Implementation of Multi-ethnic Algorithm-Guided Warfarin Dosing

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

II. IMPLEMENTATION
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   B. Multi-ethnic Warfarin Dosing Strategy
   C. Pilot Implementation Results

III. LESSONS LEARNED / FUTURE DIRECTIONS
Icahn School of Medicine at Mount Sinai

- **1968** School opened
- Freestanding medical school at the forefront of scientific training, biomedical research, and patient care

- 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.
The Charles Bronfman Institute for Personalized Medicine (IPM): BioMe™ Biobank

• > 35,000 patients enrolled; 500 new subjects per month.
Table 1  Summary of the genotyping platform used by five US institutions to implement array-based, preemptive pharmacogenetic testing

<table>
<thead>
<tr>
<th>Institution (reference)</th>
<th>Genotyping platform</th>
<th>Number of genes assayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic (43)</td>
<td>PGRNseq</td>
<td>84</td>
</tr>
<tr>
<td>Mount Sinai Medical Center (42)</td>
<td>Sequenom iPLEX ADME PGx</td>
<td>36</td>
</tr>
<tr>
<td>St. Jude Children’s Research Hospital (65)</td>
<td>Affymetrix DMET Plus Array</td>
<td>230</td>
</tr>
<tr>
<td>University of Florida and Shands Hospital (35)</td>
<td>Life Technologies Quant Studio Open Array</td>
<td>120</td>
</tr>
<tr>
<td>Vanderbilt University Medical Center (69)</td>
<td>VeraCode ADME Core Panel</td>
<td>34</td>
</tr>
</tbody>
</table>

### IMPLEMENTATION: PRE-EMPTIVE PGx TESTING

#### IPM PGx
- 1000 BioMe patients
- Internal Medicine Associates (IMA) clinic
- Genotyping (Agena)
- Providers are consented and surveyed
- Unlimited number of drug-gene pairs
- CLIPMERGE
- EHR data collection

#### eMERGE PGx
- 663 BioMe and non-BioMe patients
- Faculty Practice Associates (FPA) clinic
- Sequencing (PGRNseq) and genotyping (Agena)
- Providers are co-investigators
- CDS for simvastatin, clopidogrel and warfarin
- CLIPMERGE
- EHR data collection

**Objective:** Develop process best-practices for implementation of personalized medicine.
- Focus on providers
- eMERGE PGx also enables discovery
IMPLEMENTATION: PRE-EMPTIVE PGX TESTING

• 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.

Figure 2. Experience with decision support aids and genome-guided prescribing.

- 90% of respondents use decision support aids.
- 90% of respondents perform genome-guided prescribing.

IMPLEMENTATION: PRE-EMPTIVE PGX TESTING

- Mount Sinai IPM PGx programs (n=1641):
  - Clopidogrel: **CYP2C19**; Simvastatin: **SLCO1B1**; Warfarin: **CYP2C9 / VKORC1**; Tramadol: **CYP2D6**; Codeine: **CYP2D6**
~77% of patients have at least one ‘actionable’ variant in CYP2C19, SLCO1B1, CYP2C9, and/or VKORC1.
IMPLEMENTATION: PRE-EMPTIVE PGX TESTING

- Implementation is enabled by CLIPMERGE:
  - Advanced data management system that is external to, but communicates with Epic.
  - Clinical decision support (CDS) in real-time at the point-of-care.
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)
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 PGx dosing algorithms have been tested retrospectively and in clinical trials.

- Warfarindosing.org; IWPC: \textbf{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>
</table>
| CoumaGen   | 2007 | RCT    | 206   | Standard dosing | Out of range (OOR) INRs                     | 1. PGx more accurate  
2. No difference in OOR INR                                                                                                           |
| Medco-Mayo | 2010 | CE     | 896/2688 | Standard dosing (concurrent+historical) | Incident event rate                         | Hospitalizations: HR 0.69  
Bleeding/thrombo: HR 0.72                                                                                                                  |
| Marshfield | 2011 | RCT    | 230   | Clinical algorithm | 1. Prediction error  
2. PTTR                                         | 1. PGx more accurate  
2. No difference in PTTR                                                                                                           |
| CoumaGen-II| 2012 | CE     | 504/1866 | Standard dosing (historical) | 1. OOR INRs  
2. PTTR                                         | 1. Fewer OOR INRs  
2. Greater PTTR  
3. Fewer events                                                                                                                              |
| EUPACT     | 2013 | RCT    | 455   | Standard dosing | PTTR                                        | 1. Greater PTTR  
2. Fewer INR >4  
3. Less time to INR                                                                                                                          |
| COAG       | 2013 | RCT    | 1015  | Clinical algorithm | PTTR                                        | 1. No difference in PTTR  
2. No difference time to INR  
3. No difference in > or < INR                                                                                                              |
| GIFT       | 2015 | RCT    | 1600  | Clinical algorithm | Composite thrombo, bleeding, INR >4, death | 2017                                                                                                                                 |

