Extract Rules of Personalized Warfarin Treatment Protocol to Improve Outcome based on Clinical and Genetic Characteristics

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In this talk, we demonstrate an example of personalizing warfarin treatment protocol to improve warfarin treatment outcome

**Quick Facts**
- Warfarin is the most common anticoagulant
- Pharmacogenetic influence CYP2C9 & VKORC1
- Notoriously difficult to select the correct dose
- Optimize International Normalized Ratio (INR) levels between 2 – 3 (therapeutic range)
- Longer time in the therapeutic range means lower risks of bleeding and thrombosis

**The Challenge**
- What is the best protocol?
- Which individual or population is likely to benefit? From what protocol?
4-Step Methods

Step 1: Generate 1.5 millions clinical avatars (simulated patients) (integrating electronic health records and genetic literature knowledge)

Step 2: Conduct 30-day warfarin treatment simulation on clinical avatars

Step 3: Identify which treatment protocol minimizes one’s risk based on clinical and genetic characteristics

Step 4: Produce decision support rule for personalized treatment protocol
4-Step Methods

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Step 4: Produce decision support rule for personalized treatment protocol
Conduct 30-day warfarin treatment simulation on simulated patients

Warfarin input

Dosing guided by a protocol

30 days

Clinical Avatar

Pharmacokinetic/Pharmacodynamic (PK/PD) model

International Normalized Ratio (INR)

Time in therapeutic range (TTR)

Protocols

1. AAA
2. CAA
3. PGAA
4. PGPGI
5. PGPGA

2-compartment model with 1st order input & output [Hamberg 2007]

INR

Days

1 2 3 4 11 12 13 ... 28 29 30

Treatment protocol example

Days 1-2
10 mg daily dose or Dose algorithm

Days 3-7

Days 8-10

Follow dosing grids to establish the weekly warfarin dose

GOAL INR: 2.0-3.0

**Action Point Low:**
- Inquire about ss/bleeding**, and if necessary, refer to an appropriate facility for care. Customize care if bleeding.

**Green Zone:**
- Retest in 14 days after day 8, monthly

**Red Zone:**
- Reduce today’s dose by a half if INR <4, and by a whole dose if INR >4.
- Decrease weekly dose by 10%
- Retest in 7 days, 14 days

**1st Yellow Zone High:**
- Retest in 14 days

**2nd Yellow Zone High:**
- Retest in 14 days

**1st Yellow Zone Low:**
- Retest in 14 days

**2nd Yellow Zone Low:**
- Reduced weekly dose by 5%
- Retest in 14 days

<table>
<thead>
<tr>
<th>INR</th>
<th>Warfarin dose on days 3, 4 (mg)</th>
<th>Action Point Low</th>
<th>Red Zone</th>
<th>Green Zone</th>
<th>1st Yellow Zone High</th>
<th>2nd Yellow Zone High</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.3</td>
<td>15, 15</td>
<td></td>
<td></td>
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<tr>
<td>1.3 – 1.4</td>
<td>10, 10</td>
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<td></td>
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<tr>
<td>1.5 – 1.6</td>
<td>10, 5</td>
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<tr>
<td>1.7 – 1.9</td>
<td>5, 5</td>
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<td>2.0 – 2.2</td>
<td>23, 2, 25</td>
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<tr>
<td>2.3 – 3.0</td>
<td>0, 5</td>
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<td>&gt;3.0</td>
<td>0, 0</td>
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</table>
# Available Treatment Protocol Options

<table>
<thead>
<tr>
<th>Treatment Plans</th>
<th>Treatment Periods</th>
<th>Initial period (days)</th>
<th>Adjustment period (days)</th>
<th>Maintenance period (days)</th>
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</thead>
<tbody>
<tr>
<td>AAA (Clinical)</td>
<td></td>
<td>AHC (1-2)</td>
<td>AHC (3-7)</td>
<td>AHC (8-30)</td>
</tr>
<tr>
<td>CAA (Clinical)</td>
<td></td>
<td>IWPC Clinical (1-2)</td>
<td>AHC (3-7)</td>
<td>AHC (8-30)</td>
</tr>
<tr>
<td>PGAA (Pharmacogenetics)</td>
<td></td>
<td>IWPC PG (1-2)</td>
<td>AHC (3-7)</td>
<td>AHC (8-30)</td>
</tr>
<tr>
<td>PGPGI (Pharmacogenetics)</td>
<td></td>
<td>Modified IWPC PG (1-3)</td>
<td>Lenzini PG (4-5)</td>
<td>Intermountain (6-30)</td>
</tr>
<tr>
<td>PGPGA (Pharmacogenetics)</td>
<td></td>
<td>Modified IWPC PG (1-3)</td>
<td>Lenzini PG (4-5)</td>
<td>AHC (6-30)</td>
</tr>
</tbody>
</table>

AHC is the treatment protocol currently implementing in the Aurora Health Care
4-Step Methods

Step 1: Generate 1.5 millions clinical avatars (simulated patients) (integrating electronic health records and genetic literature knowledge)

Step 2: Conduct 30-day warfarin treatment simulation on clinical avatars

Step 3: Identify which treatment protocol minimizes one’s risk based on clinical and genetic characteristics

Step 4: Produce decision support rule for personalized treatment protocol
Produce decision-support rules of which type of treatment protocol maximizes outcome for a specific type of patient subgroup.

