Translational Pharmacogenomics at Mount Sinai and Beyond

Aniwaa Owusu Obeng, PharmD

Assistant Professor
The Charles Bronfman Institute for Personalized Medicine
Department of Medicine
Department of Genetics and Genomic Sciences
Icahn School of Medicine at Mount Sinai

Clinical Pharmacogenomics Coordinator
The Mount Sinai Hospital
Pharmacy Department
I. BACKGROUND
   A. Pharmacogenomics and its Potential Benefits

II. INTRODUCTION
   A. Mount Sinai Health System
   B. Mount Sinai Pre-emptive Pharmacogenomics Programs

III. IMPLEMENTATION
   A. Warfarin Pharmacogenetics
   B. Multi-ethnic Dosing Strategy and Implementation

IV. LESSONS LEARNED / FUTURE DIRECTIONS
After diagnosis, patients are prescribed therapy with no reference to the patient’s genetic information.

- Known as
  - “Trial and error”
  - “One size fits all”
One size does not fit all: Relative efficacy of drug and disease, according to Spear et al.

Over 2 million serious ADRs per year

106,000 deaths yearly
  - 20% of all injuries or death to hospitalized patients

4th leading cause of death
  - Ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents and automobile deaths

$136 billion yearly
  - More than costs of care for CV and DM
Adverse Drug Events

2007 – 2009: pts ≥ 65 years
99,628 annual hospitalizations
166,174 annual ED visits

Figure 1. Estimated Rates of Emergency Hospitalizations for Adverse Drug Events in Older U.S. Adults, 2007–2009.
Drug Response is Multifactorial

- Genetics

Pharmacogenomics (PGx)

- The study of how genes affect a person’s response to medications.

- Pharmacology (the science of drugs) PLUS genomics (the study of genes and their functions)

- Potential benefits
  - Improve utility of existing therapies
  - Increase drug effectiveness
  - Improve drug safety

- Inform discovery and development of novel therapeutic agents
Pharmacogenomics (PGx)

Drug toxic but beneficial

Drug NOT toxic and NOT beneficial

Same diagnosis, same prescription

Drug toxic but NOT beneficial

Drug NOT toxic and beneficial
- Pythagoras in 510 BC
- Broad beans (Vicia faba)
- Over 2000 years later attributed to glucose-6-phosphate dehydrogenase (G6PD)
- Hemolytic anemia

- Uric acid end-product (hydrogen peroxide)
- Primarily class II “Mediterranean” allele of G6PD
- RBCs of G6PD-deficient patients → insufficient NADPH
- Reduced protection from oxidative damage
- Rasburicase is contraindicated in G6PD−deficient individuals

1930s – early observations of unusual drug reactions.

1959 – Sir Friedrich Vogel coined the term “pharmacogenetics”.

1962 – first textbook on this discipline.

2000s – introduction of the term “pharmacogenomics”.

**PGx and FDA-Approved Medications**

**FDA-approved medications n = 1200**
- 85%: PGx information in drug label
- 15%: Affected by actionable pharmacogenes

**Prescriptions in the US n = 4 billion**
- 82%: PGx information in drug label
- 18%: Prescriptions for PGx high risk meds

**Prescriptions for PGx high risk meds n = 720 million**
- 93%
- 7%

*Source: Relling MV, Evans WE. Nature. 2015*
Shifting the Status Quo

**PERSONALIZED MEDICINE: Tailored Treatments**

**MEDICINE OF THE PRESENT**
One Treatment Fits All

- Patients with colon cancer
  - Therapy
  - Effect
  - No effect
  - Adverse effects

**MEDICINE OF THE FUTURE**
More Personalized Diagnostics

- Patients with colon cancer
  - Biomarker Diagnostics (Blood, DNA, urine, and tissue analysis)
  - Therapies
  - Effect
  - Effect
  - Effect
PGx at Mount Sinai
Icahn School of Medicine at Mount Sinai

Freestanding medical school at the forefront of scientific training, biomedical research, and patient care

1968

34 DEPARTMENTS

23+ CLINICAL AND RESEARCH INSTITUTES

5,600+ FACULTY MEMBERS

2,000+ RESIDENTS AND FELLOWS

556 MEDICAL STUDENTS

90 MD/PhD STUDENTS

258 PhD STUDENTS

240 MASTERS STUDENTS

600+ POSTDOCTORAL STUDENTS

#4 IN RESEARCH DOLLARS PER PRINCIPAL INVESTIGATOR AMONG U.S. MEDICAL SCHOOLS

For you. For life.
The Charles Bronfman Institute for Personalized Medicine (IPM): BioMe™ Biobank

- Prospective collection of DNA and plasma samples linked to EHR for genomic medicine research.

