Precision Medicine Symposium

PGx Beyond Drug Metabolizing enzymes, An Integrative Physiology Approach

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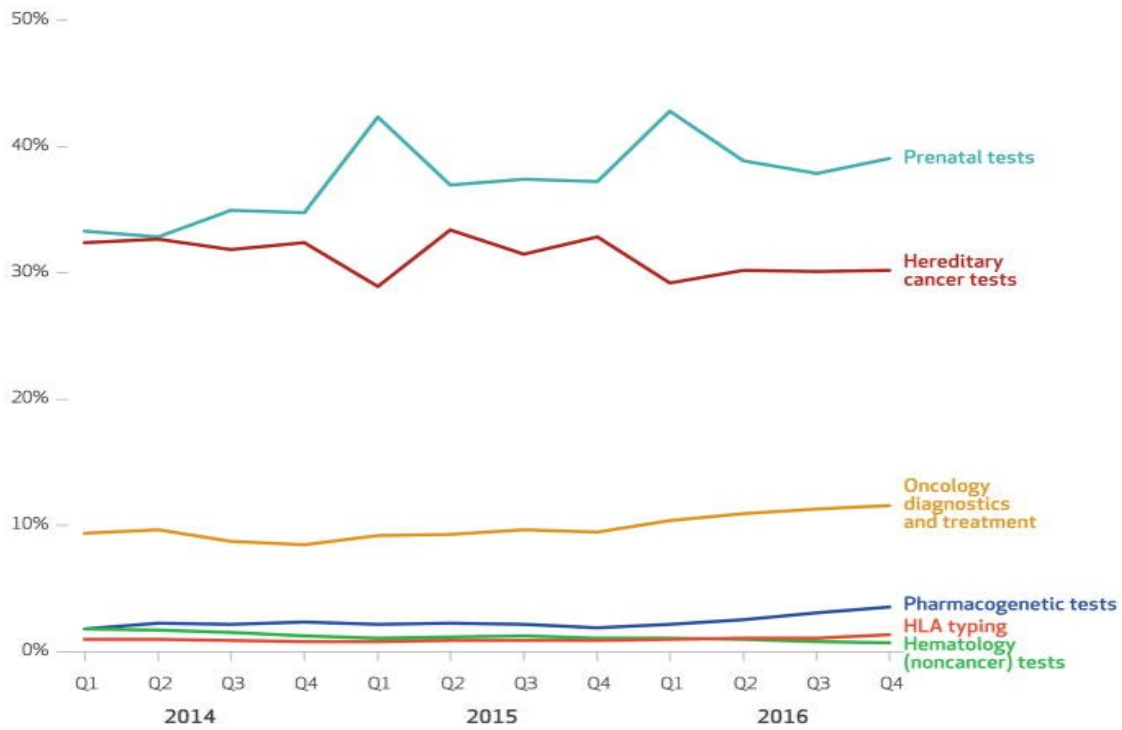
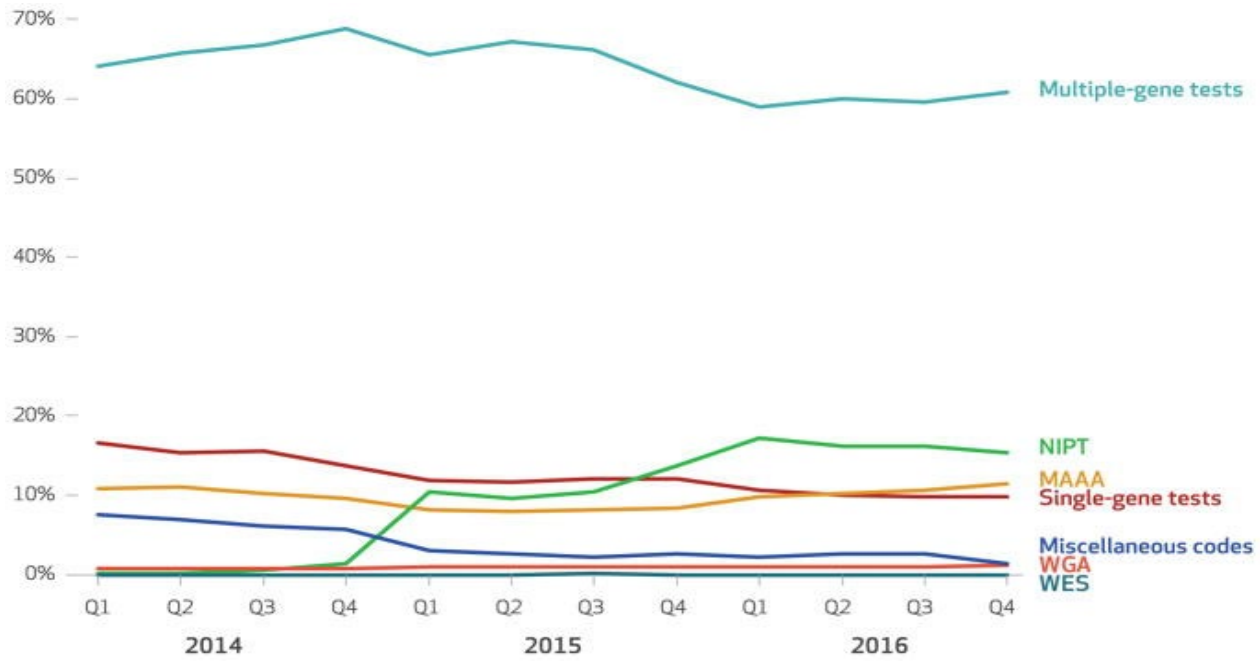
"There are approximately 75,000 genetic tests on the market, with about ten new tests entering the market daily[1]"



Percentages of spending on genetic testing in six clinical domains, by quarter, 2014–16

[1]Phillips KA, Deverka PA, Hooker GW, Douglas MP. Genetic Test Availability And Spending: Where Are We Now? Where Are We Going?. *Health Aff (Millwood)*. 2018;37(5):710–716. doi:10.1377/hlthaff.2017.1427

