

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

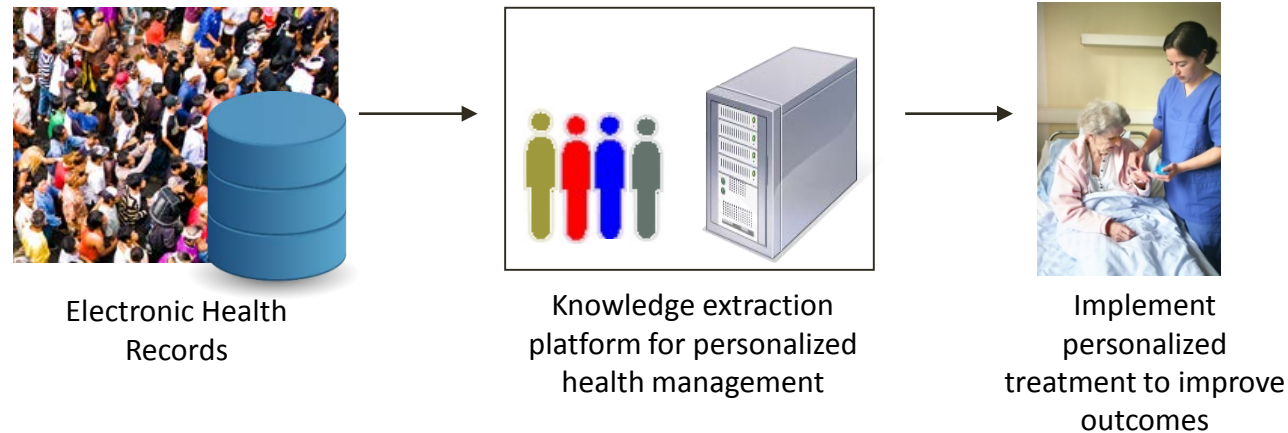
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In this talk, we demonstrate an example of personalizing warfarin treatment protocol to improve warfarin treatment outcome

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

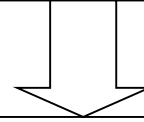
The Challenge

- What is the best protocol?
- Which individual or population is likely to benefit? From what protocol?

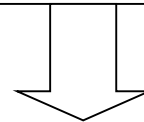
4-Step Methods

Treatment
Simulation

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

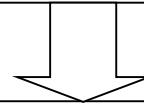


Step 2: Conduct 30-day warfarin treatment simulation on clinical avatars



Treatment
Optimization

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

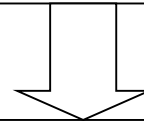


Step 4: Produce decision support rule for personalized treatment protocol

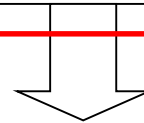
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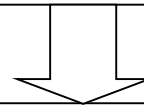


