



FDA Webinar: Precision Medicine and Minority Health

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April 23, 2019

THE PRECISION MEDICINE INITIATIVE



Biomarkers



- Predictive
- Diagnostics
- Prognostics
- Risk

Biomarkers, including Genomic Variants, are a Key Component to Precision Medicine

Sample



DNA



Genetic Test Results

Risk

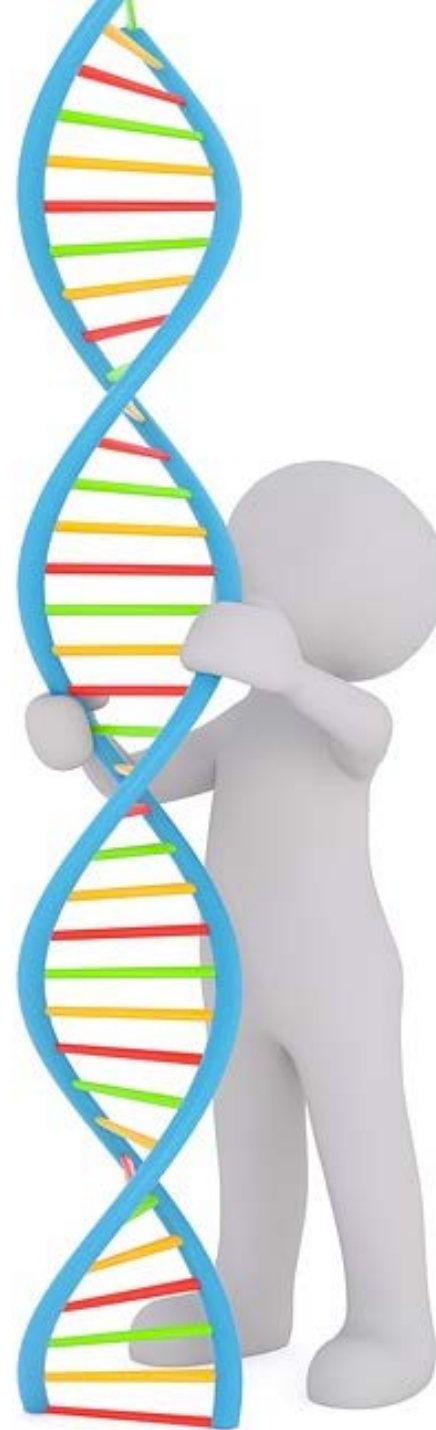
Diagnosis

Prognosis

Predict
Treatment

Monitor Disease

Precision Healthcare



Patient Report

Molecular
Findings

Causative
Agent

Stochastic
Modeling

Therapeutic
Prospects

Disease
Treatment/
Management

Tempered Excitement for Precision Medicine

Published in final edited form as:

Per Med. 2012 November ; 9(8): 839–847. doi:10.2217/PME.12.100.

precision

Why ~~personalized~~ medicine will fail if we stay the course

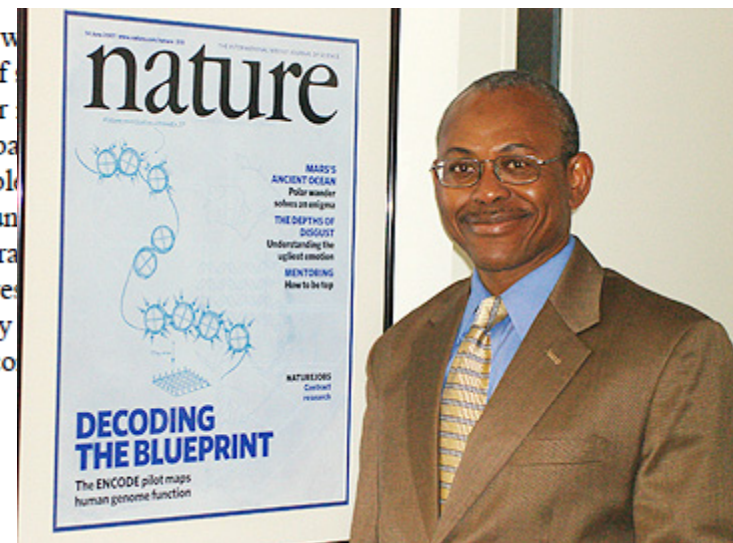
Edward Ramos^{*†,1}, Shawneequa L Callier^{‡,2}, and Charles N Rotimi¹

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Abstract

Genomic science and associated technologies are providing scientists and clinicians with insights that are transforming the delivery of healthcare and the overall well-being of patients. However, these insights inform us that historical population sampling approaches for rare and common genetic variations are not representative of the complex ancestral backgrounds of today's patients. In order for personalized medicine to be meaningful and applicable to all global populations, we will need to know how common and rare genetic variants found in different parts of the world influence health and drug response. This article demonstrates the importance of increasing ethnic and racial diversity among participants in genomic research. It highlights areas of opportunity for improving our understanding of genomic diversity in diverse populations, and provides examples of successful models that help to resolve these complex



Executive summary

Promise of personalized medicine

- Traditional medical practice involving family history and lifestyle data will be enhanced with the use of genomic technology.
- Genetic testing and screening technologies aim to make prevention, diagnosis and treatment strategies more efficient and effective.
- The current genetic profiling of diseases, tumors and individuals has led to ground-breaking drug therapy and treatment strategies.