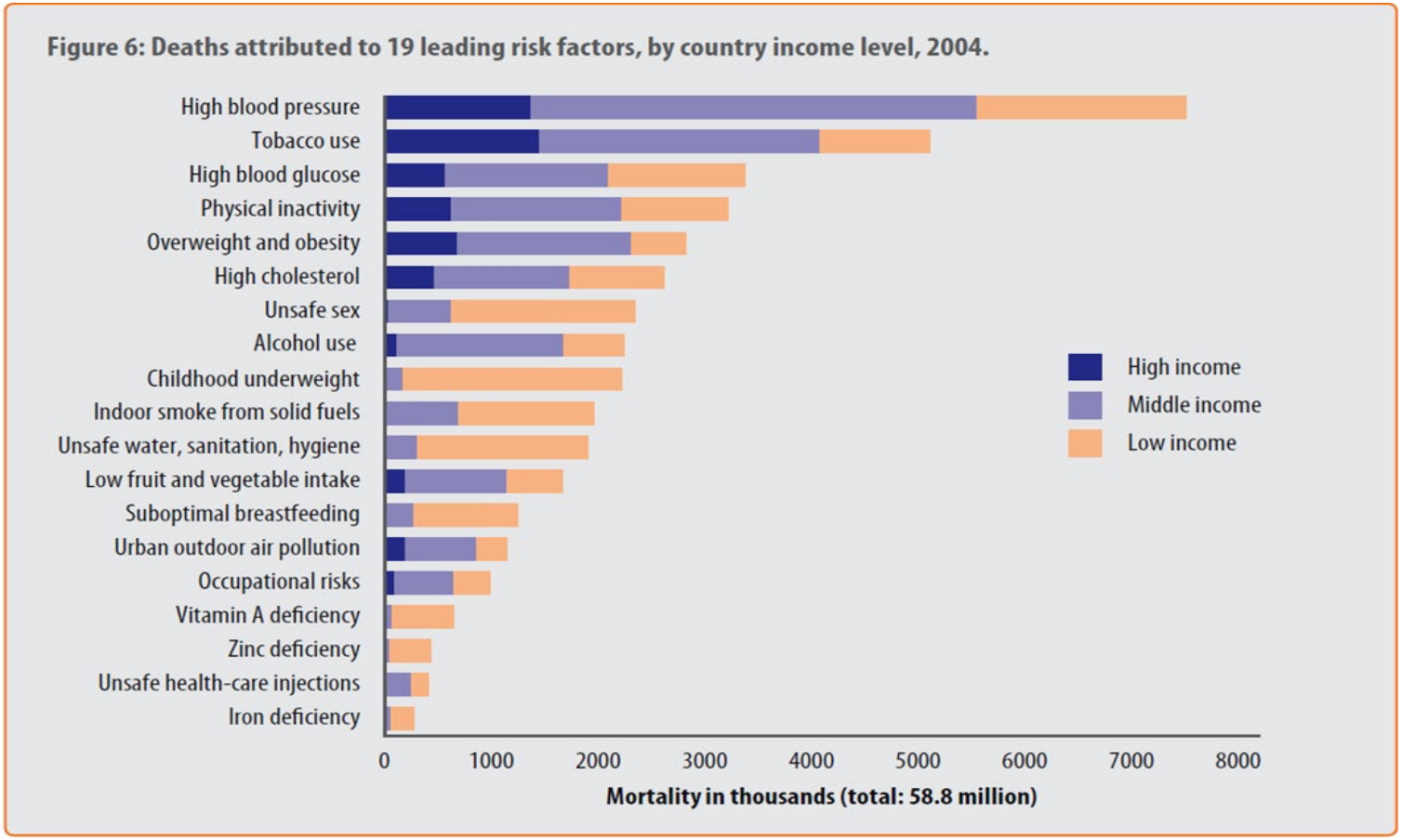
Of the 75K available tests, 86% of the genetic tests were single-gene tests. The remaining tests were panel tests, including 9,311 multi-analyte assays with algorithmic analyses, 85 noninvasive prenatal tests (NIPT), 122 whole exome sequencing tests (WES), and 873 whole genome (WGS) analysis tests[1]



Percentages of spending on types of genetic testing, by quarter, 2014–16

[1]Phillips KA, Deverka PA, Hooker GW, Douglas MP. Genetic Test Availability And Spending: Where Are We Now? Where Are We Going?. *Health Aff (Millwood)*. 2018;37(5):710–716. doi:10.1377/hlthaff.2017.1427

Hypertension as a risk factor



World Health Organization: Global Health Risks 2009 - ISBN 978 92 4 156387 1

Underserved Populations

AMERICAN COLLEGE of CARDIOLOGY

Racial Differences in Antihypertensive Drug Use and BP Control

Feb 03, 2017

Authors:	Gu A, Yue U, Desai RP, et al.
Citation:	Racial and Ethnic Differences in Antihypertensive Medication Use and Blood Pressure Control Among US Adults With Hypertension: The National Health and Nutrition Examination Survey, 2003 to 2012. *Circ Cardiovasc Qual Outcomes* 2017:Jan 17:[Epub ahead of print].
Summary By:	Melvyn Rubenfire, MD, FACC

Study Questions:

Are there racial differences in antihypertensive drug utilization patterns and blood pressure (BP) control by insurance status, age, sex, and presence of comorbidities?

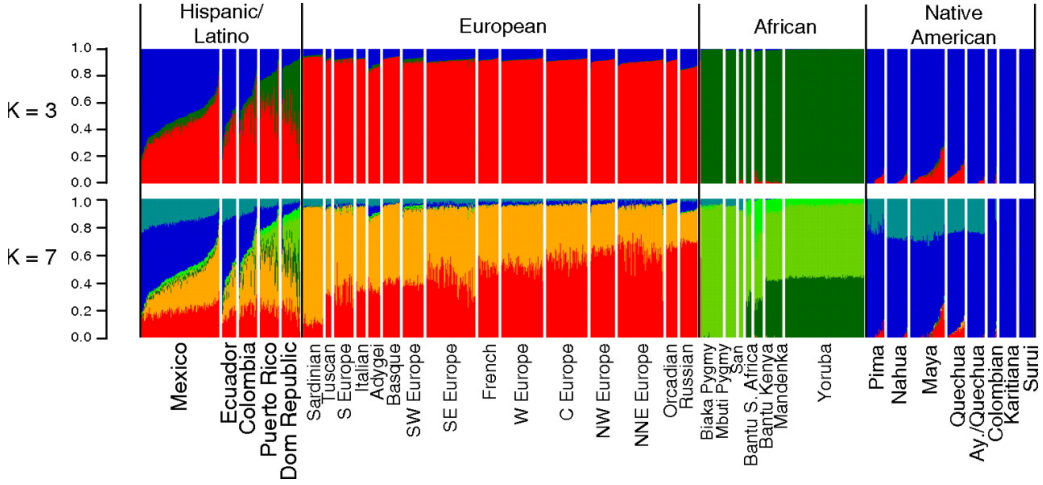
Results:
There was a significantly ($p < 0.001$ for each) greater percentage of blacks and Hispanics between 18-39 years, higher rates of diabetes, less CKD, nearly a 2-fold higher poverty-to-income ratio, and baseline mean sBP and mean dBP were about 3/2 mm Hg higher. During the study period, all three racial groups (whites, blacks, and Hispanics) experienced a substantial increase in hypertension treatment and control. **The overall treatment rates** were **73.9%, 70.8%, and 60.7%. Hypertension control rates with JNC 7 were 42.9%, 36.9%, and 31.2% for whites, blacks, and Hispanics, respectively** ($p < 0.001$), and a >10% better control was noted in JNC 8 for each group. When stratified by insurance status, blacks (odds ratio [OR], 0.74 for insured and 0.59 for uninsured) and Hispanics (OR, 0.74 for insured and 0.58 for uninsured) persistently had lower rates of hypertension control compared with whites. Unlike black patients, Hispanics received less intensive antihypertensive therapy (OR for combination therapy, 0.77). Racial disparities also persisted in subgroups stratified by age (≥60 and <60 years of age) and presence of comorbidities, but worsened among patients <60 years of age.

