Pharmacogenomics in Patient Care: The Future is Now

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Dean and Distinguished Professor
UF College of Pharmacy
2015 State of the Union: Precision Medicine Initiative

2016 budget: $215M allocated to Precision Medicine through NIH, FDA, informatics
Precision Medicine

Precision medicine is the future of medicine

The concepts are not new, but the tools are much more robust and complex

Pharmacogenomics is among the most actionable elements of precision medicine at present

And pharmacists can and should lead the way
Patients with same diagnosis

Predicted increased toxicity risk
Decrease dose or use different drug

Predicted good response to tested drug

Predicted poor or nonresponse
Use different drug

Clinical Potential of Pharmacogenetics
Achieving the clinical potential

- Discovery of genetic variants influencing drug response
- Developing evidence base and tools for clinical use of pharmacogenetics
- Clinical implementation of pharmacogenetics
- Documentation of impact on clinical outcomes
NIH-NHGRI supporting efforts in Genomic Medicine Implementation

IGNITE – Implementing GeNomics In pracTicE Network

- Focused on unravelling the challenges associated with translating genomic medicine to clinical practice
- 6 funded groups
  - University of Florida
  - Duke University
  - Mt Sinai
  - Vanderbilt
  - University of Maryland
  - Univ of Indiana
Clinical Implementation of Pharmacogenetics: CPIC Guidelines

• Guidelines for 34 drugs for guiding drug therapy based on germ-line variation
  – Does not include drugs for which therapy is guided based on somatic variation
Optimal clinical implementation of pgx

- Panel based testing with data stored in EHR as discreet data to trigger clinical decision support alerts

- Challenges:
  - Most payors will not cover cost of panel-based testing
  - Many of the commercial panels report data in PDF format, dramatically limiting utility
If starting slowly

• Implement CYP2C19 followed by CYP2D6

• 16 of 34 CPIC guideline drugs include CYP2C19 or CYP2D6 or both

• Drugs they cover are very commonly used (e.g.):
  – Clopidogrel
  – Opiates
  – SSRIs
  – TCAs
CYP2C19: Examples at 3 stages of maturity

- Clopidogrel
- Voriconazole
- Proton Pump Inhibitors
### CYP2C19

#### Gene alleles

<table>
<thead>
<tr>
<th>Allele</th>
<th>SNP</th>
<th>CYP2C19 Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>N/A</td>
<td>Normal function</td>
</tr>
<tr>
<td>*2</td>
<td>681G&gt;A</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*3</td>
<td>636G&gt;A</td>
<td>Loss of function</td>
</tr>
<tr>
<td>*17</td>
<td>-808C&gt;T</td>
<td>Gain of function</td>
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</table>

#### Phenotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
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<tbody>
<tr>
<td>*1/*1</td>
<td>NM – Normal Metabolizer</td>
</tr>
<tr>
<td>*1/*2 or *1/*3</td>
<td>IM - Intermediate Metabolizer</td>
</tr>
<tr>
<td>*2/*2, *2/*3, *3/*3</td>
<td>PM - Poor Metabolizer</td>
</tr>
<tr>
<td>*1/*17</td>
<td>RM – Rapid Metabolizer</td>
</tr>
<tr>
<td>*17/*17</td>
<td>UM - Ultrarapid Metabolizer</td>
</tr>
</tbody>
</table>
Common loss of function allele (*2)
- *2 carriers – 28% of whites; 36% of blacks; up to 70% of Asians

Clopidogrel in CYP2C19 *2 carriers
- Reduced generation of active metabolite
- Reduced effect on platelet reactivity
- Increased risk of MACE post PCI
CPIC Guidelines: CYP2C19 and Clopidogrel: 2013 Update

ACS/PCI Patients

CYP2C19 Genotyping

UM (*1/*17, *17/*17) → Clopidogrel at a standard dose

EM (*1/*1) → Alternative antiplatelet (Prasugrel or Ticagrelor)

IM (e.g. *1/*2) →

PM (e.g. *2/*2) →
Personalized Medicine Program - Clinical launch June 2012

UF delivers promise of personalized medicine to heart patients

Personalized medicine — a concept in which an understanding of a patient’s genetic makeup is used to enhance treatment — has arrived at UF&Shands, the University of Florida Academic Health […]
EHR Clinical Decision Support

PROBLEM
This patient’s CYP2C19 genotype is associated with very impaired metabolic activation of the prodrug clopidogrel (Plavix) and elevated risk for stent thrombosis or other cardiovascular events following PCI.