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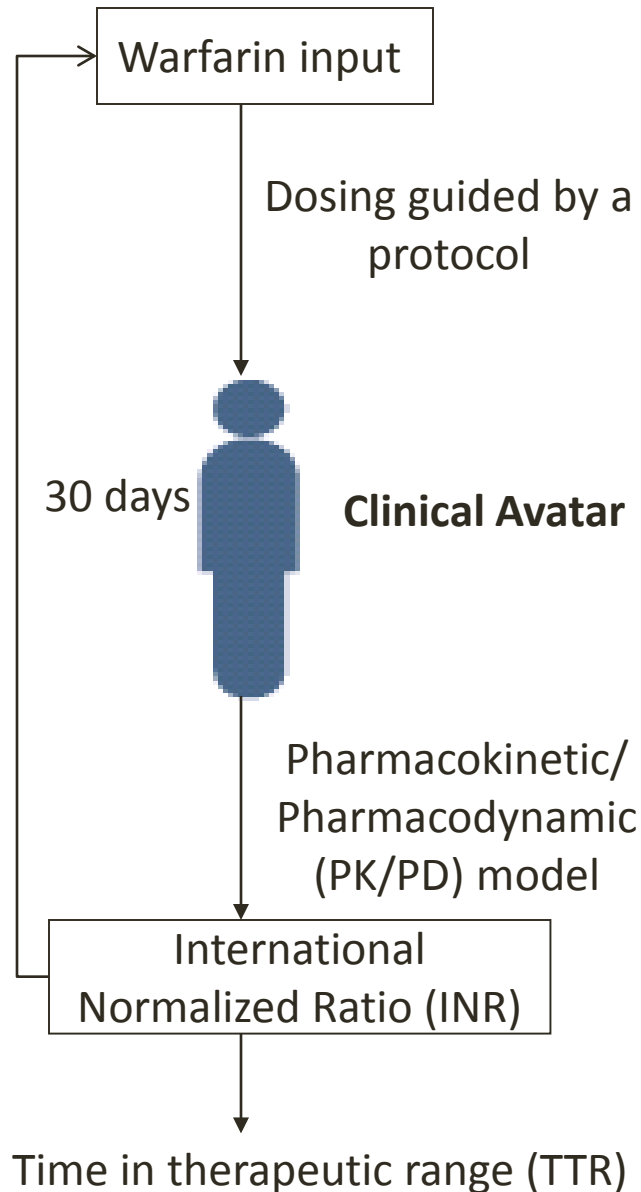
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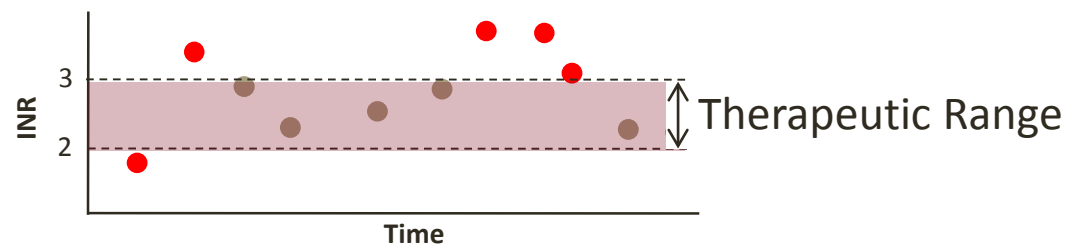
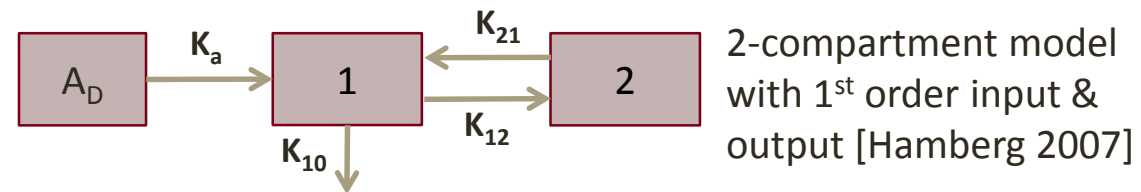
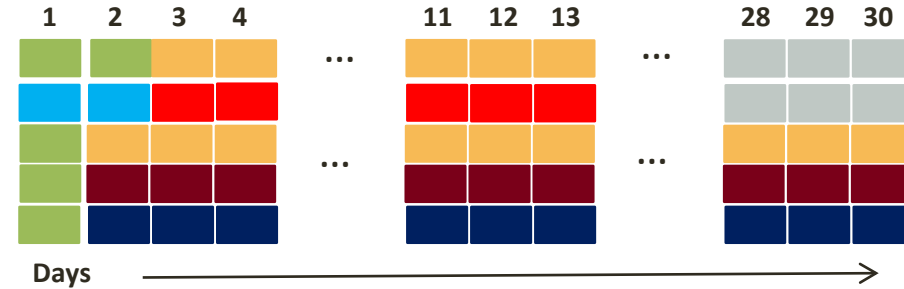
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Conduct 30-day warfarin treatment simulation on simulated patients



Protocols

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



Fusaro VA, Patil P, Chi CL, Contant CF, Tonellato PJ. A systems approach to designing effective clinical trials using simulations. *Circulation*. 2013 Jan 29;127(4):517-26.