Genomic diversity of individuals

- We live in a multiethnic society with a growing number of admixed populations.
- Although patients may identify with one or two ethnicities, genetic data often tells a complex story about their genetic ancestry.
- All individuals, regardless of ethnicity, may carry genetic variations that correspond with rare alleles found in understudied populations.

Maximizing the relevancy of genomic research

- Historically, genetic association studies have focused narrowly on segments of European populations, leading to outcomes that only serve a portion of the global population.
- Translation of population-level data may include nuances that are overgeneralized in a clinical setting.
- Failure to research genetically diverse populations as we prepare for the era of personalized medicine could lead to disparate applications of genomic technology among all populations.

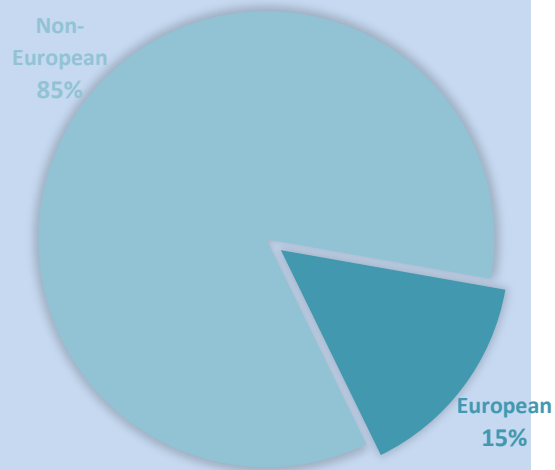
Genomic research models for the future

- Small collaborative projects are providing excellent examples of research occurring among genomically diverse groups.
- Cohorts of individuals from non-European ancestry populations are providing novel insights into genotype–phenotype associations.
- Genomic science and medicine will benefit greatly from the inclusion of multiple global populations.

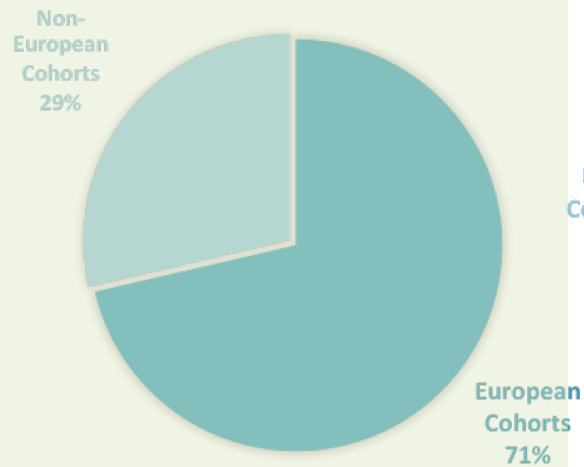
Insufficient Evidence of Generalizability

Genetics and Genomics Research: A View from Databases

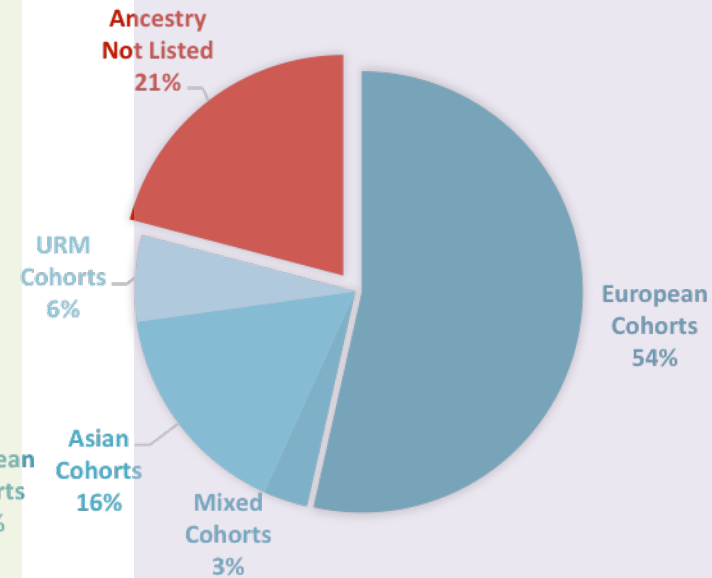
CURRENT WORLD POPULATION



GENOMICS RESEARCH COHORTS ACROSS DATABASES*



GENOMICS RESEARCH COHORTS ACROSS DATABASES*



Landry, L, Ali, N., Williams, D., Rehm, H., Bonham, V. (2018). Lack of ancestral diversity in genomic databases – a barrier to clinical translation in precision medicine. Health Aff (Millwood), 37(5):780-785.

