage their expectations about testing
   C. Offer online CME as an incentive to complete education
   D. Have health care providers undergo personal genotyping
4. Which of the following is a federal law that protects individuals from genetic discrimination in health insurance and employment?
   A. Health Insurance Portability and Accountability Act (HIPAA)
   B. Freedom of Information Act (FOIA)
   C. Common Rule (45 CFR part 46)
   D. Genetic Information Nondiscrimination Act (GINA)
Show Me the Evidence!
The Era of Precision Medicine

• Precision Medicine: An approach to disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person
  • Also known as “Personalized Medicine” or “Precision Health”

• Precision Pharmacotherapy: Customize medications to subgroups of patients, categorized by shared molecular and cellular biomarkers, to improve treatment outcomes
Pharmacogenomics

• Component of precision and personalized medicine
• How does genetic variation contribute to variability in drug disposition, response, and toxicity?
• Use genetic information to guide optimal drug selection and dosing to maximize efficacy and minimize adverse effects

National Human Genome Research Institute, www.genome.gov
Pharmacogenomics is the:

• “low hanging fruit of precision medicine”
• “early win” for precision and personalized medicine
• “magic bullet” for predicting drug response
• Thousands of clinical pharmacogenomic studies in the literature
• Not all pharmacogenomic knowledge merits clinical implementation!
• Need to demonstrate:
  • Clinical Validity: Ability of a test to accurately predict the presence or absence of the medication-related phenotype of interest
  • Clinical Utility (actionability): Likelihood that a test will alter clinical outcomes or treatment strategies

How do we prioritize the existing evidence?
Pharmacogenomics Knowledgebase (PharmGKB)

• Pharmacogenomic knowledge resource that collects, curates and disseminates knowledge about the impact of human genetic variation on drug responses
• www.pharmgkb.org
Grading the Evidence

- **Level 1A**: Annotation for a variant-drug combination in a CPIC or medical society-endorsed pharmacogenetic guideline, or implemented at a PGRN site or in another major health system.

- **Level 1B**: Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p values and preferably will have a strong effect size.

- **Level 2A**: Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a Very Important Pharmacogene (VIP) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.

- **Level 2B**: Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.

- **Level 3**: Annotation for a variant-drug combination based on a single significant study (not yet replicated) or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association.

- **Level 4**: Annotation based on a case report, non-significant study, or in vitro, molecular, or functional assay evidence only.

www.pharmgkb.org
Clinical Pharmacogenetics Implementation Consortium (CPIC)

- Established in 2009 as a shared project between PharmGKB and the Pharmacogenomics Research Network (PGRN)
- Address the need for guidelines to instruct clinicians on how to modify drug therapy based on genetic information
- Provide peer-reviewed, evidence-based clinical guidelines for select gene-drug pairs
- 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
- \[https://cpicpgx.org/\]
Over 35 Medications with CPIC Guidelines

- **Cardiology**
  - Clopidogrel (CYP2C19)
  - Simvastatin (SLCO1B1)
  - Warfarin (CYP2C9, VKORC1, CYP4F2)

- **Oncology and Transplant**
  - Thiopurines (TPMT)
  - 5-Fluorouracil (DPYD)
  - Rasburicase (G6PD)
  - Tamoxifen (CYP2D6)
  - Ondansetron (CYP2D6)
  - Tacrolimus (CYP3A5)

- **Rheumatology**
  - Thiopurines (TPMT)
  - Allopurinol (HLA-B)

- **Infectious Diseases**
  - Abacavir (HLA-B)
  - Atazanavir (UGT1A1)
  - Voriconazole (CYP2C19)

- **Pain Management**
  - Codeine (CYP2D6)
  - Tramadol (CYP2D6)

- **Psychiatry and Neurology**
  - SSRIs (CYP2D6, CYP2C19)
  - Tricyclic Antidepressants (CYP2D6, CYP2C19)
  - Carbamazepine (HLA-B, HLA-A)
  - Phenytoin (HLA-B, CYP2C9)

Vo TT. Pharmacotherapy 2017; 37:1014-1022
https://cpicpgx.org/
• **CPIC level A or B**: prescribing action recommended; alternative therapies or dosing are highly likely to be effective and safe

• **CPIC level C**: no prescribing change based on genetics; alternatives are unclear or evidence is weak but testing is common or gene is CPIC level A or B for other drugs

