Pharmacogenomic genotypes define genetic ancestry in patients and enable population-specific genomic implementation

Wenndy Hernandez, PhD, Keith Danahey, MSIS, MScA, Xun Pei, MS, MB, Kiang-Teck J. Yeo, PhD, Edward Leung, PhD, Samuel L. Volchenboum, MD, PhD, Mark J. Ratain, M.D., David O. Meltzer, MD, Barbara E. Stranger, PhD, Minoli A. Perera, PharmD, PhD, Peter H. O'Donnell, MD

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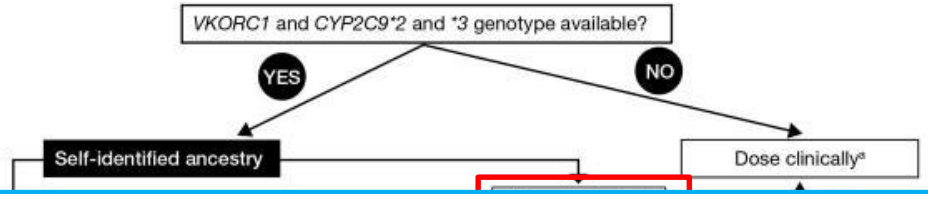
THE UNIVERSITY OF CHICAGO

Biological Sciences Division/Department of Medicine

Background

- Warfarin PGx algorithms resulted in increased risk to African Americans (AAs)
- Resulted in guidance to consider population-specific drug dosing algorithms for warfarin
- Warfar ancest



≥70% AFR

Pharmacogenomics J. 2014 June ; 14(3): 223–228. doi:10.1038/tpj.2013.34.

Ethnicity-Specific Pharmacogenetics: The Case of Warfarin In African Americans

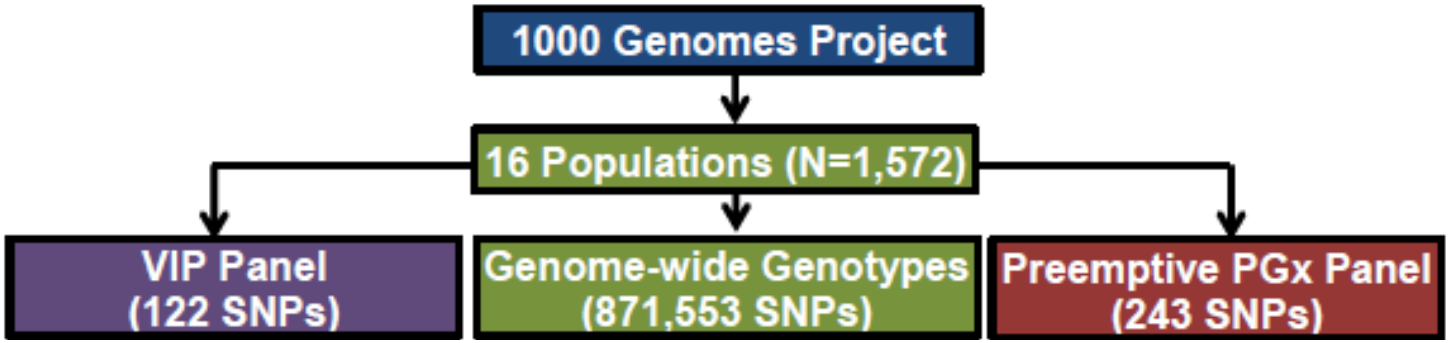
Wenndy Hernandez, Ph.D.[1], Eric R. Gamazon, Ph.D.[1], Keston Aquino-Michaels, B.A.[1], Shitalben Patel, M.S.[2], Travis J. O'Brien, Ph.D.[3], Art F. Harralson, Pharm.D.[3,4], Rick A. Kittles, Ph.D.[5], April Barbour, M.D.[6], Matthew Tuck, M.D.[7], Samantha D. McIntosh, M.D.[6,7], Jacqueline N. Douglas, Pharm.D.[7], Dan Nicolae, Ph.D.[1], Larisa H. Cavallari, Pharm.D.[2], and Minoli A. Perera, Pharm.D,, Ph.D[1]

Johnson JA, et al. Clin Pharmacol Ther. 2017
Hernandez W, et al. Pharmacogenomics J. 2014

Objective

To test the ability of focused clinical pharmacogenomic (PGx) SNP panels to estimate individual genetic ancestry (IGA) and implement population-specific warfarin guidance within our PGx results delivery system for AA patients starting warfarin.