Conclusions:
Black and Hispanic patients have poorer hypertension control compared with whites, and these differences are more pronounced in younger and uninsured patients. While black patients received more intensive antihypertensive therapy, **Hispanics were undertreated.** Future studies should further explore all aspects of these disparities to improve cardiovascular outcomes.

https://www.acc.org/latest-in-cardiology/journal-scans/2017/02/03/14/29/racial-and-ethnic-differences-in-antihypertensive-medication

Underserved Populations

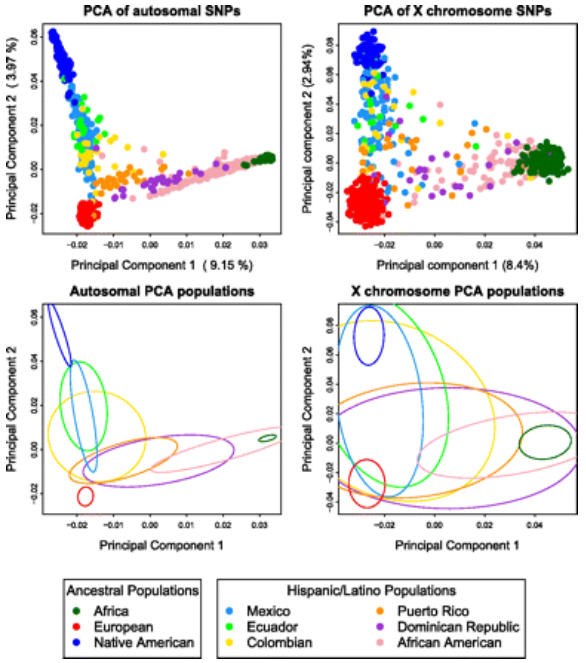
- Hispanic/Latino populations possess a complex genetic structure that reflects recent admixture among and potentially ancient substructure within Native American, European, and West African source populations.
- Our results suggest future genome-wide association scans in Hispanic/Latino populations may require correction for local genomic ancestry at a subcontinental scale when associating differences in the genome with disease risk, progression, and drug efficacy, as well as for admixture mapping.



Genome-wide patterns of population structure and admixture among Hispanic/Latino populations

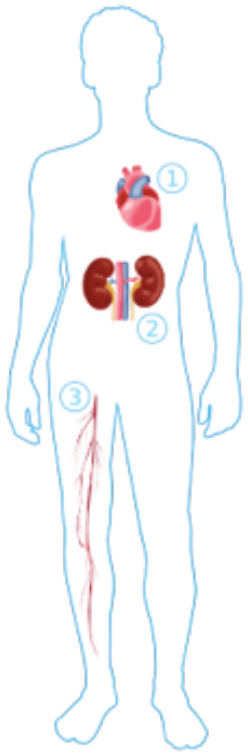
Katarzyna Bryc, Christopher Velez, Tatiana Karafet, Andres Moreno-Estrada, Andy Reynolds, Adam Auton, Michael Hammer, Carlos D. Bustamante, and Harry Ostrer

PNAS May 11, 2010 107 (Supplement 2) 8954-8961; published ahead of print May 5, 2010 https://doi.org/10.1073/pnas.0914618107



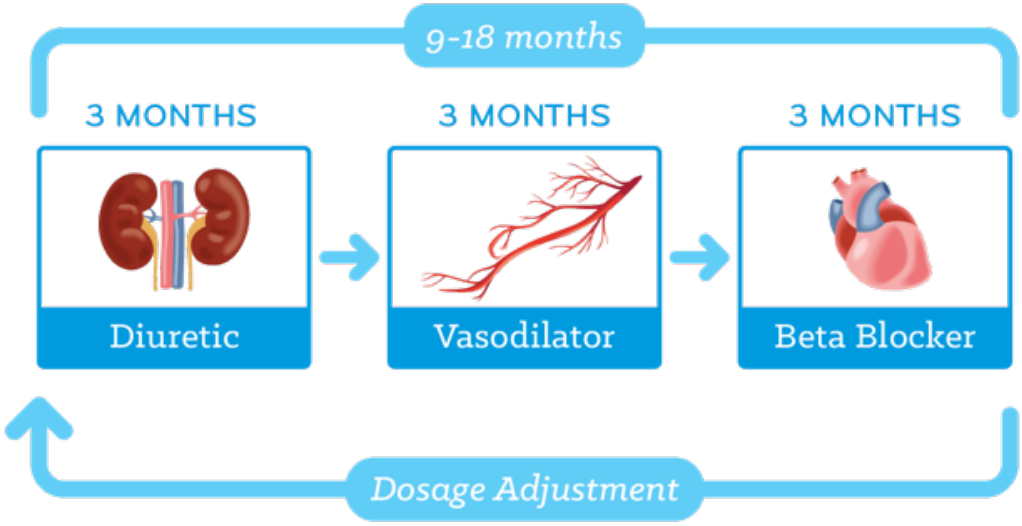
http://www.pnas.org/content/107/Supplement_2/8954

Physiology & Genetics of Blood Pressure:



- **Heart:** Your genes impact how hard the heart beats and heart rate (beta blockers used to treat)
- **Kidney:** Your genes impact sodium reabsorption (diuretics used to treat)
- **Vessels:** Your genes impact vascular constriction and sodium reabsorption (vasodilators used to treat)

The Problem with Standard of Care



Drugs are layered: Each Increase in # of Medications = **85% increase in nonadherence**

Therapy is not Uniform (or always down)

Response below is to **Hydrochlorothiazide** monotherapy:

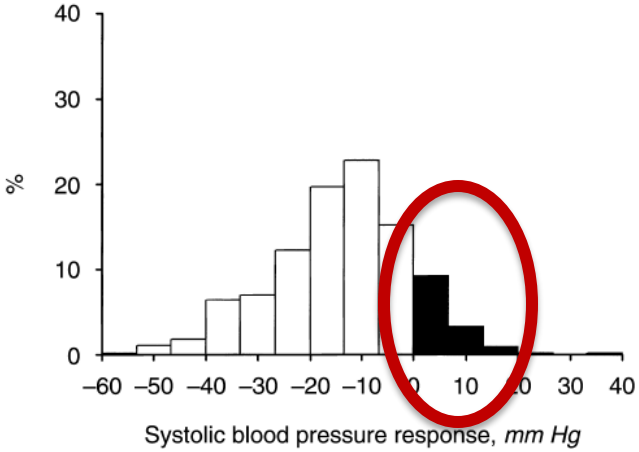


Fig. 1. Frequency distribution histogram of systolic blood pressure (BP) responses to four weeks of hydrochlorothiazide, 25 mg per day, in the combined sample of 225 African Americans and 280 Caucasians. Symbols are: (□) decreases in BP; (■) increases in BP. Data are mean = −14.4, SD = 13.4, N = 505.