• **CPIC level D**: PharmGKB annotation only; no prescribing action recommended; alternatives unclear or evidence is weak; testing is rare

https://cpicpgx.org/
## CPIC Recommendations

### Example: Clopidogrel in the setting of ACS/PCI

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Clopidogrel Recommendations</th>
<th>Classification of Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19 Ultrarapid Metabolizer</td>
<td>Label-recommended dosage and administration of clopidogrel.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2C19 Rapid Metabolizer</td>
<td>Label-recommended dosage and administration of clopidogrel.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2C19 Normal Metabolizer</td>
<td>Label-recommended dosage and administration of clopidogrel.</td>
<td>Strong</td>
</tr>
<tr>
<td>CYP2C19 Intermediate Metabolizer</td>
<td>Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor</td>
<td>Moderate</td>
</tr>
<tr>
<td>CYP2C19 Poor Metabolizer</td>
<td>Alternative antiplatelet therapy (if no contraindication), e.g., prasugrel, ticagrelor</td>
<td>Strong</td>
</tr>
</tbody>
</table>

CPIC recommendations do NOT apply to use of clopidogrel for medical management of ACS, atrial fibrillation, stroke, or peripheral artery disease.

Adapted from https://www.pharmgkb.org/guideline/PA166104948
PharmGKB-Assigned Categories of Information in FDA Labels

- **Testing required**: The label states or implies that some sort of gene, protein, or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., should be conducted before using this drug. This requirement may only be for a particular subset of patients. PharmGKB considers labels that state the variant is an indication for the drug, as implying a test requirement. If the label states a test “should be” performed, this is also interpreted as a requirement.

- **Testing recommended**: The label states or implies that some sort of gene, protein, or chromosomal testing, including genetic testing, functional protein assays, cytogenetic studies, etc., is recommended before using this drug. This recommendation may only be for a particular subset of patients. PharmGKB considers labels that say testing “should be considered” to be recommended testing.

- **Actionable PGx**: The label does not discuss genetic or other testing for gene/protein/chromosomal variants, but does contain information about changes in efficacy, dosage, or toxicity due to such variants. The label may mention contraindication of the drug in a particular subset of patients but does not require or recommend gene, protein, or chromosomal testing.

- **Informative PGx**: The 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.

www.pharmgkb.org
Other Evidence Resources

- Dutch Pharmacogenetics Working Group (DPWG)
- Professional society guidelines for certain gene-drug pairs, examples:
  - Canadian Pharmacogenomics Network for Drug Safety (e.g., carbamazepine)
    - DHHS antiretroviral guidelines (abacavir)
    - American College of Rheumatology (allopurinol)
- Clinical Genome Resource (ClinGen)
- Among others...
Clinically-Actionable Examples Relevant to Primary Care

- **Warfarin: Genes, CYP2C9 and VKORC1**
  - Variants associated with altered warfarin dose requirements.

- **Clopidogrel: Gene, CYP2C19**
  - Variants associated with increased risk of major adverse CV effects.

- **Simvastatin: Gene, SLCO1B1**
  - Variants associated with increased risk of myopathy.

- **Allopurinol: Gene, HLA-B**
  - Increased risk of cutaneous hypersensitivity reactions

- **Codeine: Gene, CYP2D6**
  - Variants associated with decreased response or increased risk of AEs.

- **SSRIs/TCAs: Genes, CYP2C19 and CYP2D6**
  - Variants associated with altered dose requirements, response, and risk of adverse effects.
There currently exist approximately 20 genes impacting 80 medications that are deemed clinically actionable in practice, meaning some type of guidance is available to modify treatment based on a genetic test result.

*Pharmacotherapy* 2017 PMID: 28699700

**How do we implement pharmacogenomics into clinical practice?**
Approaches to Implementing Pharmacogenomics
Implementation Components

Support

Education

Evidence

Evaluation

Testing

Informatics

Clinical Workflow

Create Customized Guide to Facilitate Clinical Implementation

https://ignite-genomics.org/guides/
Create Customized Guide to Facilitate Clinical Implementation

<table>
<thead>
<tr>
<th>Have you completed the following implementation steps?</th>
<th>Not Yet Started</th>
<th>In Progress</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gather institutional support for CYP2C19-Clopidogrel</td>
<td></td>
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<tr>
<td>Develop CYP2C19-Clopidogrel genetic test ordering and interpretation process</td>
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<tr>
<td>Establish reimbursement sources/processes for CYP2C19-Clopidogrel genetic test</td>
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<tr>
<td>Integrate CYP2C19-Clopidogrel genetic data into the EHR</td>
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<tr>
<td>Develop provider education for CYP2C19-Clopidogrel</td>
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<tr>
<td>Develop patient education for CYP2C19-Clopidogrel</td>
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</tr>
<tr>
<td>Establish workflow for clinical pharmacogenetics implementation of CYP2C19-Clopidogrel</td>
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</tbody>
</table>

https://ignite-genomics.org/guides/cyp2c19-clopidogrel-testing/
Create Customized Guide to Facilitate Clinical Implementation