- DNA and plasma samples linked to de-identified EHR (Mount Sinai Data Warehouse).
  - Affymetrix, Illumina, panels, exomes

- Originally developed to enable genomic discovery, later evolved to facilitate clinical implementation.

- Permission to re-contact participants for future research.
Translational PGx at Mount Sinai

Department of Genetics and Genomic Sciences

Icahn Institute for Genomics and Multiscale Biology

Clinical Partners

The Charles Bronfman Institute for Personalized Medicine

Threefold Aims of PGx at Mount Sinai

▶ Educational Initiatives
  – Patients
    • Brochures, videos, social media memes
  – Providers
    • Six week long rotation for pharmacy students / residents
    • Pharmacogenomics Journal Club Meetings
    • Presentations
    • Summer volunteer opportunities for students and trainees

▶ Clinical pharmacogenomics

▶ Translational Research
Implementation: Provider Education

- One hour training session, online video available.
  - Only ~40% of surveyed providers felt knowledgeable about genomic testing.

- Complete pre- and post-training questionnaires.

- Additional information on drug-gene pairs embedded in the CDS.

- Post-CDS surveys.
At Mount Sinai, we believe that:

100% of patients should receive medications that work for them.

100% of patients should receive medications that are safe for them.

Because when it comes to your health, One size does not fit all.

********

As a patient in the Mount Sinai Health System, Your doctor may order a genetics test to help select the right medication at the right dose for YOU!

********

Contact Us to Schedule a Pharmacogenetics Consultation

Translational Initiatives in Pharmacogenomics
The Charles Bronfman Institute for Personalized Medicine

Tel: 212-241-7371
Email: CLIPMERGETEAM@mssm.edu

1468 Madison Ave
Annenberg Building, 18th Floor
Room 18-16
New York, NY 10029

Your Guide to Pharmacogenetics Testing
Threefold Aims of PGx at Mount Sinai

- Educational Initiatives

- Clinical pharmacogenomics
  - Ongoing projects: IPM PGx and eMERGE PGx
  - Implementation of PGx across the Mount Sinai Health system

- Translational Research
  - Expand the evidence base for drug-gene pairs
  - Develop and successfully implement best practice for clinical PGx
## Pharmacogenomics Implementation Programs

<table>
<thead>
<tr>
<th><strong>IPM PGx</strong></th>
<th><strong>eMERGE PGx</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ 1500 BioMe patients</td>
<td>▶ 663 BioMe and non-BioMe patients</td>
</tr>
<tr>
<td>▶ IMA clinic</td>
<td>▶ FPA clinic</td>
</tr>
<tr>
<td>▶ Pre-emptive genotyping</td>
<td>▶ Pre-emptively sequenced</td>
</tr>
<tr>
<td>▶ Providers are consented and surveyed</td>
<td>▶ Providers are co-investigators</td>
</tr>
<tr>
<td>▶ Unlimited number of drug-gene pairs</td>
<td>▶ CDS for simvastatin, clopidogrel and warfarin</td>
</tr>
<tr>
<td>▶ CLIPMERGE</td>
<td>▶ CLIPMERGE</td>
</tr>
<tr>
<td>▶ EHR data collection</td>
<td>▶ EHR data collection</td>
</tr>
</tbody>
</table>
Patients Enrolled: 1641
Participating Physicians: 420

Demographics:
- **Male**: 28%
- **Female**: 72%
- **European**: 22%
- **African**: 31%
- **Hispanic**: 42%
- **Asian**: 2%
- **Other**: 3%

Total Patients Enrolled: 1641
Total Participating Physicians: 420
Implementation: Pre-emptive PGx Testing