Genetic Research Translates into Clinical Biomarkers



FDA/NIH Leadership Council Biomarker Program

Lack of Genetic Research in Minorities

POSSIBLE IMPACT ON BIOMARKERS

Missed Biomarkers

Predictive error for PGx

? Safety/ efficacy of Therapies

Conflicting Evidence of Risk

Missed/Inconclusive Diagnosis/ Prognosis

Confounding, effect modification, spurious associations

What Research Is Showing Us





Clinical Utility

Access

Personal Utility

Clinical Utility

Evaluation of Genetic Tests

Figure 1.
ACCE Evaluation Process for Genetic Testing



Source: Office of Public Health Genomics at Centers for Disease Control and Prevention, 2004. Used with permission.

Challenge Question:

Is the clinical utility of a genetic test the same for all individuals?

The Medseq Case Study:

Review of a Clinical Research Genome Report for
an African American participant

Pharmacogenomic Predictions

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http://pcpgm.partners.org/lmm



CENTER FOR PERSONALIZED
GENETIC MEDICINE



Name: **John Doe**
DOB: **01/23/45**
Sex: **Male**
Race: **Caucasian**

Accession ID: **0123456789**
Specimen: **Blood, Peripheral**
Received: **01/23/45**

Family #: **F12345**
Referring physician: **John Smith, M.D.**
Referring facility: **Double Helix Hospital**

GENERAL GENOME REPORT

RESULT SUMMARY

A. MONOGENIC DISEASE RISK: 2 VARIANTS IDENTIFIED

This test identified 2 genetic variant(s) that may be responsible for existing disease or the development of disease in this individual's lifetime.

Disease (Inheritance)	Phenotype	Gene Variant	Classification
A1. Episodic ataxia type II (Autosomal Dominant)	Poor coordination and balance	CACNA1A p.Arg2156GlyfsX32	Pathogenic
A2. Hypertrophic cardiomyopathy (Autosomal Dominant)	Progressive heart failure	MYBPC3 p.Thr146AsnfsX7	Pathogenic

B. CARRIER RISK: 3 VARIANTS IDENTIFIED

This test identified carrier status for 3 autosomal recessive disorder(s).

Disease	Phenotype	Gene Variant	Classification	Carrier Phenotype*
B1. Cystic fibrosis	Chronic lung and digestive disease	CFTR c.1585-1G>A	Pathogenic	Infertility (moderate evidence)
B2. Myotonia congenita	Muscle disease	CLCN1 p.Arg894X	Pathogenic	Latent myotonia (case report only)
B3. Usher syndrome type II	Hearing loss and retinitis pigmentosa	USH2A p.Gly204ArgfsX12	Pathogenic	None reported

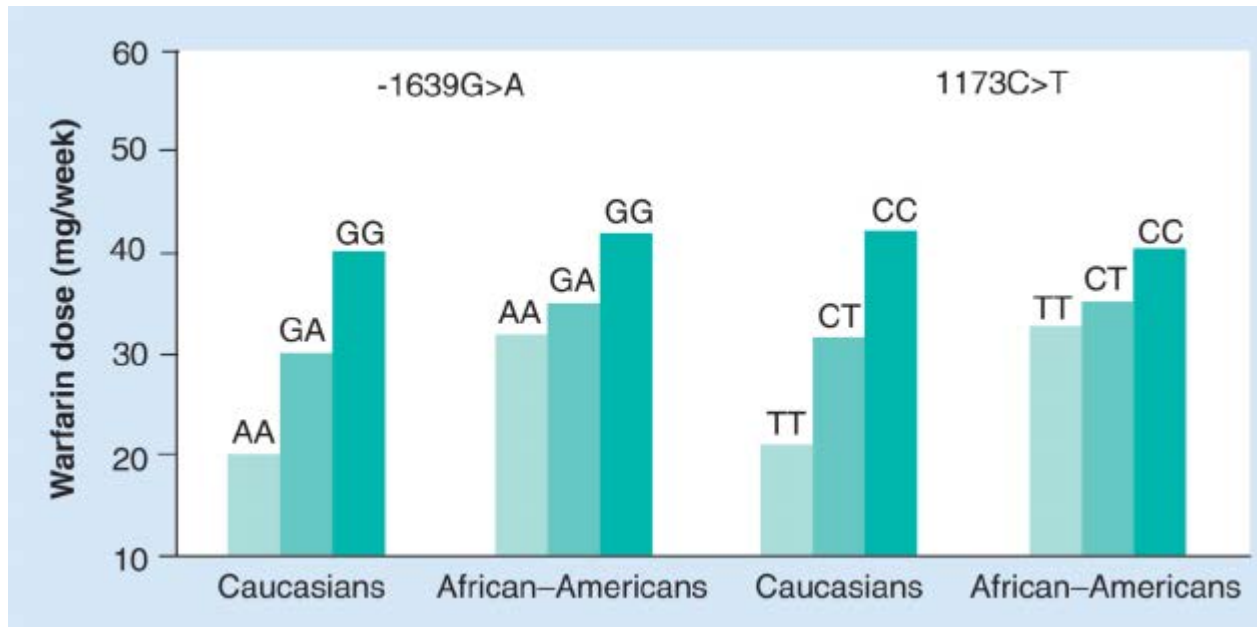
As a carrier for recessive genetic variants, this individual is at higher risk for having a child with one or more of these highly penetrant disorders. To determine the risk for this individual's children to be affected, the partner of this individual would also need to be tested for these variants. Other biologically related family members may also be carriers of these variants.*Carriers for some recessive disorders may be at risk for certain mild phenotypes. Please see variant descriptions for more information.