Available tools:

Step 1: Gather Institutional Support for CYP2C19 Testing

With respect to clinical implementation of pharmacogenetics, gathering institutional support can be defined as follows:

1. Collecting and disseminating institution-specific data to justify implementation (e.g. formulary considerations, medication-use frequency, specialty therapeutic areas, clinician expertise, patient demographics)

2. Gathering evidence to support clinical utility of your implementation (e.g. primary literature, clinical practice guidelines, likelihood of a clinically actionable result, relevant patient outcomes associated with genotype-guided therapy)

Provided resources include an overview of the supporting evidence, clinical guidelines, relationship between the gene-drug pair, and sample data collection metrics that can be disseminated to raise stakeholder (e.g. physicians, pharmacists, laboratory specialists, informaticians, educators) and administrative support for the implementation.

- Evidence Overview of CYP2C19-Clopidogrel Presentation
  IGNITE Network

- Publication List: CYP2C19-Clopidogrel Evidence Overview
  IGNITE Network

- CPIC Guideline for CYP2C19-Clopidogrel
  Clinical Pharmacogenetics Implementation Consortium

- CPIC Tutorial Series Video: Clopidogrel and CYP2C19 Summary
  PharmGKB, Clinical Pharmacogenetics Implementation Consortium

See all tools +
Implementation Components

- Support
- Evidence
- Evaluation
- Testing
- Informatics
- Clinical Workflow
- Education

Implementation Components

- Support
- Education
- Evidence
- Evaluation
- Clinical Workflow
- Testing
- Informatics

Support: Engagement and Provider Buy-in

**Stakeholders**
- Administrators
- Clinical leadership
- Providers
- Patients

**Personnel**
- Implementation leader and clinical staff
- Physician champions
- Laboratory specialists
- Informaticians

Multidisciplinary Team

Center for Pharmacogenomics and Personalized Medicine
Clinical and Translational Science Institute
Department of Pharmacotherapy and Translational Research
PMP Committee
Clinical Pharmacy Support
UF Health Pathology Laboratories
IT / Informatics Team

UF HEALTH PRECISION MEDICINE PROGRAM

Optimize patient care
Implementation Components

Support, Evaluation, Evidence, Clinical Workflow, Informatics, Testing

| Gene Selection | 1) What gene(s) is/are applicable to my clinical setting?  
2) How are the genes aggregated for testing? (single gene, disease specific panel, broad panel testing)  
3) Can the laboratory provide a customized panel of genes?  
4) What variants are interrogated and are they representative of my patient population? |
|---|---|
| Logistics | 1) What type of sample is required?  
2) What is the turnaround time?  
3) Are samples stored for future testing?  
4) Are samples used for research purposes?  
5) What info is included on the consent form, if required? |
| Reporting of results | 1) How are the results returned to a provider/patient?  
2) Are the results easy to interpret for a provider/patient?  
3) Is the evidence for each recommendation available?  
4) Does the evidence support the recommendations?  
5) What educational materials are available to aid in discussion of the results? |
| Test cost and reimbursement | 1) Does the laboratory bill patient insurance directly?  
2) What patient financial assistance programs does the laboratory provide?  
3) Does the laboratory provide a maximum cost for the patient? |

Implementation Components

Support

Evidence

Evaluation

Testing

Clinical Workflow

Education

Informatics

Clinical Decision Support

• Assists clinicians with decisions by displaying relevant information at various points in the course of care
  
  • Most common form is an alert triggered when certain conditions are met

• Requires **discrete variables** in the electronic health record (EHR) to enable proper design

Clinical Decision Support

Clinical Decision Support

• To maximize effectiveness, advisory information must
  • Be delivered to the **appropriate clinician** at the time of **decision making**
  • Include **relevant** content in the appropriate context
  • Be **concise** to allow quick and explicit interpretation
  • Provide clear **response** options
  • Not create unnecessary distractions
  • Be **noticeable** when warning about patient safety

Clinical Decision Support

PROBLEM
This patient's TPMT genotype is associated with very impaired metabolism of mercaptopurine by TPMT, which can cause an elevated risk of myelosuppression at normal doses.