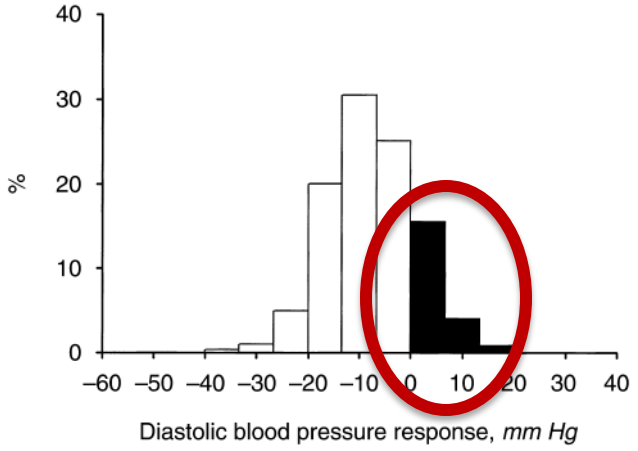


Fig. 2. Frequency distribution histogram of diastolic blood pressure (DBP) response to four weeks of hydrochlorothiazide, 25 mg per day, in the combined sample of 225 African Americans and 280 Caucasians. Symbols are: (□) decreases in BP; (■) increases in BP. Data are mean = −7.8, SD = 8.4, N = 505.

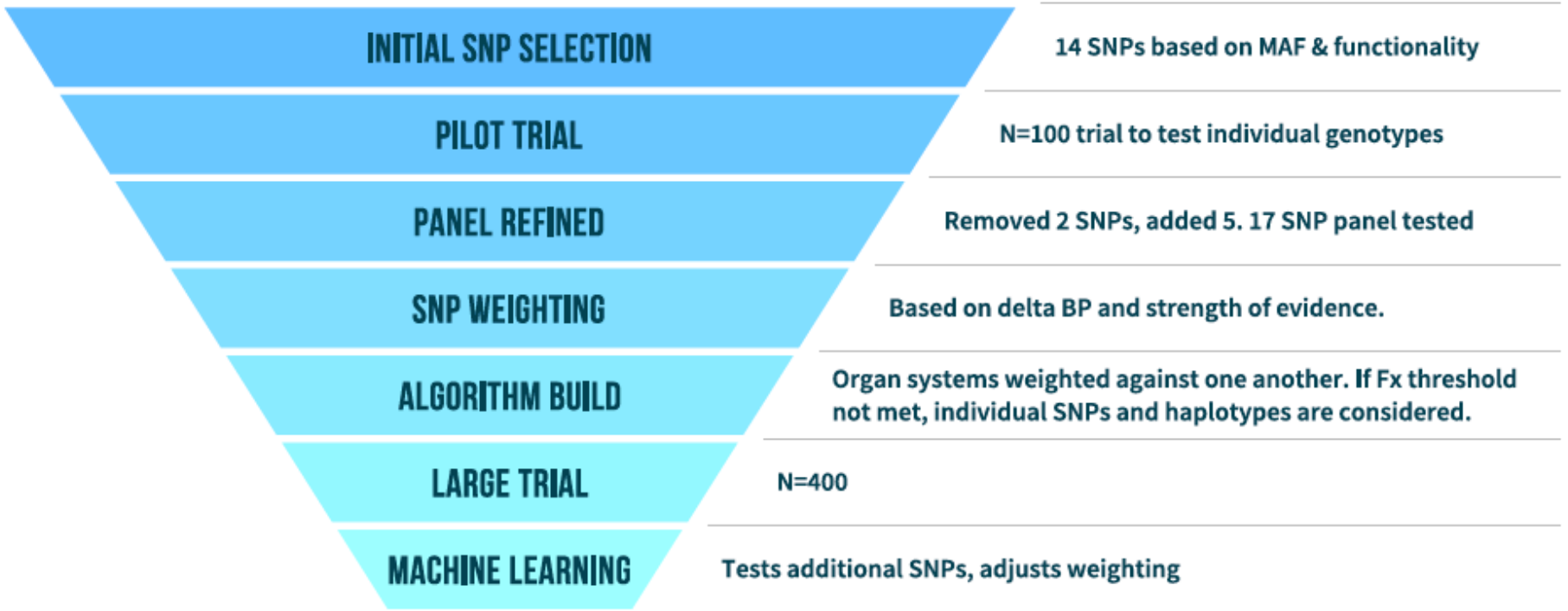
In large and well-controlled studies there is an increase in BP in some patients with most types of therapy