REASONS
Reduced clopidogrel activation in this genotype results in significantly reduced platelet inhibition, increased residual platelet aggregation, and decreased clopidogrel efficacy.

RECOMMENDATIONS - MODIFY TREATMENT BY CHOOSING ONE OF THE FOLLOWING:

(A) Prescribe prasugrel (EFFIENT) 10 mg daily
*Contraindications: History of stroke or transient ischemic attack, active bleeding
*Caution: Increased bleeding risk: Age > 75 years, Body weight < 60 kg

OR

(B) Prescribe ticagrelor (BRILINTA) 90 mg twice daily
*Contraindications: History of intracranial hemorrhage, active bleeding, severe hepatic impairment
*Caution: Aspirin doses >100 mg/day reduce ticagrelor effectiveness and should be avoided.

More information on clopidogrel and CYP2C19

Last CYP2C19=2*8 on 4/12/2012

Acknowledge Reason: [ ]

[ ] Open order: Place order for prasugrel (EFFIENT) 10 mg daily. Note: remove order for clopidogrel on next screen.
   (Last done by Ellen Kershner at 2:50 PM on 4/16/2012)

[ ] Open order: Place order for ticagrelor (BRILINTA) 90 mg twice daily. Note: remove the clopidogrel order on next screen.
   (Last done by Inpatient Physician, MD at 12:12 PM on 5/16/2012)

[ ] Open order: Proceed with clopidogrel (PLAVIX) 75 mg daily. Note: please remove the bottom or second clopidogrel order as it will duplicate.
   (Last done by Inpatient Physician, MD at 12:17 PM on 4/26/2012)

Message sent: This alert has been sent via In Basket
Clopidogrel Pilot: Results

• First year, CYP2C19 ordered on patients with LHC for suspicion of coronary disease
  – 1097 with CYP2C19 test ordered
  – PCI only – 247/291 patients (84%)
    • First 2 months (June and July 2012) 30/48 (63%)
    • Last 2 months (May and June 2012) 40/41 (98%) <0.001
  – Actionable genotypes post-PCI – n=80
    • 6/6 (100%) PMs had drug therapy changed
    • 50/74 (67%) IMs had drug therapy changed
Successful clinical implementation but... does it matter clinically?
CYP2C19 genotype/phenotypes and treatment

Total: n=408
LOF carriers: n= 126; 31%
LOF carriers with alternative therapy: N=68; 54%
Alternative tx: prasugrel in 84%
UM = RM and UM = 30%
Outcomes with CYP2C19 genotype-guided antiplatelet therapy

**Survival rate (%)**

- LOF alternative
- non-LOF
- LOF clopidogrel

**Time to event (months)**

<table>
<thead>
<tr>
<th>LOF alternative vs LOF clopidogrel: p=0.012</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOF alternative vs Non-LOF: p=0.345</td>
</tr>
</tbody>
</table>

**Number at risk**

- **LOF alternative**: 68, 59, 54, 51, 47, 45, 40
- **Non-LOF**: 282, 213, 191, 181, 167, 153, 144
- **LOF clopidogrel**: 58, 37, 32, 29, 26, 24, 22
- **Total**: 408, 309, 277, 261, 240, 222, 206
Genotype-guided antiplatelet therapy: 7 academic medical centers in US

Total Cohort
n=1815

LOF
n=572 (31.5%)

Clopidogrel
n=226 (39.5%)

Alternative
n=346 (60.5%)*†

non-LOF
n=1243 (68.5%)

Clopidogrel n=1050 (84.5%)
Alternative n=193 (15.5%)†

*p<0.0001 for ALTERNATIVE between LOF and NON-LOF groups
†Prasugrel comprised >60% of ALTERNATIVE therapy

LOF = Loss of function
Kaplan-Meier Survival Curve

Log-rank p = 0.016

Cumulative MACE Rate (%)

Time (months)

NO. at risk
LOF_CLOP 226 112 89 76 63 39 3
LOF_ALT 346 245 221 195 161 112 9

LOF = Loss of function
Kaplan-Meier Survival Curve

Adjusted Hazard Ratio
LOF-Clopidogrel vs LOF Alternative: 2.21 (1.13-4.33)  p=0.021
LOF-Alternative vs non-LOF: 0.81 (0.48-1.35)  p=0.41

LOF = Loss of function
Voriconazole & CYP2C19

• Voriconazole is treatment of choice for invasive fungal infections (IFI)
• Voriconazole – extensive metabolism via CYP2C19
• Trough concentrations < 2 mcg/ml associated with worse clinical outcomes
• HYPOTHESIS: CYP2C19 rapid and ultra-rapid metabolizer phenotypes (*1/*17 and *17/*17) associated with greater risk of subtherapeutic trough Cps
  – Some data in pediatrics, limited in adults
Voriconazole and CYP2C19