- ~77% of patients have at least one ‘actionable’ variant in **CYP2C19, SLCO1B1, CYP2C9**, and/or **VKORC1**.

n=1641

- 1 gene: 1270 (77%)
- 2 genes: 450 (27%)
- 3 genes: 82 (5%)
- 4 genes: 16 (1%)
**Clinical Implementation of Personalized Medicine through Electronic Health Records and Genomics**

Gottesman et al.
BPAs Fired from Jan 2015 to August 2018

441 alerts so far!
10 BPAs per month on average
IPM Drug-gene Evaluation

Potential Drug-Genes for Clinical Implementation

Pre-Clinical Implementation Workup

Overview
NYS CLIA & Decision Table
Recommendations
CLIPMERGE CDS Development
PGx Implementation Group Approval

Post Implementation Evaluation

Feedback, continued review & revision

Clopidogrel
Simvastatin
Warfarin
Codeine
Tramadol
Nortriptyline
SSRIs – Citalopram, Escitalopram, Sertraline, Paroxetine
Phenytoin
Proton pump inhibitors
Amitriptyline, Imipramine, aripiprazole, clozapine, etc.
Clobazam
Azathioprine, Mercaptopurine
Ondansetron
Carbamazepine
Warfarin Pharmacogenetics
Warfarin Pharmacogenetics: Background

• Widely used oral anticoagulant for prevention of thrombosis and embolism.
  • AF, DVT, PE, MV

• Wide interindividual differences in drug response:
  • Narrow therapeutic range
  • High risk of bleeding or stroke

• Requires frequent monitoring by INR (typical target 2-3).

• Warfarin dosing variability is due to many factors:
  • Age, gender, drug interactions, diet (vitamin K), alcohol, smoking, pharmacogenetics (PK and PD)
**Pharmacogenomics of Warfarin**

- **CYP2C9**: Variant alleles (or SNPs) associated with *increased sensitivity* to Warfarin
  - CYP2C9 *1 – normal metabolization
  - CYP2C9 *2/*3 – reduced metabolization

- **VKORC1**: Variant allele of *VKORC1* gene (-1639G>A) associated with *lower dose requirement*
  - G/G – normal dose
  - G/A – intermediate dose
  - A/A – low dose
Warfarin Pharmacogenetics: Background

• Warfarin PGx dosing algorithms have been tested retrospectively and in clinical trials.
  • Warfarindosing.org; IWPC: CYP2C9*2, *3, VKORC1 -1639G>A
Warfarin Pharmacogenetics: Trials

- Warfarin PGx dosing algorithms have been tested retrospectively and in clinical trials.
  - Warfarindosing.org; IWPC: CYP2C9*2, *3, VKORC1 -1639G>A

<table>
<thead>
<tr>
<th>WPGx Trial</th>
<th>Year</th>
<th>Design</th>
<th>n</th>
<th>Comparison Arm</th>
<th>Primary End point</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoumaGen</td>
<td>2007</td>
<td>RCT</td>
<td>206</td>
<td>Standard dosing</td>
<td>Out of range (OOR)</td>
<td>1. PGx more accurate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>INRs</td>
<td>2. No difference in OOR INR</td>
<td>Hospitalizations: HR 0.69</td>
</tr>
<tr>
<td>Medco-Mayo</td>
<td>2010</td>
<td>CE</td>
<td>896/ 2688</td>
<td>Standard dosing (concurrent+historical)</td>
<td>Incident event rate</td>
<td>2. No difference in PTTR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hospitalizations: HR 0.69</td>
<td>Bleeding/thrombo: HR 0.72</td>
</tr>
<tr>
<td>Marshfield</td>
<td>2011</td>
<td>RCT</td>
<td>230</td>
<td>Clinical algorithm</td>
<td>1. Prediction error</td>
<td>1. PGx more accurate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. PTTR</td>
<td>2. No difference in PTTR</td>
</tr>
<tr>
<td>CoumaGen-II</td>
<td>2012</td>
<td>CE</td>
<td>504/ 1866</td>
<td>Standard dosing (historical)</td>
<td>1. OOR INRs</td>
<td>1. Fewer OOR INRs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. PTTR</td>
<td>2. Greater PTTR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Fewer events</td>
</tr>
<tr>
<td>EUPACT</td>
<td>2013</td>
<td>RCT</td>
<td>455</td>
<td>Standard dosing</td>
<td>PTTR</td>
<td>1. Greater PTTR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Fewer INR&gt;4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. Less time to INR</td>
</tr>
<tr>
<td>COAG</td>
<td>2013</td>
<td>RCT</td>
<td>1015</td>
<td>Clinical algorithm</td>
<td>PTTR</td>
<td>1. No difference in PTTR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. No difference time to INR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3. No difference in &gt; or &lt; INR</td>
</tr>
<tr>
<td>GIFT</td>
<td>2015</td>
<td>RCT</td>
<td>1600</td>
<td>Clinical algorithm</td>
<td>Composite thrombo, bleeding, INR &gt;4, death</td>
<td>2017</td>
</tr>
</tbody>
</table>