REASONS
Reduced TPMT metabolism of thiopurines results in significantly increased production of non-desired cytotoxic metabolites, which can cause bone marrow depression.

RECOMMENDATIONS
(A) For non-malignant conditions consider alternative non-thiopurine immunosuppressant therapy

OR

(B) For malignant conditions, refer to the chemotherapy treatment protocol for dose reduction recommendations.

Select "Cancel" to modify or discontinue the current order.
Select "Accept" to proceed with the current order

More information on thiopurines and TPMT

For questions about this alert or the personalized medicine program, please contact: PMP-HELP@ctsi.ufl.edu or (352) 380-1441.

Last TPMTGEN=\texttt{2/3A} on 1/17/2014

Clinical Decision Support

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Last TPMTGEN=“2”*3A on 1/17/2014

Implementation Components

Clinical Workflow

• Inpatient vs. outpatient
  • System-wide or single site/specialty
  • Part of clinical or research project
  • Stand-alone clinic or integrated into existing clinic
  • Only clinical decision support

• Workflows vary depending on therapeutic area and gene-drug pair:
  • Medication use
  • Patient population
  • Physician champions

Clinical Workflow

• May include:
  • Automatic consult upon genotype test order
  • Working up the patient
  • Writing a note in the EHR and/or clinical decision support alert
    • Drug/dose recommendation
    • Relaying this to appropriate clinicians
  • Storing genotype information in EHR
Outpatient Workflow Example

Patient-PCP Visit
PCP refers patient to Pharmacogenetics Consult Clinic

Pharmacogenetics Consult Clinic: Patient-Pharmacist Visits

1. Pharmacogenetics education
   - Medication reconciliation
   - Collection of past medication responses
   - Sample collection for pharmacogenetic testing (if applicable)

2. Pharmacogenetics education
   - Counseling on test results and implications
   - Implement intervention(s) - if PCP accepts pharmacist’s recommendations

Pathology Lab processes and analyzes sample
Result interpretation and recommendations to PCP

Courtesy of UF College of Pharmacy Video Production Team
Inpatient Workflow Example

• University of Illinois Health: 495-bed tertiary care hospital

• Clinical genotyping for **warfarin**:
  • Tests run at 9 am every day
  • Results typically available within 6 hours
    • *VKORC1 c.-1639G>A*
    • *CYP4F2 1347G>A (V433M)*

• Pharmacist-led consult service
Inpatient Workflow Example

• **August 2012 - April 2014:** Automatic consult and mandatory genetic testing with every new warfarin order

• **April 2014 - Present:** Automatic consult and optional genetic testing with every new warfarin order
  - Pharmacist recommends warfarin dose daily based on clinical factors, potential drug-drug interactions, and genotype (if available)
  - Patients approached to consent for participation in research
    - EHR data extraction: inpatient and outpatient data
Inpatient Workflow Example

Pharmacogenomics Alert

You are starting warfarin and no recent INR is available. Please click below to order an INR. A consult with the personalized medicine team will automatically be placed to assist you with dosing warfarin. To learn more about personalized warfarin dosing and our warfarin dosing guidelines visit the evidence link below. Please page the personalized medicine team at #4361 with questions.

To order genetic testing to assist with warfarin dosing, click below. The personalized medicine consult team will assist you with interpreting the genotype result.

Add Order for:
- Warfarin Genotype → Routine - Scheduled Phlebotomy, Lab to Draw Specimen, Not Collected
- PT (Protime/INR) → Routine - Scheduled Phlebotomy, Lab to Draw Specimen, Not Collected

Evidence Link

OK

Courtesy of Edith Nutescu, PharmD, UIC
Personalized Medicine Program (PMP) Warfarin Workflow

New Warfarin Order meeting rules *

Warfarin genotype test to be done?

Yes

Physician orders genotype test

Molecular Pathology (MP) Lab Notified

Blood Sent to MP Lab

Time Received

Before 9am

After 9am

Same day

Result Placed in Cerner

MP notifies PMP Pharmacist of results

No

PMP Consult automatically placed

PMP consult inbox and check if genotype ordered

PMP initial assessment

Initial note & dose recommendation **

PMP Pharmacist signs the notes

PMP Pharmacist updates note with genotype result and new dose

Contacts primary team to discuss results and recommended warfarin dose

Forwards note to primary service's clinical pharmacist or PMP Attending for uncovered clinical services

* CDS rules -- New warfarin order (any indication, inpatient or 23 hour, no warfarin order within 6 months prior to genotype test)