• Prospectively studied 70 patients with documented or suspected IFI treated with voriconazole
  – trough concentration monitoring at 4-5 days
  – genetic sample collection
Figure 1. Mean voriconazole trough levels

Steady state trough plasma concentration (mg/L)

- Other genotypes (n=43)
- *1/*17 (n=24)
- *17/*17 (n=3)

Hamadeh, Pharmacogenet Genom, in press
Figure 2. Prevalence of subtherapeutic troughs

- CYP2C19 UM (n=27): 51.8%
- Other phenotypes (n=43): 16.3%

P = 0.0028
Voriconazole CPIC Guidelines

• **CYP2C19** PM and IM: consider alternative therapy to avoid supratherapeutic [ ]s with normal doses

• **CYP2C19** RM and UM: Consider alternative therapy to avoid subtherapeutic [ ]s.
Voriconazole and CYP2C19: next steps at UF

• Preparing clinical implementation for high risk patients with recommendation of higher dose in CYP2C19 RM/UMs
  – Aligning protocol with Moffitt Cancer Center to enable greater power for clinical outcomes

• Developing PK/PG dosing model based on genetic and peak and trough concentration data (with Stephan Schmidt)
CYP2C19 and PPIs

- Nearly all PPIs undergo significant metabolism via CYP2C19
- PPI efficacy highly dependent on achieved drug concentration
- PPIs have been associated recently with significant adverse effects, likely concentration related
  - Bone fracture risk
  - Risk of infections (GI and pulmonary)
  - Kidney effects (CKD, ESRD, acute interstitial nephritis)
  - Dementia

HYPOTHESES:
- **CYP2C19 RM/UM** have increased risk of poor efficacy
- **CYP2C19 IM/PM** have increased risk of serious AEs
**CYP2C19 phenotype and PPI efficacy**

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>GOF (N=21)*</th>
<th>No GOF (N=53)</th>
<th>RR (CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI Dose, mg/kg</td>
<td>1.3 (0.5)</td>
<td>1.0 (0.6)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>% time pH &lt; 4</td>
<td>5.7</td>
<td>2.7</td>
<td>1.6 (1.1-2.3)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Acid Clearance time, min</td>
<td>181 (271)</td>
<td>107 (158)</td>
<td>2.2 (1.5-3.2)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*GOF = Gain-of-function--*17 carriers
No GOF = those with no *17 alleles
Mean (SD) unless otherwise noted

Lang, Lima PMID 25844821
CYP2C19 phenotype and PPI efficacy: Rate of fundoplication surgery (ARS)

Unpublished data, Lima and Francosi, Nemours Children’s Hosp
CYP2C19 phenotype and PPI AEs

* p<0.01

Lima JJ PMID 23623526
IGNITE PPI project

- Aim 1: Define clinical outcomes in PPI-treated patients based on CYP2C19 genotype
  - UF and Vanderbilt: > 10,000 patients with CYP2C19 genotype and exposure to PPI (33% GOF and 20% LOF)
  - Hypothesis:
    • LOF carriers will have better control of GERD and more AEs
    • GOF will have worse GERD control and fewer AEs (infections, CKD, fractures)
  - Tested by building computable phenotypes and testing within EHR
IGNITE PPI project

• Aim 2: Implement pharmacogenetic testing of the \textit{CYP2C19} gene-PPI drug pair in a comparative effectiveness genotype-supported vs. conventional PPI dosing trial.

• Hypothesis: GOF carriers in the genotype-supported arm have better GERD control than GOFs in the usual care group
  – Will evaluate PPI efficacy based on symptom rating scales
  – Currently powered only for efficacy; larger such trial could test AE hypothesis

IGNITE collaboration between UF PMP, GI team and Nemours (Lima & Francosi)
Additional evidence-building required but clinical potential for pgx-guided PPI is significant
Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Pharmacogenetics-Guided Warfarin Dosing: 2017 Update

JA Johnson¹, KE Caudle², L Gong³, M Whirl-Carrillo³, CM Stein⁴, SA Scott⁵, MTM Lee⁶, BF Gage⁷, SE Kimmel⁸,⁹, MA Perera¹⁰, JL Anderson¹¹, M Pirmohamed¹², TE Klein³, NA Limdi¹³, LH Cavallari¹ and M Wadelius¹⁴

PMID 28198005
Pharmacogenetic discoveries of warfarin dose requirements

Genetic variants associated with warfarin dose in African-American individuals: a genome-wide association study


Summary

Background VKORC1 and CYP2C9 are important contributors to warfarin dose variability, but explain less variability for individuals of African descent than for those of European or Asian descent. We aimed to identify additional variants contributing to warfarin dose requirements in African Americans.