Methods



VIP, Very Important Pharmacogenes; AFR, African; EAS, East Asian; EUR, European; ASW, Americans of African Ancestry in SW USA; CEU, Utah Residents (CEPH) with Northern and Western Ancestry; AFR, African; EAS, East Asian; EUR, European.

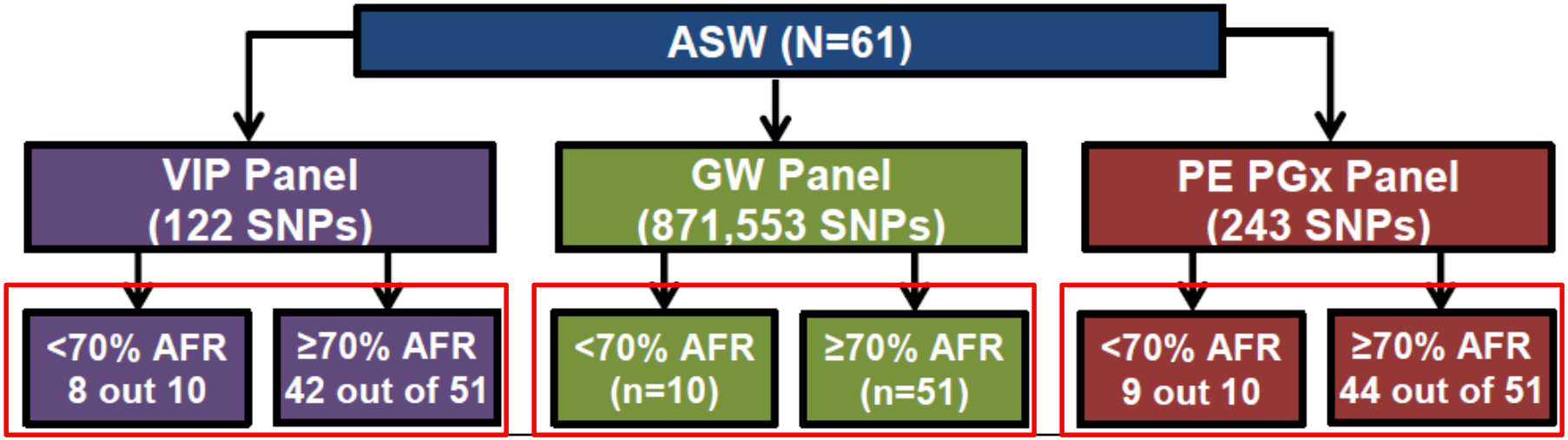
Results
Evaluating Accuracy of Clinical PGx SNP Panels

Validation Cohort		GW (871,553)	PE PGx (243)			VIP (122)		
Ancestry		Proportion ±SD	Proportion ±SD	†MAE ±SE	†P	Proportion ±SD	‡MAE ±SE	‡P
ASW	AFR	0.78 ±0.16	0.78 ±0.18	0.06 ±0.01	0.53	0.79 ±0.19	0.07 ±0.01	0.3
	EAS	0.02 ±0.08	0.05 ±0.10	0.03 ±0.01	0.1	0.05 ±0.07	0.05 ±0.01	0.1
	EUR	0.20 ±0.11	0.17 ±0.14	0.07 ±0.01	0.08	0.16 ±0.18	0.13 ±0.01	0.04
CEU	AFR	0.00 ±0.00	0.01 ±0.01	0.01 ±0.00	0.46	0.01 ±0.03	0.01 ±0.00	0.12
	EAS	0.00 ±0.00	0.01 ±0.03	0.01 ±0.00	0.82	0.02 ±0.07	0.02 ±0.01	0.08
	EUR	0.99 ±0.00	0.98 ±0.03	0.02 ±0.00	0.32	0.97 ±0.08	0.03 ±0.01	0.09

Clinical PGx panels can accurately estimate IGA when compared to genome-wide genotyping

ASW, Americans of African Ancestry in SW USA; CEU, Utah Residents (CEPH) with Northern and Western Ancestry; AFR, African; EAS, East Asian; EUR, European; MAE, mean absolute error; SD, standard deviation; SE, standard error.