Scott SA and Lubitz SA. Pharmacogenomics, 2014.
Common warfarin PGx dosing algorithms do not perform well in non-Caucasian populations.
  - Particularly among African-Americans
  - COAG: 27% self-reported black

NYC-Mount Sinai multi-ethnic CYP2C9 (*2 and *3) + VKORC1 (-1639G>A) allele frequencies:

Caucasian

- Wild-type (CYP2C9 and VKORC1): 78%
- Variant carriers (CYP2C9 and/or VKORC1): 22%

African-American

- Wild-type (CYP2C9 and VKORC1): 76%
- Variant carriers (CYP2C9 and/or VKORC1): 24%

Warfarin PGx: African Ancestry Variants

- **DISCOVERY:** Novel variants in the African-American population (IWPC-GWAS).
  - CYP2C region: rs12777823 \((p=0.5\times10^{-12})\); AA MAF: 25%
  - Explains ~5% of dosing variability in AA population.

- **ALGORITHMS:** Improvements in African-Americans.
  - CYP2C9*5, *6, *8, *11; and rs12777823
  - Inclusion of these variants improved prediction for both WD and IWPC algorithms.

- **ALGORITHMS:** Improvements in African-Americans.
  - Race-specific pharmacogenetic algorithms, rather than race-adjusted algorithms, should be used to guide warfarin dosing.
Warfarin PGx: **CYP2C9** and **VKORC1**

- **Mount Sinai IPM PGx / eMERGE PGx Cohort (n=1641):**

  **CYP2C9:**
  - *1/*1: 1231
  - *1/*2: 233
  - *1/*3: 113
  - *1/*5: 10
  - *1/*6: 20
  - *2/*2: 19
  - *2/*3: 10
  - *3/*5: 1
  - *3/*6: 1

  **VKORC1:**
  - -1639G>A
    - GG: 53%
    - GA: 36%
    - AA: 11%
**Objective**: enable point-of-care warfarin dose prediction for patients of different ancestries.

**Four possible outcomes:**
1. PGx algorithm dosing (IWPC)
2. FDA label-based dosing (tables)
3. Clinical algorithm dosing (IWPC)
4. Empiric dosing
WARFARIN PGx: IMPLEMENTATION STRATEGY

• **Stage 1:**

  ![Flowchart Diagram]

  - **WARFARIN PRESCRIPTION THROUGH EHR**
    - *Was warfarin initiated within the last six weeks?*
      - **YES**
      - **NO**
    - *Is patient enrolled in IPM PGx or eMERGE PGx?*
      - **YES**
        - *Are CYP2C9 and VKORC1 genotype results available in CLIPMERGE?*
          - **YES**
          - **NO**
      - **NO**
Warfarin PGx: Implementation Strategy

• **Stage 2:**

  - Is CYP2C9 genotype *2/*2, *2/*3, or *3/*3?
    - YES
    - NO

  - Is patient Caucasian as per EHR?
    - YES
    - NO

  - Is CYP2C9 genotype *1/*1, *1/*2, or *1/*3?
    - YES
    - NO
Warfarin PGx: Implementation Strategy

• **Stage 3:**

Is CYP2C9 genotype *1/*1, *1/*2, or *1/*3?