Treatment protocol example

Days 8-10

Days 1-2

10 mg daily dose or Dose algorithm

Days 3-7

Day 3 INR	warfarin dose on days 3,4 (mg)	Day 5 INR	warfarin dose on day 5, 6, 7 (mg)
< 1.3	15, 15	< 2.0	15, 15, 15
1.3 – 1.4	10, 10	2.0 – 3.0	7.5, 5, 7.5
		3.1 – 3.5	0, 5, 5
		> 3.5	0, 0, 2.5

Day 3 INR	warfarin dose on days 3,4 (mg)	Day 5 INR	warfarin dose on day 5, 6, 7 (mg)
1.5 – 1.6	10, 5	< 2.0	7.5, 7.5, 7.5
1.7 – 1.9	5, 5	2.0 – 3.0	5, 5, 5
		3.1 – 3.5	2.5, 2.5, 2.5
		> 3.5	0, 2.5, 2.5

Day 3 INR	warfarin dose on days 3,4 (mg)	Day 5 INR	warfarin dose on day 5, 6, 7 (mg)
2.0 – 2.2	2.5, 2.5	< 2.0	5, 5, 5
2.3 – 3.0	0, 2.5	2.0 – 3.0	2.5, 5, 2.5
		3.1 – 3.5	0, 2.5, 0
		> 3.5	0, 0, 2.5

Day 3 INR	warfarin dose on days 3,4 (mg)	Day 5 INR	warfarin dose on day 5, 6, 7 (mg)
>3.0	0, 0	< 2.0	2.5, 2.5, 2.5
		2.0 – 3.0	2.5, 0, 2.5
		3.1 – 4.0	0, 2.5, 0
		> 4.0	0, 0, 2.5

-Follow dosing grids to establish the weekly warfarin dose

GOAL INR 2.0-3.0

INR 1.0-1.59	Action Point Low: -Inquire about s/s of clotting*, and if necessary, refer to an appropriate facility for care -Immediate extra dose (average of day 5-7 dose for day 8) -Increase weekly dose by 10% -Retest in 5 days, 14 days
INR 1.6-1.79	Red Zone Low: -Give an extra half dose today (average of days 5-7 for day 8) -Increase weekly dose by 5% -Retest in 7 days, 14 days
INR 1.8-1.99	1st Yellow Zone Low: -Retest in 14 days 2nd Yellow Zone Low: -Increase weekly dose by 5% -Retest in 14 days
INR 2.0-3.0	Green Zone: -Retest in 14 days after day 8, monthly
INR 3.01-3.39	1st Yellow Zone High: -Retest in 14 days 2nd Yellow Zone High: -Decrease weekly dose by 5% -Retest in 14 days
INR 3.4-4.99	Red Zone High: -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
INR > 5.0	Action Point High: -Inquire about s/s bleeding**, and if necessary, refer to an appropriate facility for care. Customize care if bleeding. -Omit 2 doses -Retest in 48 hours -When retested INR falls into green or yellow zones, decrease weekly dose by 15% and retest in 7 days, 14 days Note: If INR > 9.0 follow special protocol (IHC guidelines)

Available Treatment Protocol Options

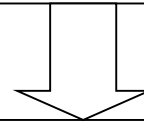
Treatment Periods Treatment Plans	Initial period (days)	Adjustment period (days)	Maintenance period (days)
AAA (Clinical)	AHC (1-2)	AHC (3-7)	AHC (8-30)
CAA (Clinical)	IWPC Clinical (1-2)	AHC (3-7)	AHC (8-30)
PGAA (Pharmacogenetics)	IWPC PG (1-2)	AHC (3-7)	AHC (8-30)
PGPGI (Pharmacogenetics)	Modified IWPC PG (1-3)	Lenzini PG (4-5)	Intermountain (6-30)
PGPGA (Pharmacogenetics)	Modified IWPC PG (1-3)	Lenzini PG (4-5)	AHC (6-30)

AHC is the treatment protocol currently implementing in the Aurora Health Care

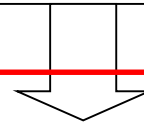
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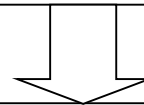