Predictive Power of PGx Panels to Identify Patients with ≥70% AFR Ancestry

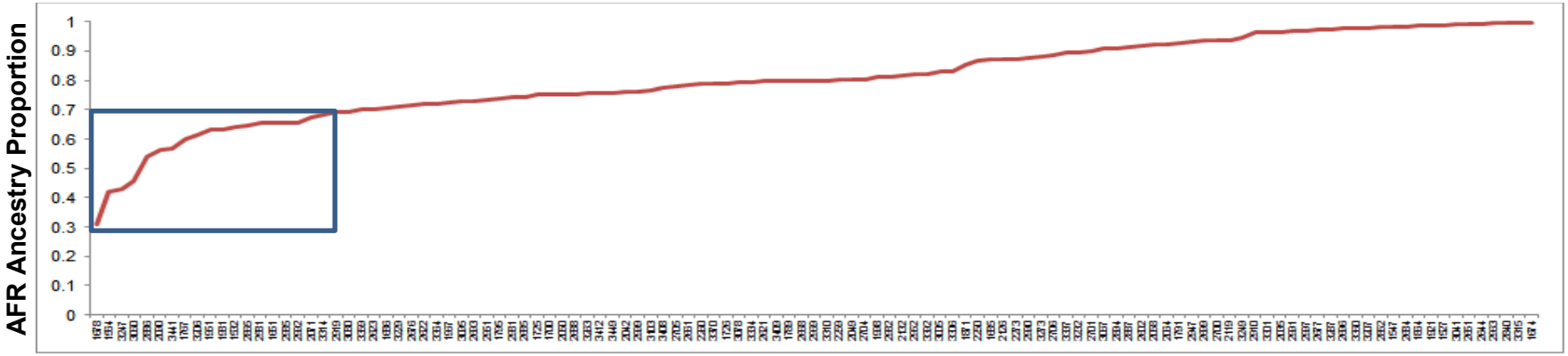


Panel	Sensitivity	Specificity	PPV	NPV
PE PGx	86.3%	90.0%	97.8%	56.3%
VIP	82.4%	80.0%	95.5%	47.0%

Clinical PGx panels can correctly assign individuals to population-specific categories and estimate IGA with a high level of accuracy

Estimated IGA of Real-World Patients Undergoing Clinical PGx Result Delivery

- ~18% fell outside the 70% genetic cut-off threshold
  - ~16% of the 1000 Genomes ASW population have <70% AFR ancestry.
- ~20% of self-identified AAs would not be assigned to the AA-specific algorithm