African American variant, rs7856096 ($P = 1.82 \times 10^{-8}$, minor allele frequency = 20.4%), in the folate homeostasis gene folypolyglutamate synthase (FGPS). We replicated this association in an independent cohort of 372 African American subjects whose stable warfarin doses represented the full dosing spectrum ($P = .046$). In a combined cohort, adding rs7856096 to the International Warfarin Pharmacogenetic Consortium pharmacogenetic dosing algorithm resulted in a 5.8 mg/week ($P = 3.93 \times 10^{-5}$) decrease in warfarin dose for each allele carried. The variant overlaps functional elements and was associated ($P = .01$) with FGPS gene expression in lymphoblastoid cell lines derived from combined HapMap African populations (N = 326). Our results provide the first evidence linking genetic variation in folate homeostasis to warfarin response. (Blood. 2014;124(14):2298-2305)
Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data

The International Warfarin Pharmacogenetics Consortium*

dose were: VKORC1 polymorphism $-1639/3673$ G$>$A ($-28\%$ per allele), body surface area (BSA) ($+11\%$ per 0.25 m$^2$), CYP2C9*3 ($-33\%$ per allele), CYP2C9*2 ($-19\%$ per allele), age ($-7\%$ per decade), target international normalized ratio (INR) ($+11\%$ per 0.5 unit increase), amiodarone use ($-22\%$), smoker status ($+10\%$), race ($-9\%$), and current thrombosis ($+7\%$). This pharmacogenetic equation explained 53–54\% of the variability in the warfarin dose in the derivation and validation ($N = 292$) cohorts. For comparison, a clinical equation explained only 17–22\% of the dose variability ($P < 0.001$). In the validation cohort, we prospectively used the pharmacogenetic-dosing algorithm in patients initiating warfarin therapy, two of whom had a major hemorrhage. To facilitate use of these pharmacogenetic and clinical algorithms, we developed a nonprofit website, http://www.WarfarinDosing.org.
A Pharmacogenetic versus a Clinical Algorithm for Warfarin Dosing

Stephen E. Kimmel, M.D., Benjamin French, Ph.D., Scott E. Kasner, M.D., Julie A. Johnson, Pharm.D., Jeffrey L. Anderson, M.D., Brian F. Gage, M.D., Yves D. Rosenberg, M.D., Charles S. Eby, M.D., Rosemary A. Madigan, R.N., M.P.H., Robert B. McBane, M.D., Sherif Z. Abdel-Rahman, Ph.D., Scott M. Stevens, M.D., Steven Yale, M.D., Emile R. Mohler III, M.D., Margaret C. Fang, M.D., Vinay Shah, M.D., Richard B. Horenstein, M.D., Nita A. Limdi, Pharm.D., Ph.D., James A.S. Muldowney III, M.D., Jaspal Gujral, M.B., B.S., Patrice Delafontaine, M.D., Robert J. Desnick, M.D., Ph.D., Thomas L. Ortel, M.D., Ph.D., Henny H. Billett, M.D., Robert C. Pendleton, M.D., Nancy L. Geller, Ph.D., Jonathan L. Halperin, M.D., Samuel Z. Goldhaber, M.D., Michael D. Caldwell, M.D., Ph.D., Robert M. Califf, M.D., and Jonas H. Ellenberg, Ph.D., for the COAG Investigators*
Warfarin Pgx RTCs

- **COAG** – efficacy trial - no difference in time in therapeutic range in first month with pharmacogenetic vs clinical algorithm (PMID 24251361)
  - Suggestion of harm in blacks

<table>
<thead>
<tr>
<th></th>
<th>Pharmacogenetic</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-blacks</td>
<td>52%</td>
<td>17%</td>
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<tr>
<td>Blacks</td>
<td>21%</td>
<td>33%</td>
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</table>

- **EU-PACT Effectiveness trial** - significant benefit of genotype-guided dosing over usual care for time in therapeutic range (PMID 24251363)
Clinical outcomes in COAG

Sum: Death, major bleeding, thromboembolism

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pharmacogenetic</th>
<th>Clinical</th>
</tr>
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<tbody>
<tr>
<td>All</td>
<td>19 events</td>
<td>39 events</td>
</tr>
<tr>
<td>Nonblacks</td>
<td>12 events</td>
<td>29 events</td>
</tr>
<tr>
<td>Blacks</td>
<td>7 events</td>
<td>10 events</td>
</tr>
</tbody>
</table>