** Daily assessment and notes will be done until 2 consecutive therapeutic INR are achieved or on day 7 of warfarin therapy

Courtesy of Edith Nutescu, PharmD, UIC
Inpatient Workflow Example

![Image of laboratory results review](image)

**Flowsheet**
- Lab
- Micro
- Pathology
- Radiology
- Immunizations

**Flowsheet:** LABORATORIES
**Level:** LABORATORIES

**Last 100 Results in the Past 3 Years**

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<td>*28</td>
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**Courtesy of Edith Nutescu, PharmD, UIC**
Inpatient Workflow Example

UI-Health Pharmacogenetics Service - Consult Note  Warfarin Dose Recommendation - Clinical Pharmacy Note

HPI: Providing PGx assisted warfarin dosing in this 72 yo Caucasian female POD12 from CABG and AVR complicated by LMCA stroke seen from MRI. Pt was not a tPA candidate, given recent surgery and time course since onset of Sx. Repeat CT head showed no acute hemorrhage or hemorrhagic transformation of stroke noted. Pt had A.fib with RVR and was started on amiodarone that was discontinued. Anticoagulation plan is warfarin and continue on low dose aspirin.

PMH: Carotid Artery Disease- last carotid showed right internal carotid 50-60% stenosis, Emphysema/COPD, s/p CABG and AVR (bioprosthetic)
Allergies: NKA

Anticoagulation Indication:
(_)DVT  (_)PE  (X)AF  (_)MVR (year, type)  (X)AVR  (_)VTE Prophylaxis (THA/TKA)  (_)Other (specify)

Goal INR: (X)2-3  (_)2.5-3.5  (_)Other (specify):

Clinical Factors for Dose Calculation:
Age: 72 yrs  Height:168 cm  Weight: 57 Kg  CrCl: 63 eGFR: 93  Baseline INR: 1.4
Race: (X)Caucasian  (_)African American  (_)Hispanic  (_)Other (specify)
Smoking status: (X) No  (X) No
Liver Disease:  (_)No  (X) No

Interacting Medications:
Medication Expected Effect on INR/Anticoagulation Status
Amiodarone  Increase INR due to inhibition of CYP2C9 and 3A4 warfarin metabolism, requiring 40% empiric dose reduction.
Piperacillin/tazobactam  may increase anticoagulant effect of warfarin

Genotype:
CYP2C9:  *1/*1 --normal warfarin metabolism
VKORC1: GA --intermediate warfarin sensitivity
CYP4F2: GG--normal vitamin K metabolism

Warfarin Dosage:

<table>
<thead>
<tr>
<th>Date</th>
<th>INR</th>
<th>Estimated Effective Dose</th>
<th>Dose Given</th>
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<tbody>
<tr>
<td>9/29/13</td>
<td>1.4</td>
<td>2-3 mg/day</td>
<td>3mg</td>
</tr>
<tr>
<td>9/30/13</td>
<td>1.4</td>
<td>2.5 to 3mg/day</td>
<td>2.5mg</td>
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<td>10/1/13</td>
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<tr>
<td>10/3/13</td>
<td>2.1</td>
<td>2 to 2.5mg/day</td>
<td></td>
</tr>
</tbody>
</table>

Anticoagulation Status Assessment and Recommendations:
1. Based on clinical and genetic factors, the estimated therapeutic warfarin dose is 2 mg/day. Today's INR is 2.1, therapeutic but rising. Recommending warfarin 2 mg x 1 tonight. Although her amiodarone was discontinued yesterday, the inhibitory effect of amiodarone on warfarin metabolism will persist due to its long half-life. Will continue to monitor INR closely.
Implementation Components

- Education
- Support
- Evidence
- Evaluation
- Clinical Workflow
- Testing
- Informatics

Education

• Providers
  • Purpose of pharmacogenetic implementation
  • Clinical workflow
  • Location of genotype results/interpretation in the EHR
  • Service contact information

• Patients
  • Genotype results
  • What genotyping is and why it was done

Provider Education

Pharmacogenetics (PGx) Consult Clinic
Considerations for Referral

<table>
<thead>
<tr>
<th>Patients taking <strong>one or more</strong> of these who may be experiencing <strong>side effects</strong> or <strong>ineffectiveness</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidepressants</strong></td>
</tr>
<tr>
<td><strong>Opioids</strong> (codeine, tramadol, oxycodone, hydrocodone)</td>
</tr>
<tr>
<td><strong>PPIs</strong></td>
</tr>
</tbody>
</table>

**Refer Patient:** Order “Appt Req Pharmacogenetics” or REF853

**Contact PGx Pharmacist:** Send inbasket message to:

P RX UF PMP MONITORING
Visit 1: Patient Education Slides

What is Pharmacogenetics?