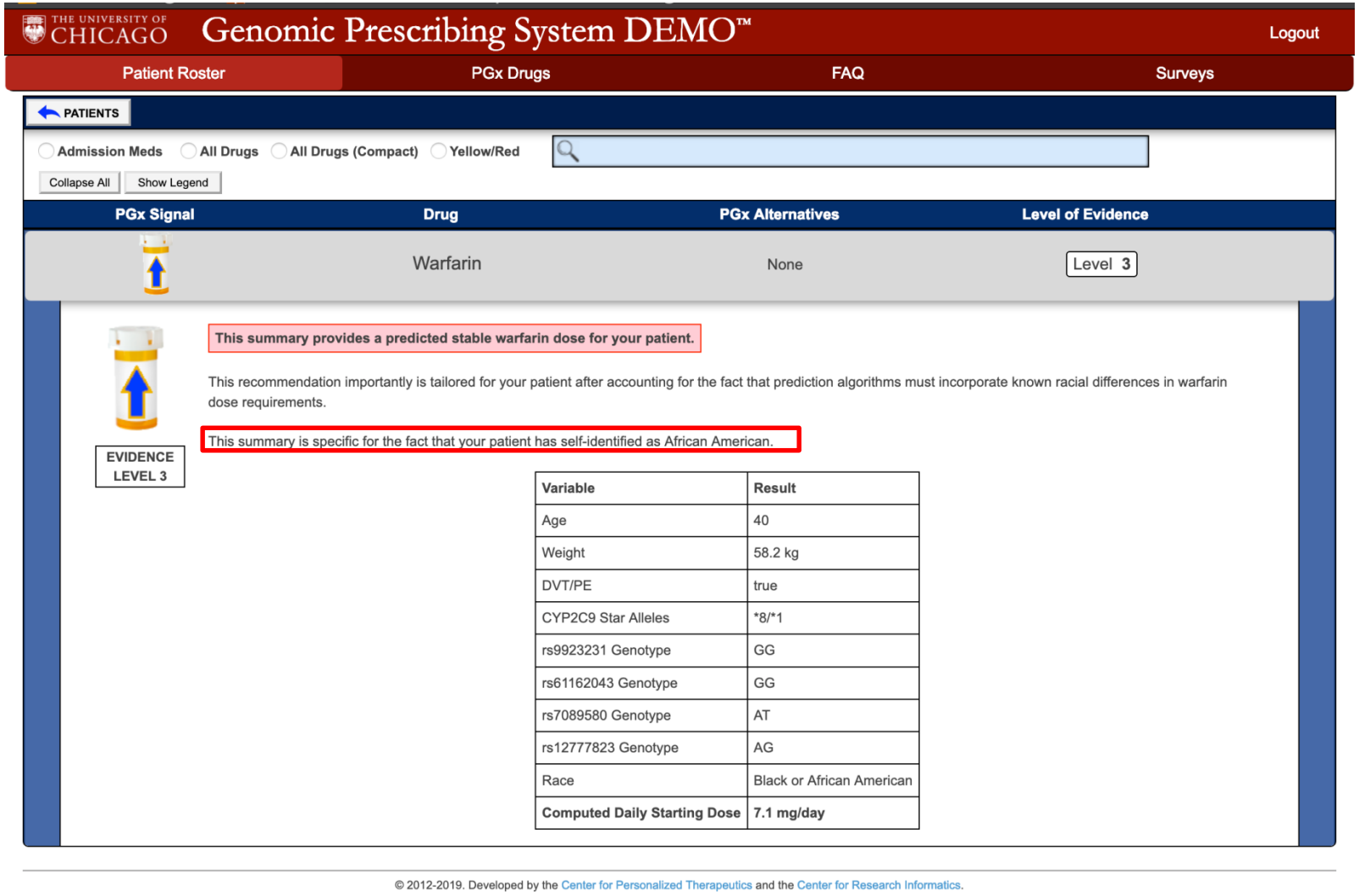
Distribution of individual ancestry estimates among African American University of Chicago patients. Blue box represents patients with <70% genetic AFR ancestry (21/115 individuals; 18.3%).

Performance Comparison of Warfarin Dosing Algorithms for African American Patients With <70% AFR Ancestry (N=26)

Algorithm	Warfarin dose (mean ±SD)	Pearson's r	Within 20%*
Therapeutic dose	48.4 ±15.2	NA	NA
AA-specific PGx	46.2 ±10.8	0.60	65.4%
IWPC PGx	43.4 ±9.4	0.33	50.0%

Warfarin dose is in mg/week
NA, not applicable
*Prediction rage fell within 20% of the actual required dose.

Population-specific warfarin dosing algorithms implemented in the institutional PGx clinical decision-support system - Genomic Prescribing System



O'Donnell PH, et al. Clin Pharmacol Ther. 2012;92(4):446-449

Conclusion

- Small clinical PGx panels can accurately estimate IGA when compared to genome-wide genotyping.
- The AA-specific warfarin algorithm outperformed the IWPC algorithm for AAs with <70% genetic AFR ancestry.
- Integration of IGA enabled the deployment of population-specific PGx CDS guidance in our clinical workflow.