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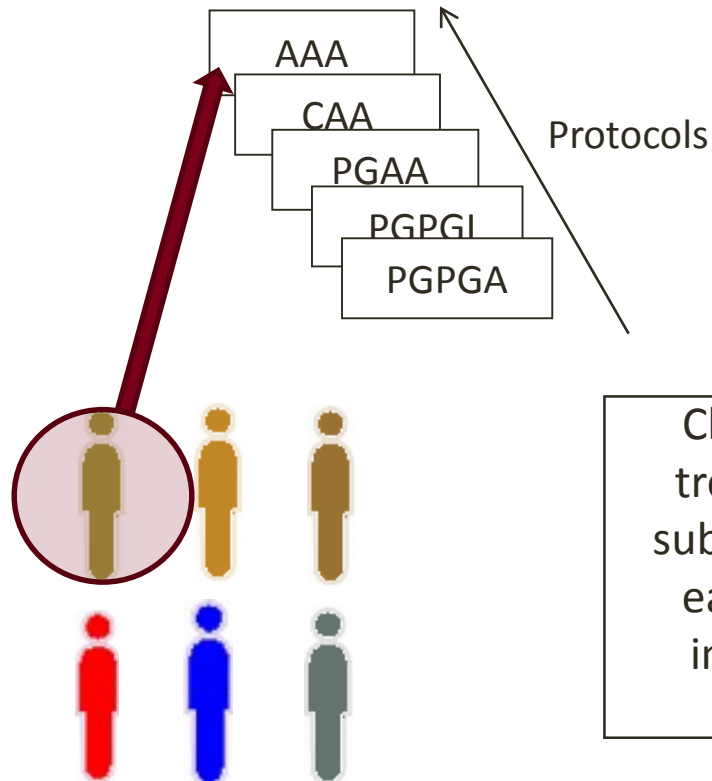
Step 3: Identify which treatment protocol minimizes one's risk based on clinical
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Step 4: Produce decision support rule for personalized treatment protocol

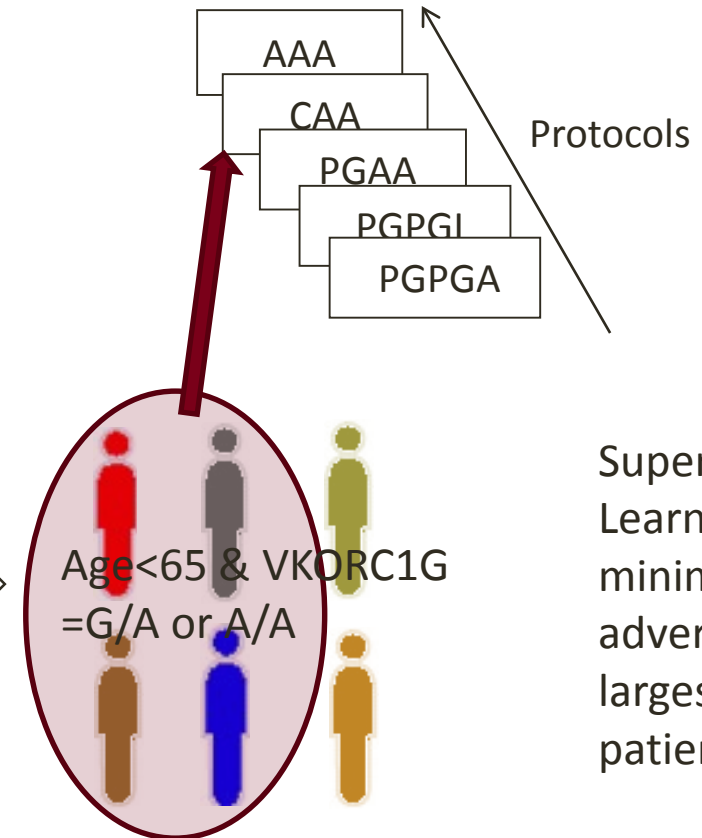
Produce decision-support rules of which type of treatment protocol maximizes outcome for a specific type of patient subgroup

Personalized treatment (individual optimization)



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

Personalized treatment (subgroup-optimization)