1. Chapman et al. *Kid. Intern.* 61. 2003

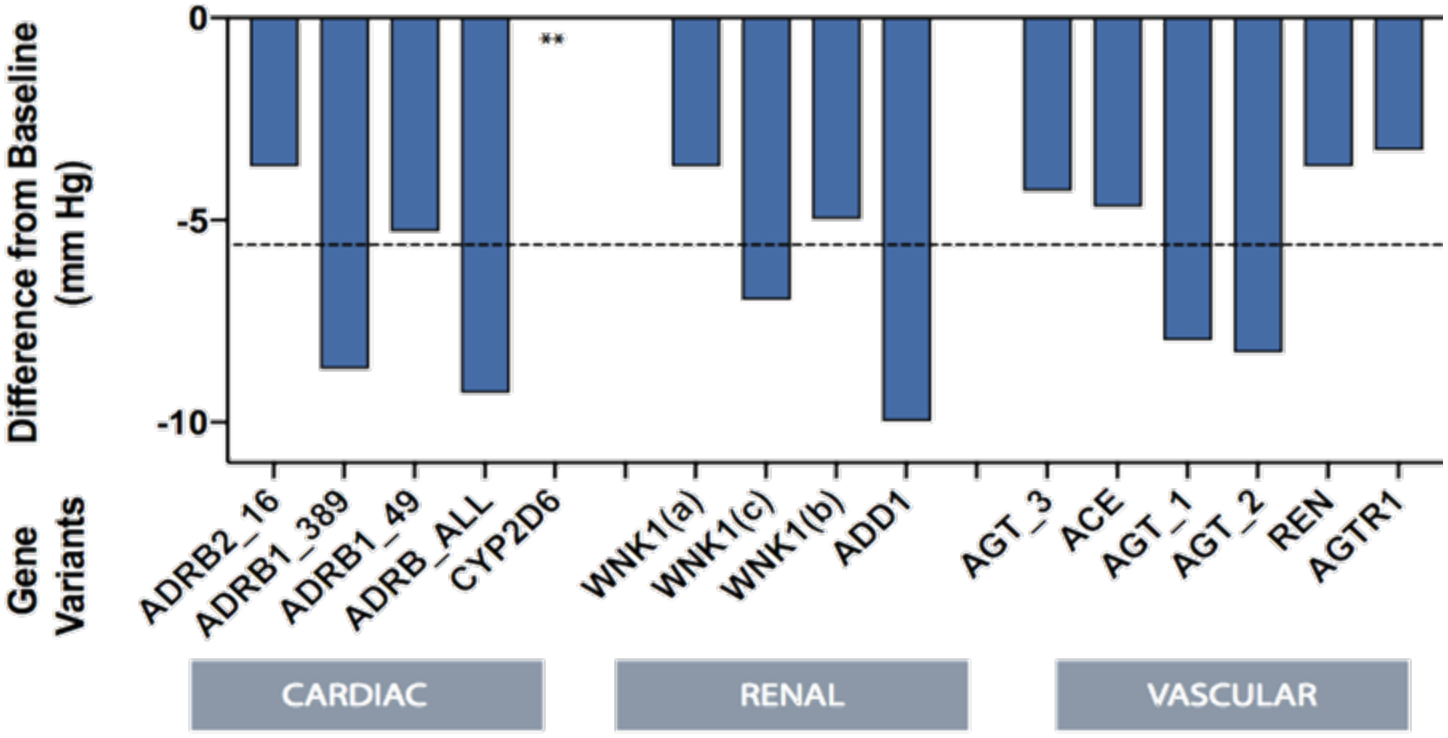
Side Effect Profile per Drug Class

	Common	Less Common	Rare
Selective β-blocker (METOPROLOL SUCCINATE EXTENDED-RELEASE TABLETS)	Tiredness and dizziness (10%), Depression (5%), Pruritus or rash (5%)	Shortness of breath and bradycardia (3%), Wheezing (bronchospasm) and dyspnea (1%), Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure; peripheral edema;	Peyronie's disease (<0.001%)
Non-selective β-blocker (LABETALOL HYDROCHLORIDE)	Dizziness (11%), Nausea (6%), Fatigue (5%)	Dyspepsia (3%), Nasal stuffiness (3%), Headache (2%), Dyspnea (2%), Vertigo (2%), Ejaculation failure (2%), Impotence (1%), Taste distortion (1%), Edema (1%),	Vomiting (<1%), Diarrhea (<1%), Paresthesia (<1%), Increased sweating (<1%)
CA+ channel blocker (VERAPAMIL HYDROCHLORIDE TABLET, EXTENDED RELEASE)	Contipation (7.3%)	Dizziness (3.3%), Nausea (2.7%), Hypotension (2.5%), Headache (2.2%), Edema (1.9%), CHF/Pulmonary Edema (1.8%), Fatigue (1.7%), Dyspnea (1.4%), Bradycardia (1.4%), AV Block-1°, 2°, and 3° (1.2%), Rash	Flushing (0.6%)
Thiazide and thiazide-like diuretic (INDAPAMIDE)	Headache Dizziness Fatigue, weakness, loss of energy, lethargy, tiredness, or malaise, muscle cramps or spasm, or numbness of the extremities Nervousness, tension, anxiety, irritability, or agitation (≥5%)	Hypokalemia Lightheadedness Drowsiness Vertigo Insomnia Depression Blurred Vision Constipation Nausea Vomiting Diarrhea Gastric irritation Abdominal pain or cramps Anorexia Orthostatic hypotension Premature ventricular contractions Irregular heart beat Palpitations Frequency of urination Nocturia Polyuria Rash Hives Pruritus Vasculitis Impotence or reduced libido Rhinorrhea	-
ACE inhibitor (LISINOPRIL)	Headache (5.7%), Dizziness (5.4%), Cough (3.5%),	Diarrhea (2.7%), Fatigue (2.5%), Upper Respiratory Infection (2.1%), Asthenia (1.3%), Orthostatic Effects (1.2%), Hypotension (1.2%), Vomiting (1.1%), Common	Dyspepsia (0.9%), Paresthesia (0.8%), Decreased Libido (0.4%), Nasal Congestion (0.4%), Influenza (0.3%), Vertigo (0.2%)
Angiotensin-II receptor blocker ((LOSARTAN POTASSIUM)	Upper Respiratory Infection (8%)	Dizziness (3%), Back Pain (2%), Nasal Congestion (2%), Muscle cram (1%), Leg Pain (1%), Sinusitis (1%)	-

Variant Selection

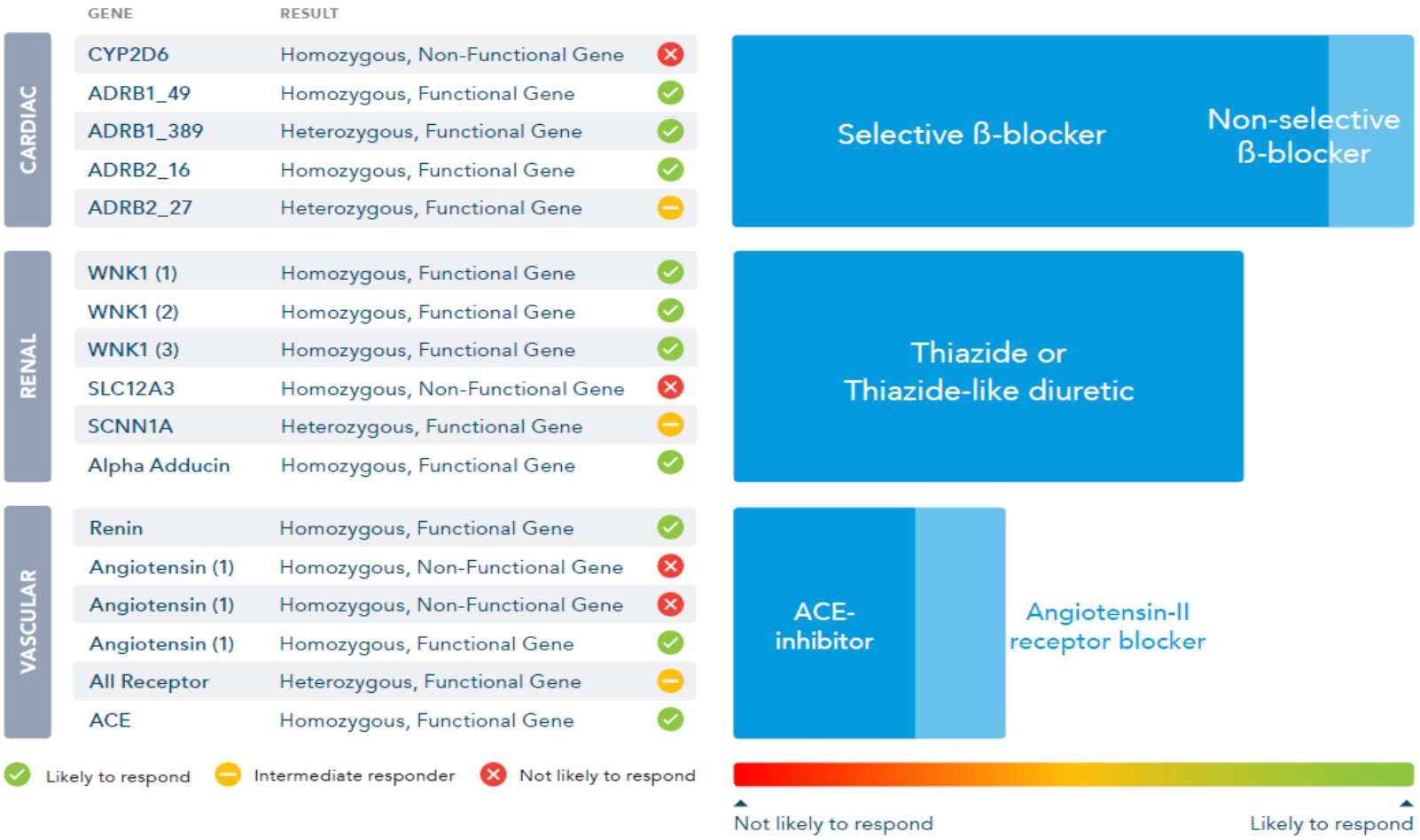


Impact on Therapy with Functional Genetics: Difference b/t functional and non functional genotypes on target drug