C. PHARMACOGENOMIC ASSOCIATIONS

This test identified the following variants associated with drug use and dosing. Additional pharmacogenomic results may be requested, but will require additional molecular confirmation prior to disclosure.

Drug	Risk and Dosing Information
C1. Warfarin	Decreased dose requirement.
C2. Clopidogrel	Typical risk of bleeding and cardiovascular events.

Warfarin Pharmacogenomic Dosing



Our African American Participant

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http://pcpgm.partners.org/imm



CENTER FOR PERSONALIZED
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Drug	Risks and Dosing Information
C1. Warfarin	Decreased dose requirement.
C2. Clopidogrel	Typical risk of bleeding and cardiovascular events.

Drug (Indication)	Summary	Variants Evaluated and Genotypes Identified	Interpretation	References (PMID)
C1. Warfarin (Anti-coagulation)	Decreased dose requirement	CYP2C9 rs1799853 rs1057916 rs28371686 rs9332131 rs7900194 rs28371685 Genotype: *5/*5 VKORC1 rs9923231 Genotype: AA	Patients with the CYP2C9 *5/*5 genotype may require a lower dose of warfarin as compared to patients with other CYP2C9 genotypes. Patients with the VKORC1 AA may require a lower dose of warfarin as compared to patients with the VKORC1 GG genotype. Patients with the combination of CYP2C9 *5/*5 genotype with the VKORC1 A/A genotype are expected to require a lower dose of Warfarin. Refer to warfarindosing.org for dosing based on genotype and other factors*. <small>Note: Warfarindosing.org does not provide predictions for *8 and *11.</small>	Johnson,2011 Perera,2013 Niinuma,2011 Johnson, 2015

4 variants associated with warfarin dosing in AA not included in dosing algorithm from Advisory Body

Johnson, J.A., Cavallari, H.H.(2015). "Warfarin Pharmacogenomics". Trends in Cardiovascular Medicine. 25. 33-41.

Cardio-Metabolic Risk

Our Existing Report

CARDIAC RISK SUPPLEMENT

RESULTS

A. POLYGENIC PREDICTED FASTING LIPID PROFILE

The following lipid profile is predicted by known genetic factors, age, and gender and is not reflective of environmental, medication or other factors. These values are based on large epidemiologic studies and are not intended to substitute for measured values.

- LDL 118 mg/dL
- HDL 47 mg/dL
- Triglycerides 140 mg/dL

B. ALLELES CONFERRING SMALL-MODERATE RISK MODIFICATION FOR 8 CARDIOVASCULAR PHENOTYPES

Phenotype	Contextual Data		Patient Results			
	Population Prevalence of Phenotype for Age 54	Proportion of Variation in Phenotype Liability Explained by Common Genetic Variants	Number of Risk Loci Evaluated	Number of Total Risk Alleles Identified*	Polygenic Relative Risk**	Percentile Rank of Relative Risk**
Abdominal aortic aneurysm	1%	Unknown	3	2/8	0.9	20-30 th %ile
Atrial fibrillation	<1%	10%	11	6/22	0.8	10-20 th %ile
Coronary heart disease	8% (Age 40-59)	<10%	80	57/120	1.4	80-70 th %ile
Type 2 Diabetes	13% (Age 45-64)	5-10%	70	69/140	1.4	80-70 th %ile
Hypertension	38%	<10%	3	1/8	1.3	70-80 th %ile
Obesity	37% (Age 40-59)	1-2%	7	6/14	1.0	50-80 th %ile
Platelet aggregation	Unknown	5-10%	4	0/8	≤0.6	0-10 th %ile
QT prolongation	Unknown	7%	3	5/8	1.0	40-50 th %ile

*# of total possible risk alleles = # risk loci x 2 alleles per loci.

** As data utilized in this analysis were derived from non-longitudinal association studies, "Relative Risk from Common Genetic Variation" pertains to near-term risk of developing a phenotype (e.g. approximately 5 year risk), not lifetime risk. "Relative Risk from Common Genetic Variation" and "Percentile Rank of Relative Risk from Common Genetic Variation" values have been estimated using the 1000 Genomes European cohort.