- Pharmacogenetics is the study of how changes in your genes affect your medication
Visit 1: Patient Education Slides

Pharmacogenetics: a puzzle piece not whole picture

Precision Medicine

Genetics

Demographics (Age, weight, etc)

Medication

Organ function

Lifestyle

Diet

Labs

Courtesy of Ben Duong, PharmD, UF
Visit 2: Patient Results Hand-out

Pharmacogenetics Consultation Service: Pharmacogenetic Test Results Report

<table>
<thead>
<tr>
<th>Patient: Alberta Gator</th>
<th>Date of Birth: 1/1/1954</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber: Dr. Smith</td>
<td>MRN: 9999999</td>
</tr>
<tr>
<td>Genetic Test(s) Ordered: CYP2C19</td>
<td>Report Date: 2/1/2019</td>
</tr>
</tbody>
</table>

Pharmacogenetic Test Results:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Phenotype</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>*2/*2</td>
<td>Poor Metabolizer</td>
<td>You carry <strong>two no function alleles</strong>, which may result in <strong>little to no activity</strong> of your CYP2C19 protein. This means that your body will likely activate or breakdown certain medications <strong>slower than the average person</strong>.</td>
</tr>
</tbody>
</table>

Courtesy of Emily Cicali, PharmD, and Meghan Arwood, PharmD, MS, UF
## Visit 2: Patient Results Hand-out

### Detailed Results:

<table>
<thead>
<tr>
<th>Gene-Drug Pair</th>
<th>Expected Effect on Medication Response</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19-omeprazole</td>
<td>Increased response expected at typical doses</td>
<td>Since your body will breakdown omeprazole more slowly, you may have an increased response at the usual dose, increasing the chances of having side effects.</td>
</tr>
</tbody>
</table>

*Other medications or clinical factors can change the amount of protein you have in your body.* Please tell your healthcare providers about any over-the-counter medications (including supplements or herbals) that you take or any medications that you start/stop or have a dose change.
Visit 2: Patient Results Hand-out

Potential Future Medications That May Be Affected By These Genes:

<table>
<thead>
<tr>
<th>Medications or Medication Classes*Δ</th>
<th>Use</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricyclic Antidepressants</td>
<td>Mood</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Selective Serotonin Reuptake Inhibitors</td>
<td>Mood</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Proton Pump Inhibitors</td>
<td>Heart Burn</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Prevent blood clots</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Fungal infection</td>
<td>CYP2C19</td>
</tr>
</tbody>
</table>

*Please talk to your healthcare provider if you are prescribed any of these medications.

Δ Not all medications in these classes will have the same response based on your genes.

Test Information:
These clinical tests were validated by and performed at the University of Florida Health Pathology Laboratories, which is certified by Clinical Laboratory Improvement Amendments (CLIA) and accredited by the College of American Pathologists (CAP). The results of this test are not intended to be used as the sole means for clinical diagnosis and/or patient management decisions.

Please note that the following variants were tested for:
Common Challenges and Solutions
## Barriers to Implementation and Potential Solutions

<table>
<thead>
<tr>
<th>Domain</th>
<th>Challenge</th>
<th>Potential Solution or Lesson Learned</th>
</tr>
</thead>
</table>
| Provider education         | Prescriber knowledge gaps          | • Prescribers learn best from **case-based education**; providing this type of education upfront as well case discussion sessions throughout is ideal  
• Having prescribers undergo **personal genotyping** is a beneficial educational method  
• Offering **online CME is not enough incentive** to complete education  
• In-person education methods (e.g. noon conference/grand rounds) are **well attended** |
| Test order and interpretation process | Identifying who to test            | • Prescribers would like **electronic decision support tools** to identify potentially appropriate patients to test |
| Test order and interpretation process | Children do not like blood draws    | • Offering **noninvasive genetic sample collections** are key for younger populations  
• **Blood draws** do not seem problematic in adults, however **may not be the most convenient option** as not all clinic locations have phlebotomy stations |
## Barriers to Implementation and Potential Solutions