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

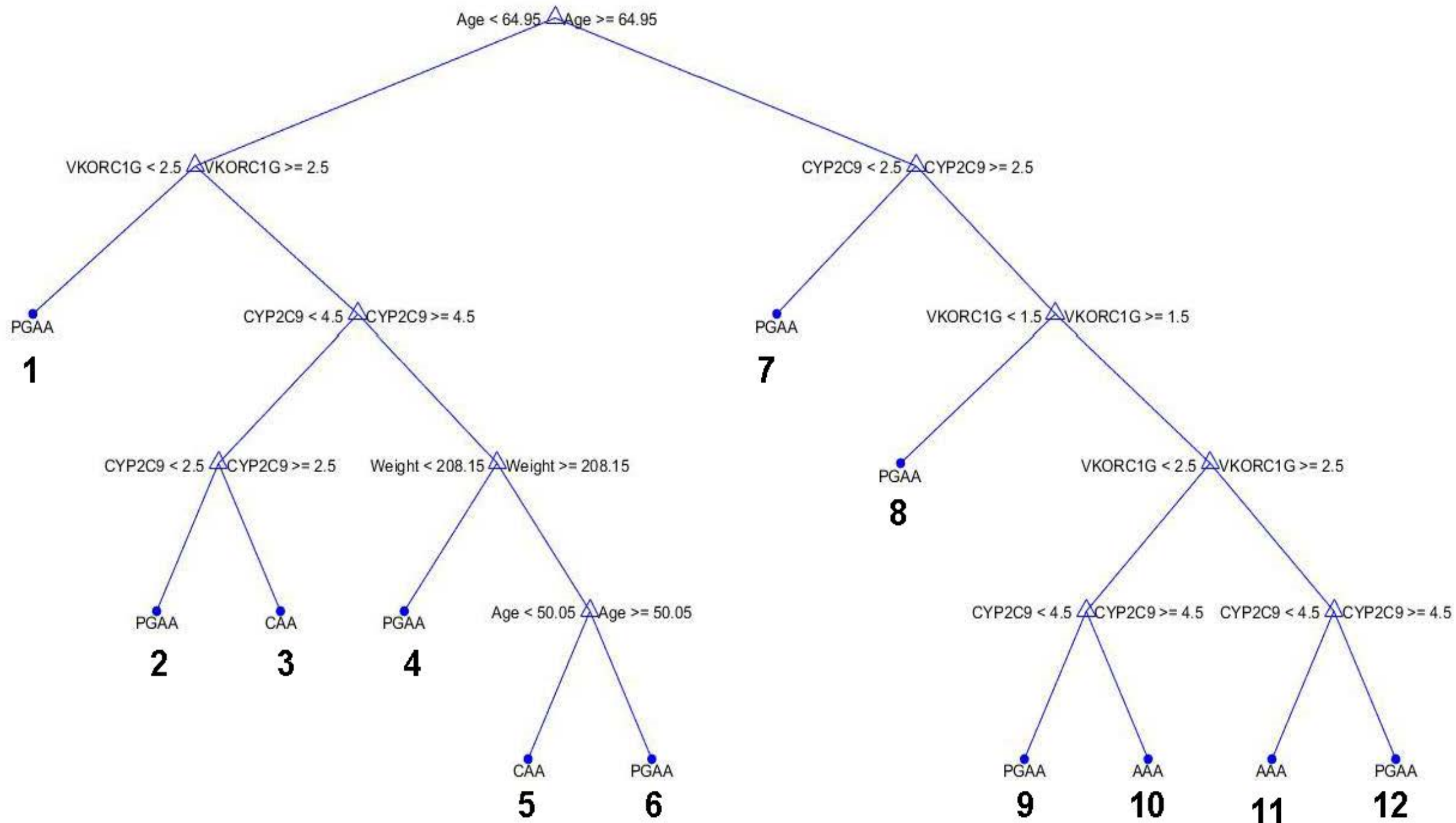
Cluster and optimize treatment for patient subgroups and produce easy-to visualize and implement decision support rules

Supervised Machine Learning Clustering: minimize overall adverse risks for the largest possible patient subgroups