METHODOLOGY

Genomic sequencing is performed using next generation sequencing on the Illumina HiSeq platform. Genomes are sequenced to at least 30X mean coverage and a minimum of 95% of bases are sequenced to at least 8X coverage. Paired-end 100bp reads are aligned to the NCBI reference sequence (GRCh37) using the Burrows-Wheeler Aligner (BWA), and variant calls are made using the Genomic Analysis Tool Kit. Risk alleles identified at 161 loci involved in cardiac disease are determined and odds ratios are combined to provide overall assessment of risk for broad phenotypes. The technical component of this test as developed and its performance characteristics determined by the Illumina CLIA Lab (San Diego, CA CLIA# 05D1092911) and the interpretive algorithms and clinical reports were generated by the Laboratory for Molecular Medicine at the Partners Healthcare Center for Personalized Genetic Medicine (LMM, 65 Landsdowne St. Cambridge, MA 02139; 617-768-8500; CLIA#22D1005307). This test has not been cleared or approved by the U.S Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

LIMITATIONS

It should be noted that the polygenic predicted values for lipid levels are based on large epidemiologic studies and may not apply to each individual patient (model from N. Stitzel and S. Sunyaev, personal communication). The summary risk assessments above, for small-moderate effect alleles, are based on combining individual risk allele data in ways that may not always apply to each individual patient.

Our African American Participant

RESULTS

A. POLYGENIC PREDICTED FASTING LIPID PROFILE

Lipid Profile predictions cannot currently be calculated for non-Caucasian individuals due to the lack of available population data from non-Caucasian populations for training predictive algorithms.

B. ALLELES CONFERRING SMALL-MODERATE RISK MODIFICATION FOR 8 CARDIOVASCULAR PHENOTYPES

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1

METHODOLOGY

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LIMITATIONS

The summary risk assessments above, for small-moderate effect alleles, are based on combining individual risk allele data in ways that may not always apply to each individual patient. Furthermore, the cardiac risk assessments are largely based on data from cohorts of European ancestry (Kong *et al*, 2015) and are less likely to apply to individuals from other populations.

2

The evidence-based genomic test and clinical report designed from predominantly European populations were not generalizable.

Do you see the same bias in clinical practice?