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:

<table>
<thead>
<tr>
<th></th>
<th>Caucasian</th>
<th>African-American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>78%</td>
<td>76%</td>
</tr>
<tr>
<td>Variant carriers</td>
<td>22%</td>
<td>24%</td>
</tr>
</tbody>
</table>

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.
  - **Drozda K, et al. Pharmacogenet Genomics, 2015.**

• **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**

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

  - **NM: 75%**
  - **IM: 23%**
  - **PM: 2%**

  **CYP2C9:***

  **VKORC1:**
  - -1639G>A
  - GG: 53%
  - GA: 36%
  - AA: 11%

  **-1639G>A**
**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:**

  ![Diagram of the implementation strategy]

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

  ![Diagram](image)

  **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

  **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

  **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

  **Empirical Dosing:**
  1. Do not display CDS
  2. Log all patients

WARFARIN PGx: POINT-OF-CARE CDS

- Clinical Decision Support:

  - Clinical Decision Support:

    - Pharmacogenetics Advisory: Warfarin
      - According to genetic testing, this patient is intermediate Warfarin Sensitivity (A/G).
      - The therapeutic warfarin dose estimated by the patient's genetic information.
      - The recommended therapeutic dose is 5.5 mg/day.

    - Please disregard this dosing recommendation.
      - Target INR: 2.3
      - Age: 52
      - Height: 155.0 cm
      - Weight: 80.3 kg
      - Race: Black or African American
      - Currently taking Carbamazepine, Phenytoin, or Rifampin/Rifampicin?
        - No
      - Currently taking Amiodarone?
        - No

    - The predicted personalized starting dose* of Warfarin for this patient is 5.5 mg/day (37 mg/week).
      - * daily doses have been rounded to the nearest 0.5 mg

    - Please disregard this dosing recommendation if any of the following applies to this patient:
      - This patient is on a stable dose of warfarin.
      - The target INR is not 2.3.
      - The clinical information used in this algorithm is inaccurate.

    - Acknowledge reason:
      - Ignore - Not relevant to this patient
      - Ignore - Insufficient evidence
      - Ignore - Don't understand advice
      - Ignore - Other reason

    - Open SmartSet CLIPMERGE preview

WARFARIN PGx: ISMMS and CPIC 2017

VKORC1 and CYP2C9*2 and *3 genotype available?

- **YES**
  - Self-identified ancestry
    - Non-African ancestry
      - **STRONG**
        - VKORC1-1639G>A and CYP2C9*2 and *3: Calculate dose based on validated published pharmacogenetic algorithms
  - African ancestry
    - CYP2C9*5, *6, *8, and *11 also tested?
      - **YES**
        - 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 American?
          - **YES**
            - rs12777823 tested?
              - **YES**
                - rs12777823 A carriers: decrease dose by 10-25%
              - **NO**
                - rs12777823 A carriers: decrease dose by 10-25%
      - **NO**
        - For initial dosing, a pharmacogenetics-based warfarin initiation dose algorithm could be considered.

- **NO**
  - Dose clinically

- **OPTIONAL**
  - 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%.

WARFARIN PGx: IMPLEMENTATION RESULTS

• How often are the dosing recommendations accepted and how accurate are they?

• A subset of providers (~10-20%) switched to novel oral anticoagulant (NOAC) after initiating warfarin.
  – Patients that were difficult to reach INR.

• Provider ACCEPTANCE manually determined by chart review of warfarin dosing patterns during initiation.
  – ‘Therapeutic’ defined by stable dose over 3 consecutive INRs.

• Algorithm-based doses ACCEPTED by providers: 56%

• Majority of algorithm-guided CDS was triggered for clinical algorithm dosing (~85%).
How often are the dosing recommendations accepted and how **accurate** are they?

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Within +/- 1 mg of daily therapeutic dose</th>
<th>78%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PREDICTED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dose accuracy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
LESSONS LEARNED and FUTURE DIRECTIONS

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 \textit{CYP2C9} star (*) alleles and African-American variants are included in the forthcoming comprehensive MGTL PGx panel.
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Thank you.
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