<table>
<thead>
<tr>
<th>Domain</th>
<th>Challenge</th>
<th>Potential Solution or Lesson Learned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test order and interpretation process</td>
<td>Turnaround time for pharmacogenetic test results</td>
<td>• Genotype should be available during patient encounters to optimize prescriber’s ability to act on it</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Prescribers, patients, and parents are willing to wait for results for drug therapy decisions in some settings</td>
</tr>
<tr>
<td></td>
<td>Phenotypes resulting as a range or indeterminate</td>
<td>• Having a testing platform that can detect which CYP2D6 allele is duplicated is ideal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blood samples may result in fewer undetermined phenotypes as compared to buccal samples</td>
</tr>
<tr>
<td>Phenotype results</td>
<td></td>
<td>• Normal metabolizers, although not a classic “actionable” phenotype, is clinically informative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Concomitant medications (e.g., CYP2D6 inhibitors) must be considered to evaluate true phenotype, especially in patients who are genotypically normal metabolizers</td>
</tr>
</tbody>
</table>

## Barriers to Implementation and Potential Solutions

<table>
<thead>
<tr>
<th>Domain</th>
<th>Challenge</th>
<th>Potential Solution or Lesson Learned</th>
</tr>
</thead>
</table>
| Test order and interpretation process | Prescriber interpretation and integration of pharmacogenetic results | • Prescribers highly depend on consults from pharmacists  
• Clear concise guidance must be provided through active alerts or consults in the EHR  
• Prescribers value eventual availability of pharmacogenetic results for their patients enrolled in control arms  
• Genotype data availability at the time of prescriber-patient encounter, and clarity for clinician of availability of the genotype data and recommended actions is likely important for high levels of adherence to genotype-guided recommendations |
| EHR integration         | Prescribers cannot recall every patient that was genotyped                                                                                  | • Prescribers do not necessarily look in the chart for pharmacogenetic results, especially if they are buried with other lab results  
  • An ideal solution is a section of the patient’s chart for genetic results, and a quick indicator to note if there are results in there  
  • A work around is ensuring the prescriber notes in their encounter note that they are ordering a pharmacogenetic test; then, they will review prior to patient’s next visit and will know to look for results  
  • Prescribers want alerts to tell them exactly what to do with results |

## Barriers to Implementation and Potential Solutions

<table>
<thead>
<tr>
<th>Domain</th>
<th>Challenge</th>
<th>Potential Solution or Lesson Learned</th>
</tr>
</thead>
</table>
| Patient perceptions  | Patient perceptions and knowledge of pharmacogenetics                      | • Patient education to manage patient’s expectations on what information pharmacogenetic results will provide is essential  
                         |                                                                            | • Having brief patient-friendly educational materials for before and after testing is ideal  
                         |                                                                            | • Patients value receiving pharmacogenetic results at the end of the study |

Implementation Strategies that Bridge Research and Clinical Practice
How Does a System Implement Pharmacogenetics?

Research Model

Clinical Model

Hybrid Model
Example of a Hybrid Model

• Research biobank: an institution collects DNA (and other) samples and clinical data from participants to learn how differences between people can affect health and disease
  • Genetic testing usually involves thousands of genes and hundreds of thousands of variants

• There exists the opportunity to return clinically-actionable results to research participants
  • To return genetic results in the clinical setting, the testing must be done in a CLIA-certified lab

• Examples of types of results to return to participants:
  • Pharmacogenetics
  • Disease risk
  • Carrier Status
  • Ancestry (non-clinical)

CLIA=Clinical Laboratory Improvement Amendments
Colorado Center for Personalized Medicine
Research Biobank

BIOBANK CLINICAL RESEARCH STUDY

1. Read and Sign Consent
   You can sign up for the Biobank on My Health Connection

2. Blood Sample is Collected
   The next time you have a routine blood draw at a UCHealth clinic, a blood sample will be taken for the Biobank

3. DNA Extraction
   Your sample will be sent to the Biobank where DNA is extracted, processed and stored in a secure location

4. Genetic Data is Generated
   Your sample is analyzed to look at differences in your DNA. Your genetic data is linked with your medical record, de-identified and made available for approved research studies

5. Return of Genetic Results
   If we learn something about you that may affect your health, we may be able to return this information to you. We will ask for your permission before returning any information

Graphic courtesy of Kathleen Barnes, PhD, University of Colorado
University of Colorado Experience