Table S8: Comparison of adverse events from randomization to the end of follow-up between the genotype-guided and clinically guided dosing groups.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Genotype-guided dosing</th>
<th>Clinically guided dosing</th>
<th>Hazard ratio (95% CI) *</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any INR 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants</td>
<td>5/373 (1)</td>
<td>14/367 (4)</td>
<td>0.34 (0.12, 0.95)</td>
<td>0.039</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1/141 (1)</td>
<td>2/134 (1)</td>
<td>0.52 (0.05, 5.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Nonblack</td>
<td>5/373 (1)</td>
<td>7/367 (2)</td>
<td>0.72 (0.23, 2.3)</td>
<td>0.57</td>
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<tr>
<td>Thromboembolism §</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All participants</td>
<td>6/514 (1)</td>
<td>9/501 (2)</td>
<td>0.67 (0.24, 1.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>Black</td>
<td>1/141 (1)</td>
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<td>Nonblack</td>
<td>5/373 (1)</td>
<td>7/367 (2)</td>
<td>0.72 (0.23, 2.3)</td>
<td>0.57</td>
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<tr>
<td>Clinically relevant non-major bleed **</td>
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<td></td>
<td></td>
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<tr>
<td>All participants</td>
<td>40/514 (8)</td>
<td>52/501 (10)</td>
<td>0.71 (0.46, 1.1) **</td>
<td>0.13</td>
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<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>9/141 (6)</td>
<td>17/134 (13)</td>
<td>0.46 (0.19, 1.1) **</td>
<td>0.072</td>
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<tr>
<td>Nonblack</td>
<td>31/373 (8)</td>
<td>35/367 (10)</td>
<td>0.85 (0.50, 1.4) **</td>
<td>0.52</td>
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<tr>
<td>All-cause death</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All participants</td>
<td>6/514 (1)</td>
<td>11/501 (2)</td>
<td>0.55 (0.20, 1.5)</td>
<td>0.25</td>
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<tr>
<td>Race</td>
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<tr>
<td>Black</td>
<td>4/141 (3)</td>
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<td>1.5 (0.33, 6.7)</td>
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<tr>
<td>Nonblack</td>
<td>2/373 (1)</td>
<td>8/367 (2)</td>
<td>0.24 (0.05, 1.1)</td>
<td>0.070</td>
</tr>
</tbody>
</table>
Warfarin CPIC Recommendations

**VKORC1 and CYP2C9*2 and *3 genotype available?**

- **YES**
  - Self-identified ancestry
    - Non-African ancestry
      - VKORC1-1639G>A and CYP2C9*2 and *3: Calculate dose based on validated published pharmacogenetic algorithms
      - For initial dosing, a pharmacogenetics-based warfarin initiation dose algorithm could be considered.
      - Carriers of CYP2C9*5, *6,*8 or *11 variant alleles (e.g., *1/*8, *1/*11, *8/*11): Decrease calculated dose by 15-30%*
      - Carriers of CYP4F2 rs2108622 T allele: Increase dose by 5-10%

- **NO**
  - African ancestry
    - Dose clinically

**CYP2C9*5, *6,*8, and *11 also tested?**

- **YES**
  - African American
    - rs12777823 tested?
      - **YES**
        - rs12777823 A carriers: decrease dose by 10–25%
      - **NO**

- **NO**

PMID 28198005
Current vs future paradigm: warfarin pgx

• Current:
  – Indication-specific test ordering, is cost of test justified, does potential benefit outweigh risk
  – CMS will not reimburse warfarin pgx testing

• Future
  – Genetic data available on patient (pgx panel or GW SNPs (e.g. 23andme) or whole exome or whole genome sequence)
  – Is it reasonable to use (vs ignore) the data?
  – May not require evidence for different “outcomes”
Clinical opportunities in pharmacogenomics: UF example

- APPE opportunities for students in pharmacogenomics
- PGY2 accredited residency in pharmacogenomics (6th resident being recruited now)
- Clinical faculty focused in pharmacogenomics
- Pharmacogenomics consult clinic (with a financial model) launching in spring
Summary

• Evidence for clinical utility of pharmacogenetics-guided drug therapy continues to evolve

• Evidence of impact on clinical outcomes must continue to be generated

• Pharmacists have substantial opportunities to play important roles in many different aspects of clinical pharmacogenetics
UF Health Personalized Medicine Program
Acknowledgements

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• **Vanderbilt:** Josh Denny, Josh Peterson

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