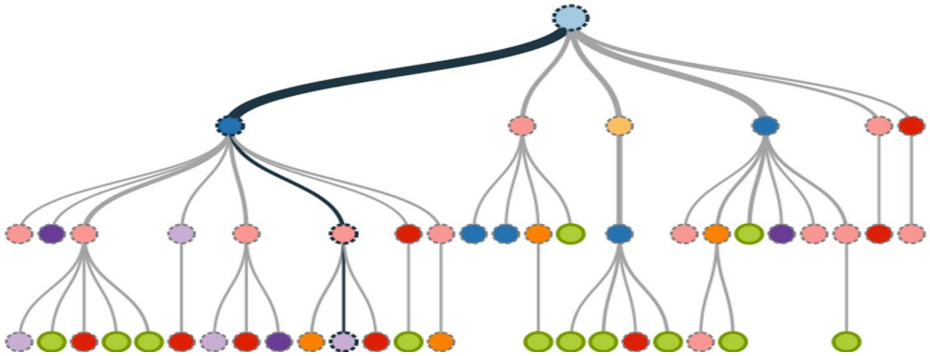


** no appreciable change

Variant Sorting and Weighting



Using AI to build better algorithms



problem – The data is big:

- Complex Genetic profiles
- Interconnected physiology of organ systems
- Multiple drugs / Variable responses
- Multiple gene/gene interactions

Solution – Use AI to solve for complexity:

- Use Random Forest to build multiple algorithms
- Use clinical trial data as training set
- Compete AI's against each other and use tuning to create most predictive

Random Forest Classifier

GCE0187 | initialSystolic: 160 | initialDiastolic: 100 | initialMap: 119.8 | currentSystolic: 134 | currentDiastolic: 94 | curr

Key			
functional	CYP2D6 CT	45	WNK1 (c) CT
intermediate	ADRB1_389 C (homo)	100	SCNN1A CT
non-functional	ADRB1_49 A (homo)	95	WNK1 (b) C (homo)
unknown	ADRB2_27 C (homo)	8	SLC12A3 (2) G (homo)
	ADRB2_16 GA	90	WNK1 (a) G (homo)
			Alpha Adducin G (homo)

Drug Class Outcome	Train Average				AI Pred
	Train Set-P	AI-Pr	PDiff = AI-P - Set-P	WP = PDiff / Set-P	Effective WP - Ineffective WP
Beta Blocker Not Effective	4.62%	2.42%	-2.19%	-47.53%	
Beta Blocker Effective	24.62%	27.46%	2.84%	11.55%	59.08%
Solo VS Combo Eff:-0.19% VS 3.03%	Solo VS Combo HIGH Eff:-0.19% VS 2.75%		Got worse: -1.6%		
Diuretic Not Effective	9.23%	6.53%	-2.7%	-29.23%	
Diuretic Effective	33.85%	37.18%	3.34%	9.86%	39.09%
Solo VS Combo Eff:-4.85% VS 17.42%	Solo VS Combo HIGH Eff:-4.85% VS 13.91%		Got worse: 3.46%		
Ace Inhibitor Not Effective	16.92%	14.83%	-2.1%	-12.4%	
Ace Inhibitor Effective	47.69%	50.73%	3.04%	6.37%	18.76%
Solo VS Combo Eff:14.24% VS 11.88%	Solo VS Combo HIGH Eff:14.24% VS 10.19%		Got worse: 6.37%		
ARB Not Effective	9.23%	8.19%	-1.04%	-11.25%	
ARB Effective	18.46%	19.39%	0.93%	5.03%	16.28%
Solo VS Combo Eff:-4.2% VS -1.02%	Solo VS Combo HIGH Eff:-4.2% VS -1.31%		Got worse: 5.12%		

The Result:

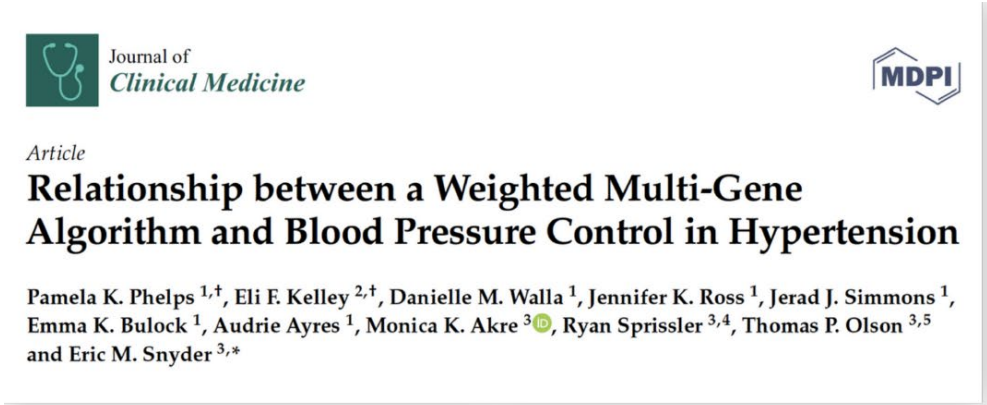
- 110 trees each assigned a random set of 6 genes
- Algorithm generated that produces a confidence score for drug response

Current Clinical Data and Research Studies

Clinical Trials

	1. Geneticure Proof of Concept	2. Fairview pilot RCT	3. Fairview Retro	4. Multicenter Trial
Type	Retrospective	Prospective	Retrospective	Prospective
Design	Chart Review/Genotyped	Random/Controlled/Blinded	Chart Review/Genotyped	Reduced time to control,lower absolute BP, fewer meds, Adherence
Subjects (n=)	100	130	700	Up to 1000
Completed	2015	2017	2018	Recruiting 2020

Publications

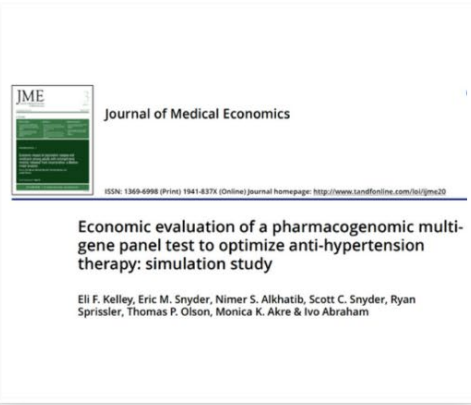

Journal of *Clinical Medicine*

MDPI

Article

Relationship between a Weighted Multi-Gene Algorithm and Blood Pressure Control in Hypertension