Brief Report

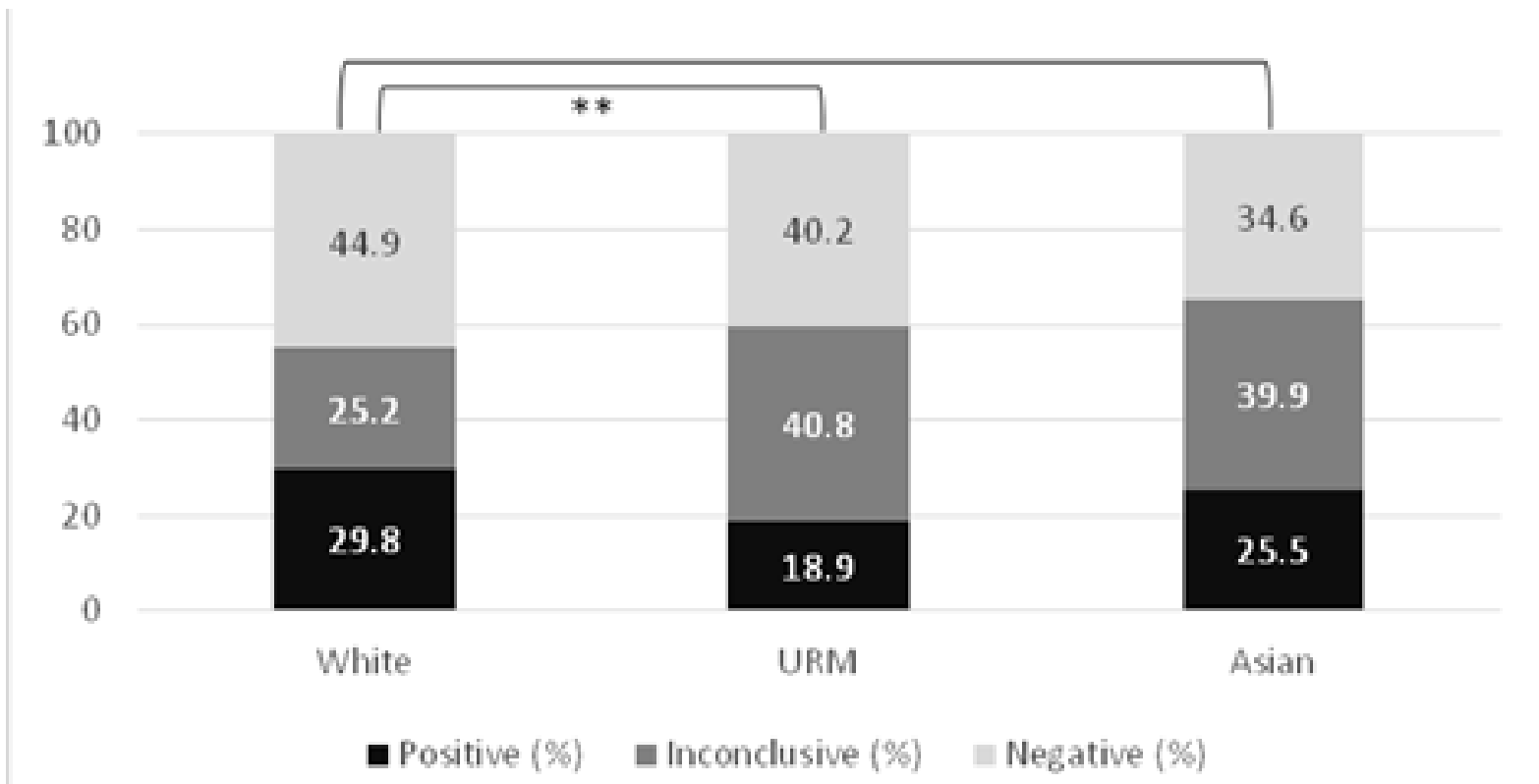
April 2018

Association of Racial/Ethnic Categories With the Ability of Genetic Tests to Detect a Cause of Cardiomyopathy

Latrice G. Landry, PhD^{1,2,3,4}; Heidi L. Rehm, PhD^{2,3,4,5}

> Author Affiliations

JAMA Cardiol. 2018;3(4):341-345. doi:10.1001/jamacardio.2017.5333



Underrepresented Minorities have a Lower Detection Rate for both Cardiomyopathy compared to their White Counterparts and a higher rate of inconclusive results.

Challenge Question:

Is the clinical utility of a genetic test the same for all individuals?

We have demonstrated there are differences in clinical utility of genetic testing by population group.

Access

Challenge Question:

True or False:

There are no differences in access to genetic testing by population group.

Genetic Testing Models

Direct To Consumer

Physician Mediated

Genetic Testing Models

Direct To Consumer

Costs \$-\$\$

Widely Available

Internet Access

Non-Invasive

Physician Mediated

Cost \$-\$\$\$\$\$

Limited Availability

Dependent on Care
System/Payer

Minimally Invasive- Invasive

Genetic Testing Models

Direct To Consumer

Physician Mediated

National Use of Genetic Testing

Differential use of available genetic tests among primary care physicians in the United States: results of a national survey

Alexandra E. Shields, PhD^{1,2,3}, Wylie Burke, MD, PhD⁴, and Douglas E. Levy, PhD^{1,2,3}

Purpose: This study assesses primary care physicians' experience ordering and referring patients for genetic testing, and whether minority-serving physicians are less likely than those serving fewer minorities to offer such services. **Methods:** Survey of a random sample of 2000 primary care physicians in the United States ($n = 1120$, 62.3% response rate based on eligible respondents) conducted in 2002 to assess what proportion have (1) ever ordered a genetic test in general or for select conditions; (2) ever referred a patient for genetic testing to a genetics center or counselor, a specialist, a clinical research trial, or to any site of care. **Results:** Nationally, 60% of primary care physicians have ordered a genetic test and 74% have referred a patient for genetic testing. Approximately 62% of physicians have referred a patient for genetic testing to a genetics center/counselor or to a specialist, and 17% to a clinical trial. Minority-serving physicians were significantly less likely to have ever ordered a genetic test for breast cancer, colorectal cancer, or Huntington disease, or to have ever referred a patient for genetic testing relative to those serving fewer minorities. **Conclusions:** Reduced utilization of genetic tests/referrals among minority-serving physicians emphasizes the importance of tracking the diffusion of genomic medicine and assessing the potential impact on health disparities. *Genet Med* 2008;10(6):404–414.

Key Words: physicians, genomics, genetic screening, clinical integration, new technologies

Table 2

Experience ordering or referring patients for genetic testing among physicians serving minority of other vulnerable patient populations

	High proportion minority		High proportion Medicaid		High proportion with primary language other than English		High proportion uninsured		Total (%)
	Top quintile (%)	Lower quintiles (%)	Top quintile (%)	Lower quintiles (%)	Top quintile (%)	Lower quintiles (%)	Top quintile (%)	Lower quintiles (%)	
	<i>n</i> (<i>P</i> value)		<i>n</i> (<i>P</i> value)		<i>n</i> (<i>P</i> value)		<i>n</i> (<i>P</i> value)		
Experience ordering genetic tests									
Breast cancer	18.1	28.5	23.9	27.9	23.9	27.5	24.1	28.1	26.9
	1058 (0.01)		1052 (0.32)		1065 (0.35)		1056 (0.27)		
Colon cancer	10.9	17.7	18.1	16.6	17.9	16.3	18.8	16.3	16.6
	1057 (0.05)		1052 (0.66)		1063 (0.63)		1055 (0.40)		
Sickle cell anemia	35.0	37.1	28.8	38.0	38.8	36.4	33.4	37.1	36.8
	1056 (0.63)		1052 (0.03)		1062 (0.56)		1055 (0.35)		
Huntington disease	5.67	18.0	13.5	16.6	13.6	17.0	13.0	6.8	16.5
	1053 (<0.001)		1048 (0.35)		1059 (0.28)		1052 (0.20)		
Any genetic test	54.0	60.5	51.9	60.7	57.0	59.8	57.2	59.8	59.6
	1065 (0.14)		1059 (0.05)		1022 (0.50)		1063 (0.51)		
Experience referring patients for genetic testing									
Genetics center or counselor	51.7	63.6	46.2	64.5	58.0	62.5	53.9	63.4	61.8
	1063 (<0.001)		1057 (<0.001)		1070 (0.28)		1061 (0.02)		
Specialist for patients' condition	51.5	64.1	50.6	64.1	56.2	63.4	58.1	63.1	62.3
	1057 (0.004)		1053 (0.002)		1064 (0.08)		1056 (0.21)		
Clinical trial	10.2	17.7	13.3	17.3	15.8	16.9	16.3	17.0	16.7
	1050 (0.03)		1045 (0.23)		1057 (0.74)		1049 (0.82)		
Any site of care	62.5	76.0	59.4	76.7	69.0	75.1	68.4	75.3	74.1
	1065 (<0.001)		1059 (<0.001)		1072 (0.11)		1063 (0.05)		