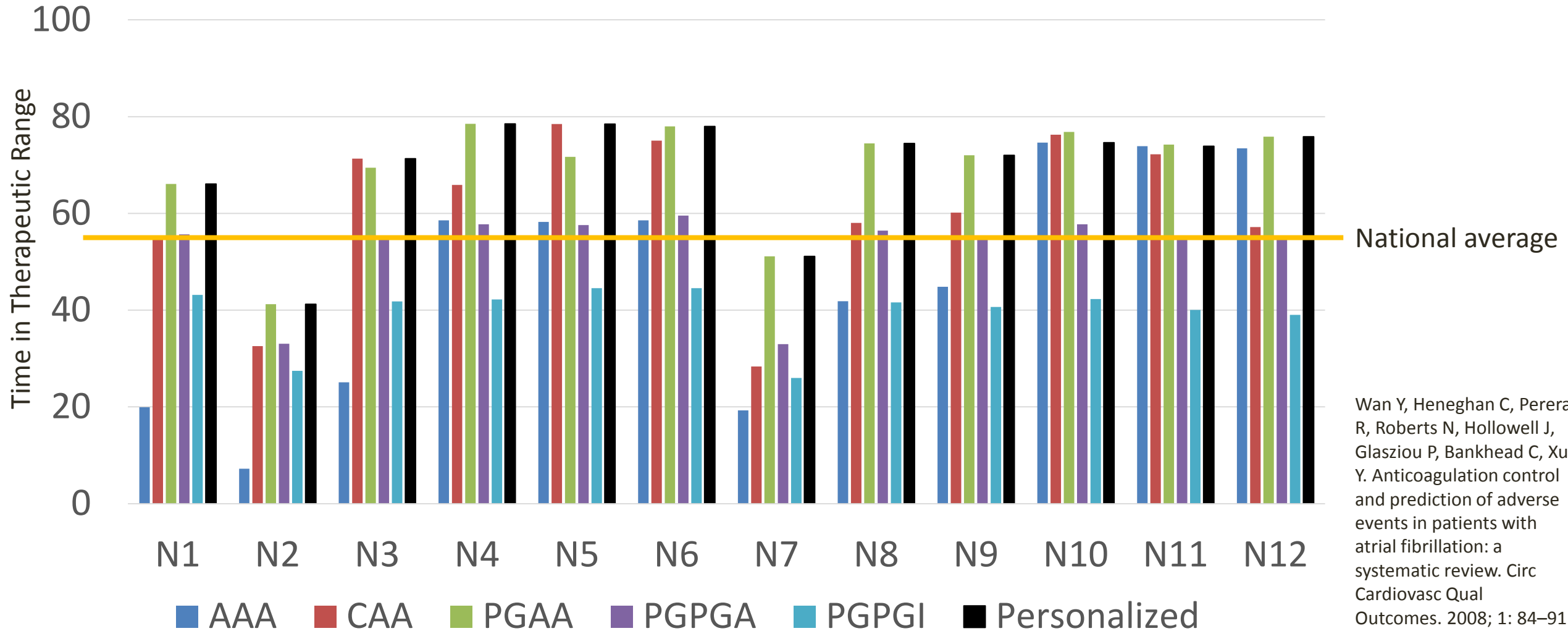
Treatment Simulation Result:
Comparison between Aurora Patients and Aurora
Clinical Avatars

Characteristic		Aurora Warfarin Patients (mean±SD)	Aurora Warfarin Clinical Avatars (mean±SD)
Age	year	67.3±14.43	67.2±14.47
Weight	lb	199.24±54.71	199.24±54.6
Height	in	66.78±4.31	66.53±4.32
Gender, %	Female	53.14	53.10
	Male	46.86	46.90
Race, %	White	95.18	95.22
	African-American	4.25	4.19
	Asian	0.39	0.40
	Am. Indian/Alaskan	0.18	0.18
	Pacific Islander	0.0001	0.0001
Tobacco, %	No	90.33	90.67
	Yes	9.66	9.33
Amiodarone, %	No	88.45	88.49
	Yes	11.54	11.51
Fluvastatin, %	No	99.97	99.98
	Yes	0.03	0.02
CYP2C9, %	*1/*1	65.77 ^a	67.39
	*1/*2	14.6 ^a	14.86
	*1/*3	9.11 ^a	9.25
	*2/*2	6.41 ^a	6.51
	*2/*3	1.93 ^a	1.97
	*3/*3	0 ^a	0
VKORC1, %	G/G	38.54 ^a	38.37
	G/A	44.02 ^a	44.18
	A/A	17.33 ^a	17.45

Treatment Optimization Result:
12 Rules to decide Personalized Treatment Protocols
based on Clinical and Genetic Characteristics



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

Acknowledgement

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- **Tatiana Lenskaia**, Bioinformatics and Computational Biology, UMN
- **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