Personalized treatment (individual optimization):

- AAA
- CAA
- PGAA
- PGPGI
- PGPGA

Cluster and optimize treatment for patient subgroups and produce easy-to-visualize and implement decision support rules.

Example: AAA protocol most improves outcome for the individual (African American, age<=65, smoker, weight > 208 lb CYP2C9=*1/*1, etc.)

Personalized treatment (subgroup-optimization):

- AAA
- CAA
- PGAA
- PGPGI
- PGPGA

Example: CAA protocol most improves outcome for the patient subgroup (Age<65 and VKORC1 genotype=G/A or A/A)

Supervised Machine Learning Clustering: minimize overall adverse risks for the largest possible patient subgroups.
Treatment Simulation Result:
Comparison between Aurora Patients and Aurora Clinical Avatars
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aurora Warfarin Patients (mean±SD)</th>
<th>Aurora Warfarin Clinical Avatars (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age year</td>
<td>67.3±14.43</td>
<td>67.2±14.47</td>
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<tr>
<td>Weight lb</td>
<td>199.24±54.71</td>
<td>199.24±54.6</td>
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<tr>
<td>Height in</td>
<td>66.78±4.31</td>
<td>66.53±4.32</td>
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<tr>
<td>Gender, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>53.14</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>46.86</td>
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<tr>
<td>Race, %</td>
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<tr>
<td></td>
<td>White</td>
<td>95.18</td>
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<tr>
<td></td>
<td>African-American</td>
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<tr>
<td></td>
<td>Asian</td>
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<td>Am. Indian/Alaskan</td>
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<td></td>
<td>Pacific Islander</td>
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<td>Tobacco, %</td>
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<td>Amiodarone, %</td>
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<td>Fluvastatin, %</td>
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<td>Yes</td>
<td>0.03</td>
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<td>CYP2C9, %</td>
<td>*1/*1</td>
<td>65.77a</td>
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<tr>
<td></td>
<td>*1/*2</td>
<td>14.6a</td>
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<td>*1/*3</td>
<td>9.11a</td>
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<td></td>
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<td>6.41a</td>
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<td>*2/*3</td>
<td>1.93a</td>
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<tr>
<td></td>
<td>*3/*3</td>
<td>0a</td>
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<tr>
<td>VKORC1, %</td>
<td>G/G</td>
<td>38.54a</td>
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<tr>
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<td>G/A</td>
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<td>A/A</td>
<td>17.33a</td>
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</tbody>
</table>
Treatment Optimization Result:
12 Rules to decide Personalized Treatment Protocols based on Clinical and Genetic Characteristics
Ago < 64.95, Ago >= 64.95

VKORC1G < 2.5, VKORC1G >= 2.5

PGAA, CYP2C9, CYP2C9 >= 2.5

PGAA, CYP2C9 < 2.5, CYP2C9 >= 2.5

Age < 50.05, Age >= 50.05

CYP2C9 < 4.5, CYP2C9 >= 4.5

CYP2C9 < 2.5, CYP2C9 >= 2.5

VKORC1G < 1.5, VKORC1G >= 1.5

PGAA, AAA, AAA, PGAA
Compared to one-fit-all, personalized treatment protocol (BLACK BARS) significantly and consistently show lower risk (on average, 15% ~ 31% risk reduction) across all subgroups (N1 to N12).
Planned and ongoing work

1. Comprehensive comparison among 4 different versions of personalized protocol
   - Individualized optimization
   - Supervised machine-learning subgroup optimization
   - Unsupervised machine-learning subgroup optimization
   - Domain expert subgroup optimization

2. Above personalized protocols reduce 2-sided risk (bleeding and thrombosis).
   We can also develop patient-centered personalized protocol to more focus on:
   - Reducing higher chance of bleeding
   - Reducing higher chance of thrombosis
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• Terry Adam, Pharmacy and Institute for Health Informatics (IHI), UMN
Without inventing new treatment protocols, outcome can be improved by personalizing treatment protocol option based on clinical and genetic characteristics.

Example: AAA protocol most improves outcome for the individual (African American, age<=65, smoker, weight > 208 lb CYP2C9=*1/*1, etc.)

Example: CAA protocol most improves outcome for the patient subgroup (Age<65 and VKORC1 genotype=G/A or A/A)