All percentages account for sample weighting.

	OR (95% CI)				
	Ever referred to genetics center or counselor (N = 943)	Ever referred to specialist (N = 941)	Ever referred to a clinical trial (N = 934)	Ever referred to any site of care (N = 945)	Ever ordered or ever referred (N = 945)
Received training in clinical genetics in CME	1.53 (1.11–2.10) ^b	2.31 (1.70–3.12) ^c	2.36 (1.58–3.53) ^c	2.21 (1.56–3.13) ^c	2.41 (1.61–3.60) ^c
Accurate knowledge of current legal protections	2.45 (1.31–4.58) ^b	1.94 (1.10–3.41) ^a	2.20 (1.30–3.72) ^b	6.13 (2.21–16.99) ^c	9.75 (2.32–40.97) ^b
Confident interpreting genetic test results	0.89 (0.41–1.90)	0.64 (0.29–1.43)	0.85 (0.36–2.00)	1.12 (0.44–2.84)	0.72 (0.24–2.13)
Feels prepared to counsel patients considering a genetic test	1.31 (0.58–2.93)	2.39 (0.98–5.84)	1.50 (0.65–3.47)	2.43 (0.76–7.74)	2.41 (0.59–9.77)
Early adopter of new diagnostic tests	1.51 (0.97–2.33)	1.20 (0.77–1.87)	1.18 (0.70–1.98)	1.27 (0.76–2.13)	2.66 (1.34–5.25) ^b
Optimistic that genetics will improve treatment	1.08 (0.67–1.73)	1.11 (0.70–1.76)	0.78 (0.41–1.48)	0.99 (0.59–1.65)	0.88 (0.50–1.53)

Also included in model but not shown: practice setting (independent practice versus those practicing in a health maintenance organization, hospital-based practice, community health center, or other setting).

Only those respondents for whom there were complete data were included in each regression analysis, with available cases for individual regressions ranging from 934 (83% of full sample) to 945 (84% of full sample) respondents.

^a $P < 0.05$.

^b $P < 0.01$.

^c $P < 0.001$.

Challenge Question:

True or **False**:

There are no differences in access to genetic testing by population group.

Personal Utility

Challenge Question:

The personal utility of genetic testing for minorities compared with non-minorities is_____?

- A. The Same
- B. Different
- C. It Depends

Journal of Community Genetics

J Community Genet (2017) 8:293–301
DOI 10.1007/s12687-017-0325-5



ORIGINAL ARTICLE

Racial minority group interest in direct-to-consumer genetic testing: findings from the PGen study

Latrice Landry^{1,2,3} · Daiva Elena Nielsen^{4,2,5} · Deanna Alexis Carere⁶ ·
J. Scott Roberts⁷ · Robert C. Green^{4,2,5,3,8} · the PGen Study Group

Interest in Health and PGx related biomarkers

Survey item	Race			Test	
	White	Black	Asian	χ^2	Adjusted ^b
Interest in types of information	<i>n (%)</i>			<i>p</i> value	<i>p</i> value
<u>Desire to learn more about my genetics because I have limited information about my family health history^d</u> (<i>n</i> = 1323)				0.006	0.005
Not at all important	282 (22.9)	4 (9.3)	10 (20.0)		
Somewhat important	487 (39.6)	17 (39.5)	11 (22.0)		
Very important	461 (37.5)	22 (51.2)	29 (58.0) ^f		
<u>Interest in finding out about my individual response to different types of medications</u> (<i>n</i> = 1485)				0.078	0.278
Not at all important	320 (23.1)	16 (36.4)	10 (18.5)		
Somewhat important	516 (37.2)	19 (43.2)	21 (38.9)		
Very important	551 (39.7)	9 (20.5)	23 (42.6)		
<u>Interest in finding out about my personal risk for specific diseases (<i>n</i> = 1486)</u>				0.012 ^e	0.0687
Not at all important	104 (7.5)	7 (15.9)	3 (5.6)		
Somewhat important	435 (31.3)	19 (43.2)	11 (20.4)		
Very important	849 (61.2)	18 (40.9)	40 (74.1)		