- **YES**
  - NECESSARY CLINICAL INFORMATION IS AVAILABLE IN CLIPMERGE TO COMPLETE ALGORITHM?
    - **YES**
      - PHARMACOGENETIC DOSING
        1. Display CDS with PGx algorithm-recommended dose
        2. File CDS text in EHR
        3. File CYP2C9 and VKORC1 genetic testing report in EHR
    - **NO**
      - FDA LABEL-BASED DOSING
        1. Display CDS with an FDA label-recommended dose
        2. File CDS text in EHR
        3. File CYP2C9 and VKORC1 genetic testing report in EHR

- **NO**
  - CLINICAL ALGORITHM DOSING
    1. Display CDS with a clinical algorithm-recommended dose
    2. File CDS text in EHR
    3. File CYP2C9 and VKORC1 genetic testing report in EHR

- **YES**
  - EMPIRICAL DOSING
    1. Do not display CDS
    2. Log all patients
Warfarin PGx: Point-Of-Care CDS

• Clinical Decision Support:
Warfarin PGx: ISMMS and CPIC 2017

VKORC1 and CYP2C9*2 and *3 genotype available?

- **YES**
  - Self-identified ancestry
  - **NO**
    - Dose clinically

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%.

1) VKORC1-1639G>A and CYP2C9*2 and *3: Calculate dose based on validated published pharmacogenetic algorithms.
2) Carriers of CYP2C9*5, *6, *8 or *11 variant alleles (e.g., *1/*8, *1/*11, *8/*11): Decrease calculated dose by 15-30%.

African ancestry

- **NO**
  - CYP2C9*5, *6, *8, and *11 also tested?

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

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

African American?

For initial dosing, a pharmacogenetics-based warfarin initiation dose algorithm could be considered.

Carriers of CYP4F2 rs2108622 T allele: Increase dose by 5-10%
1. Warfarin is still commonly prescribed and managed in IMA clinic.
   • Provider education is critical.
   • Target Coumadin clinics.

2. Ancestry informed algorithm-based point-of-care warfarin dosing is accepted by majority of exposed providers.
   • Enabled more accurate prescribing than empirical dosing.

3. Clinical algorithm-based warfarin dosing is an option for implementation in non-Caucasian patient populations.
   • Additional CYP2C9 star (*) alleles and African-American variants are included in the forthcoming comprehensive MGTL PGx panel.
Our Team – IPM PGx Program

Aniwaa Owusu Obeng
Clinical Pharmacogenomics Coordinator

Stuart Scott
Clinical and Laboratory Genetics

Steve Ellis
IT - CLIPMERGE

Tom Kaszemacher
IT - CLIPMERGE
Acknowledgements

**IPM:**
Erwin Bottinger, MD
Judy Cho, MD
Stuart Scott, PhD
Steve Ellis
Tom Kaszemacher
Noura Abul-Husn, MD, PhD
Omri Gottesman, MD
Rajiv Nadukuru
Vaneet Lotay
Amanda Merkelson
Ana Mejia
Bernadette Liggayu
Patrick Shanley

**GGS and Genome Institute:**
Robert J. Desnick, PhD, MD
Eric E. Schadt, PhD
Inga Peter, PhD
Yao Yang, PhD
Mariana Botton, PhD

**FPA and IMA:**
Aida Vega, MD
Eva Waite, MD

**MGTL:**
Lisa Edelmann, PhD
Ruth Kornreich, PhD
Rajasekar R-Chakravarthi

**Epic Team**
Kristin Myers
Joseph Kannry, MD
Kevin Delaney
Aditi Vakil
Riya Deepak
Elizabeth Kerch
Noel Howard
Paul Francaviglia
Karen Trommer
Jason Martin
Daniel Edonyabo
Daniel Katselnik

**NIH / NIGMS (PGRN)**
Questions?

Translational Initiatives in Pharmacogenomics
Icahn School of Medicine at Mount Sinai

Email: aniwaa.owusu-obeng@mssm.edu
Translational Pharmacogenomics at Mount Sinai and Beyond

Aniwaa Owusu Obeng, PharmD

Assistant Professor
The Charles Bronfman Institute for Personalized Medicine
Department of Medicine
Department of Genetics and Genomic Sciences
Icahn School of Medicine at Mount Sinai

Clinical Pharmacogenomics Coordinator
The Mount Sinai Hospital
Pharmacy Department