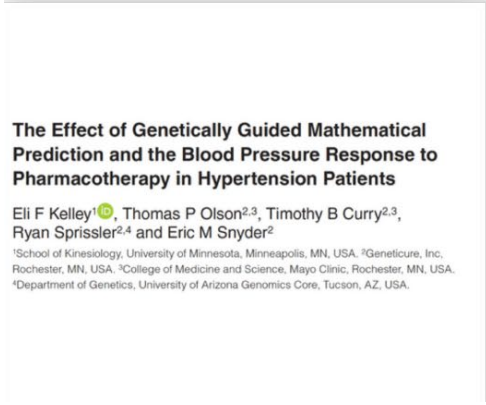
Pamela K. Phelps [1,†], Eli F. Kelley [2,†], Danielle M. Walla [1], Jennifer K. Ross [1], Jerad J. Simmons [1], Emma K. Bulock [1], Audrie Ayres [1], Monica K. Akre [3], Ryan Sprissler [3,4], Thomas P. Olson [3,5] and Eric M. Snyder [3,*]


Journal of Medical Economics

ISSN: 1369-6998 (Print) 1941-837X (Online) Journal homepage: http://www.tandfonline.com/loi/ijme20

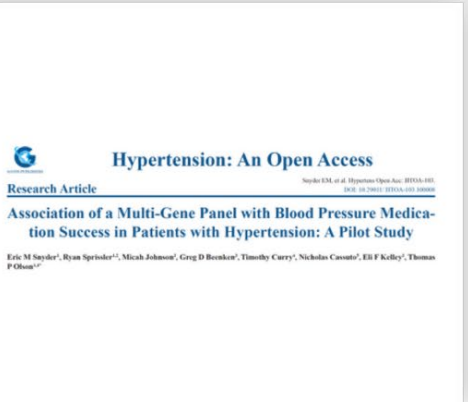
Economic evaluation of a pharmacogenomic multi-gene panel test to optimize anti-hypertension therapy: simulation study

Eli F. Kelley, Eric M. Snyder, Nimer S. Alkhatib, Scott C. Snyder, Ryan Sprissler, Thomas P. Olson, Monica K. Akre & Ivo Abraham


The Effect of Genetically Guided Mathematical Prediction and the Blood Pressure Response to Pharmacotherapy in Hypertension Patients

Eli F Kelley[1], Thomas P Olson[2,3], Timothy B Curry[2,3], Ryan Sprissler[2,4] and Eric M Snyder[2]

[1]School of Kinesiology, University of Minnesota, Minneapolis, MN, USA. [2]Geneticure, Inc, Rochester, MN, USA. [3]College of Medicine and Science, Mayo Clinic, Rochester, MN, USA. [4]Department of Genetics, University of Arizona Genomics Core, Tucson, AZ, USA.


Hypertension: An Open Access

Research Article

Association of a Multi-Gene Panel with Blood Pressure Medication Success in Patients with Hypertension: A Pilot Study

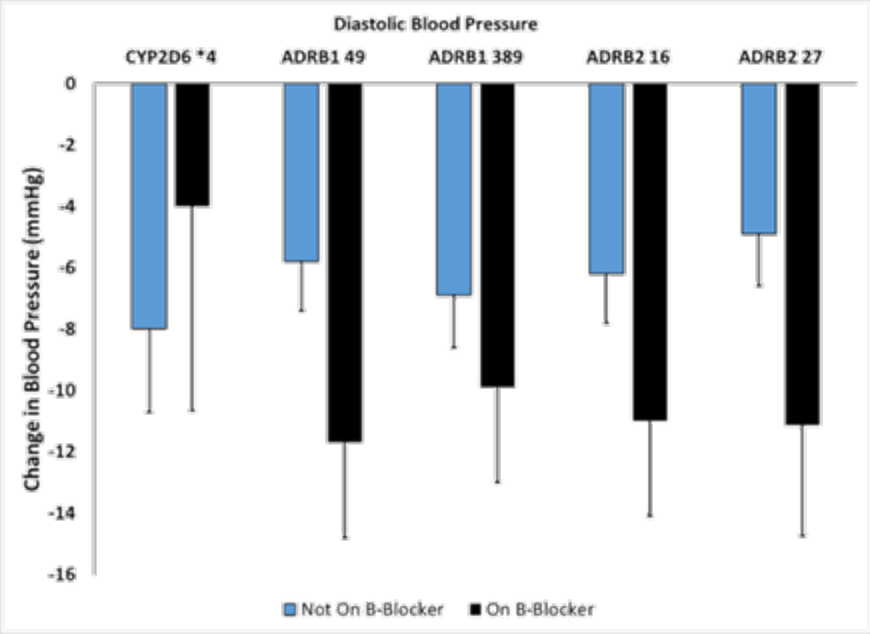

The importance and challenges of developing a pharmacogenetics test for hypertension

Eric M Snyder[1], Eli F Kelley[2], Ryan Sprissler[1,3] & Thomas P Olson*[,1,4]

[1]Geneticure, Inc., Rochester, MN 55902, USA
[2]School of Kinesiology, University of Minnesota, Minneapolis, MN 55455, USA
[3]University of Arizona Genomics Core, Tucson, Arizona, AZ 85721 USA
[4]Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, MN 55905, USA
*Author for correspondence: olson.thomas2@mayo.edu

Retro study #1 – testing the genotypes

Change in Diastolic Blood Pressure in Patients with Functional Genotypes who are on a B-Blocker vs. Patients Who are Not on a B-Blocker