- Over 80,000 patients consented for the research Biobank
- Pharmacogenomics Implementation Committee Colorado (PICColo)
  - Make selected pharmacogenetic test results for research Biobank participants available for clinical use in UCHealth’s electronic health record
- First pharmacogenetic implementation - CYP2C19 and clopidogrel
  - CYP2C19 genetic results are returned to the participant’s electronic health record
  - Clinical decision support tools fire an alert to the provider at the point-of-care when clopidogrel is prescribed to a person with an at-risk genotype
Requirements of the Hybrid Model

• Multidisciplinary team
• CLIA-certified laboratory
• Process to vet what genetic results are considered “actionable”
• Sophisticated IT infrastructure
• Consent
  • Research and clinical return of results
• Challenge - how and when to notify patients of their results
• Challenge - not all genetic test results are created equally
• Challenge - cost
Ethical Implications of Clinical Pharmacogenetic Testing
Ethical, Legal and Social Implications (ELSI)

<table>
<thead>
<tr>
<th>Ethical</th>
<th>• Discrimination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Stigmatization</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Legal</th>
<th>• Informed consent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Ownership of data and/or samples</td>
</tr>
<tr>
<td></td>
<td>• Reporting requirements</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Social</th>
<th>• Race and ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Testing in vulnerable populations</td>
</tr>
<tr>
<td></td>
<td>• Availability of testing and cost</td>
</tr>
<tr>
<td></td>
<td>• Family implications</td>
</tr>
<tr>
<td></td>
<td>• Knowledge and education of healthcare professionals</td>
</tr>
</tbody>
</table>

https://www.cdc.gov/genomics/gtesting/acce/
Protections Against Genetic Discrimination

• Genetic discrimination: An individual with a known genetic disorder or genetic polymorphism, is treated differently by his/her employer or insurance company

• Genetic Information Nondiscrimination Act (GINA): Federal law enacted in 2008 to protect individuals from discrimination based on their genetic information in health insurance and employment

http://ginahelp.org/
Genetic Information Nondiscrimination Act

• Under GINA, health insurers cannot:
  • Use a person’s genetic information to make eligibility, coverage, or premium-setting decisions
  • Request or require a person or their family members to undergo genetic testing or provide genetic information

• Under GINA, employers cannot:
  • Use a person’s genetic information in employment decisions (e.g., hiring, firing, job assignments, or promotions)
  • Request or require genetic information about an employee or family member as a condition of employment

• GINA does NOT provide protections against or apply to:
  • A condition that is already diagnosed or manifest, even if that condition is genetic.
  • Life, disability, or long-term care insurers
  • Information about current health status

http://ginahelp.org/
Specific Considerations for Pharmacogenetic Tests

• What information do the pharmacogenetic results reveal?
• What are the implications of the pharmacogenetic results for the patient’s care?
• Does the patient want to have the pharmacogenetic test and know the results?
• How/where will the pharmacogenetic results be stored and who will have access to results?
• How will privacy and confidentiality of the pharmacogenetic results be maintained?
Closing Remarks

• Pharmacogenetics is aimed at understanding how genetic variation contributes to interindividual variability in drug disposition, response, and toxicity

• Resources exist to help clinicians determine if a drug-gene pair has sufficient validity and utility for implementation into practice

• Several strategies exist for clinical implementation of pharmacogenetics in outpatient and inpatient settings

• Successful clinical implementation relies on a strong EHR infrastructure, clinical decision support tools, and provider education
1. Which of the following groups publishes peer-reviewed, evidence-based clinical guidelines for specific gene-drug pairs?
   A. Food and Drug Administration (FDA)
   B. Clinical Pharmacogenetics Implementation Consortium (CPIC)
   C. Centers for Disease Control (CDC)
   D. National Institutes of Health Pharmacogenetics Research Network (NIH-PGRN)
Assessment Questions

2. Which of the following represents a barrier to implementing pharmacogenomics with respect to result integration in the electronic health record?

A. Prescribers would like tools to identify which patients to test
B. Prescribers report lack of comfort in using pharmacogenetic test results
C. Prescribers cannot recall every tested patient and results may get buried
D. Prescribers desire randomized controlled evidence in many scenarios
3. Which of the following is the best potential solution to overcome prescriber knowledge gaps?

A. Create a section in the chart specifically for genetic test results
B. Educate patients to manage their expectations about testing
C. Offer online CME as an incentive to complete education
D. Have health care providers undergo personal genotyping
4. Which of the following is a federal law that protects individuals from genetic discrimination in health insurance and employment?

A. Health Insurance Portability and Accountability Act (HIPAA)
B. Freedom of Information Act (FOIA)
C. Common Rule (45 CFR part 46)
D. Genetic Information Nondiscrimination Act (GINA)