*Avg On B-blocker: ~11.6mmHg

*Avg Not On B-blocker: ~6.5mmHg

= 40% Reduction in Stroke
= 26% Reduction CV Death

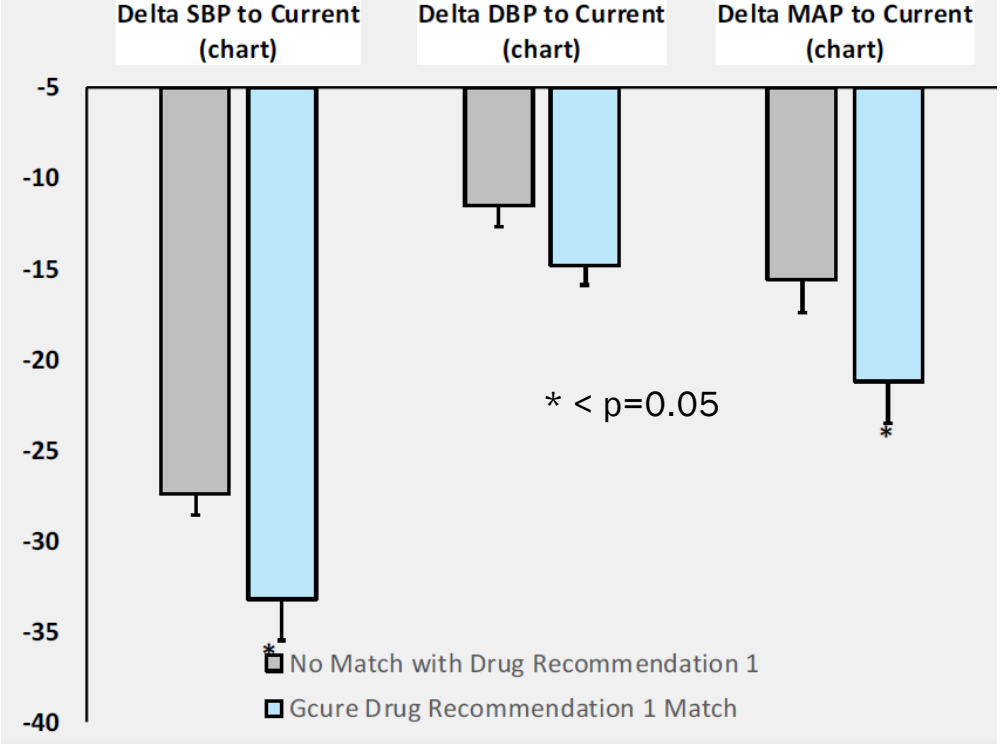
Pilot RCT trial – Inferiority study

- Both arms achieved > 90% control rates at 6 months
- Geneticure arm used slightly few meds to gain control
- SOC arm had many more serious adverse events (SAE)
    - ~70% of SAE occurred in SOC arm
    - Most were due to diuretic side effects

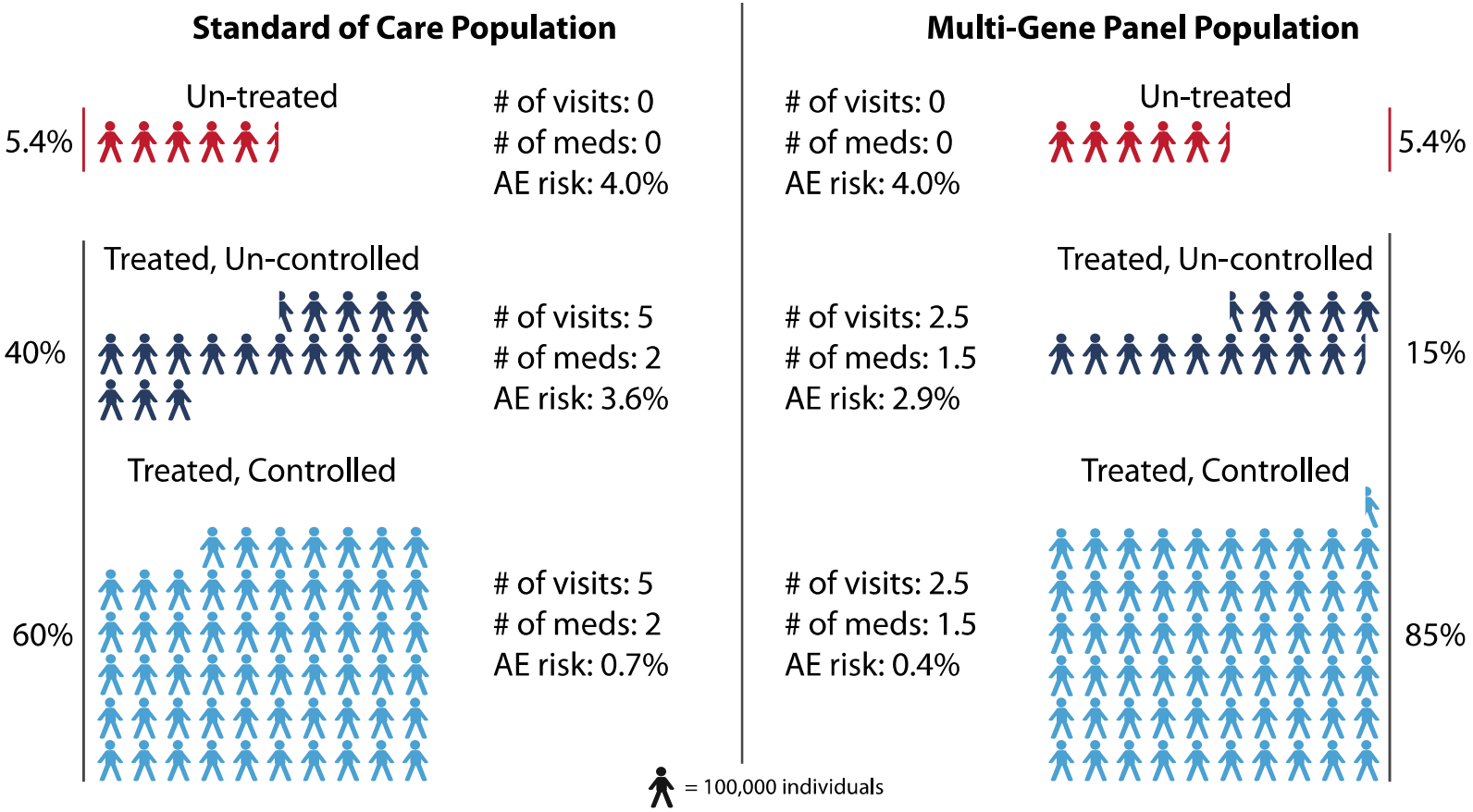
Retro Study #2 – testing the algorithm

Difference in BP from diagnosis to current 1-yr avg if patient is on the FIRST drug recommended by the Geneticure algorithm vs. not

- **Avg SBP: 5.8mmHg (21% lower)**
- **Avg DBP: 3.3mmHg (29% lower)**
- **Avg MAP: 5.6mmHg (36% lower)**



Simulation Population and Assumptions



[1]Gu Q, Burt VL, Dillon CF, et al. Circulation 2012;126:2105-2114.

[2]Johnson MW, Sprissler R, Olson T, et al. FASEBJ, 2016.

Health Economics Results

Standard of Care Population

Un-treated
total = $7,970,400,000
5.4%
$14,760/

Treated, Un-controlled
total = $55,800,756,000
40%
$15,813/

Treated, Controlled
total = $19,425,769,440
60%
$3,778/

Direct Cost Elements by Treatment Population

Categories

- Genetic Testing
- Medications
- Adverse Events
- Evaluation and Management

Volume Scale

=$10 billion

Aggregated Savings	
Un-treated	---
Treated, Un-controlled	$40,950,637,200
Treated, Controlled	$1,362,099,016

Values are over a 3-year period.

Multi-Gene Panel Population

Un-treated
total = $7,970,400,000
$14,760/
5.4%

Treated, Un-controlled
total = $17,230,491,300
$13,309/
15%

Treated, Controlled
total = $17,884,100,674
$2,502/
85%

Thanks for listening