Traits and Ancestry related biomarkers

Survey item	Race			Test	
	White	Black	Asian	χ^2	Adjusted ^b
Interest in types of information	<i>n</i> (%)			<i>p</i> value	<i>p</i> value
<u>Ancestry (<i>n</i> = 1487)</u>				0.001 ^e	0.191
Not at all interested	59 (4.3)	1 (2.3)	3 (5.6)		
Somewhat interested	325 (23.4)	1 (2.3)	16 (29.6)		
Very interested	1005 (72.3)	42 (95.4)	35 (64.8)		
<u>Traits (<i>n</i> = 977)^c</u>				0.0001	0.0006
Not at all interested	18 (2.0)	1 (2.7)	4 (13.3) ^f		
Somewhat interested	248 (27.3)	2 (5.4)	4 (13.3)		
Very interested	644 (70.8)	34 (91.9) ^e	22 (73.3)		

MedSeq Extension Participant Characteristics

Characteristic	N=10
Age, mean years (range)	51 (34 – 63)
Gender	
Male	3
Female	7
Race/Ethnicity	
Hispanic African-American	1
Non-Hispanic African-American	9
Education level	
Did not graduate from college	5
College graduate or higher	5
Annual household income	
<\$100,000	5
≥\$100,000	5

Utilization: Personal Utility

INTERVIEWER: Can you tell me a little bit about making the decision to be part of the study?

SUBJECT (E05-P14): I got the letter, and... when I read about the study and that they were looking for more African heritage participants it didn't really take me long to decide that I wanted to do it. I evaluated that the risk was low and the benefit to our research community and medical field was worth it to me.

INTERVIEWER: Okay. Can you tell me about your decision to be part of this study?

SUBJECT (E07-P14): I think I was told that less minority or no minority was in there and my primary care physician identified me so I felt even if it didn't help me, at least it will help other minorities.

INTERVIEWER: Can you tell me about making the decision to be part of this study?

SUBJECT (E09-P14): Actually, it is the doing my part as far as helping African-Americans. That was my main push to do it.

Challenge Question:

The Personal Utility of Genetic Testing for minorities compared with non-minorities is____?

A. The Same

B. Different

C. It Depends

START

Understanding the Gaps

Building Solutions

Translational Toolbox

Clinical

Computational

Policy

Foundation for Precision Medicine



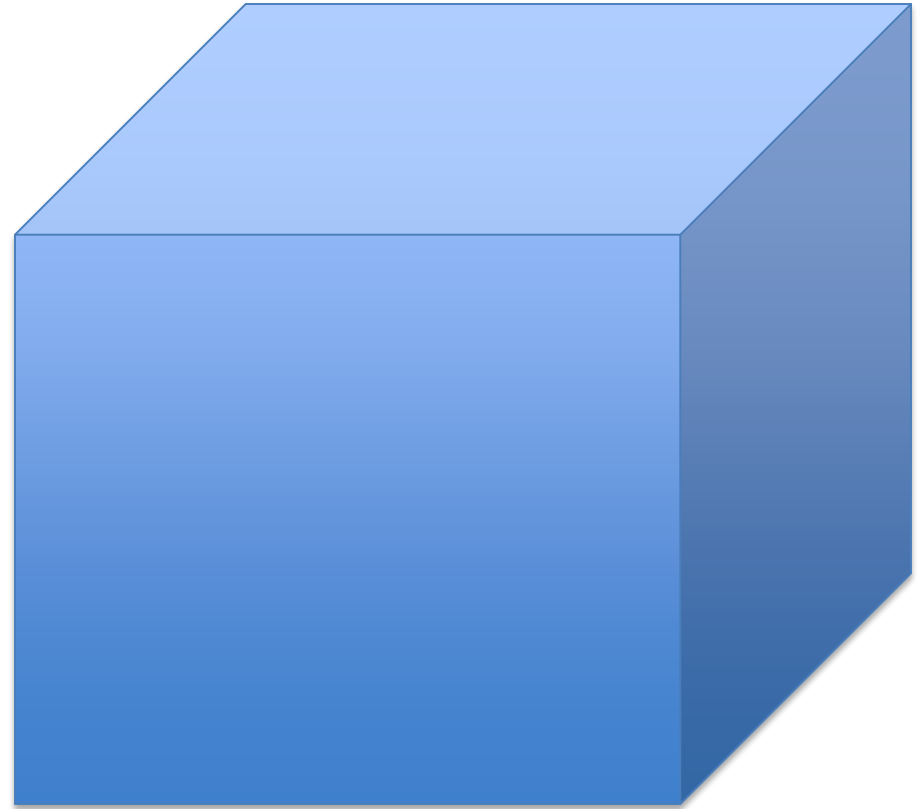
The Toolbox for Targeting Disparities in Genomic Medicine

Collaboration

Academia

Government

Industry



Collaboration

Academia

Government

Industry

Increasing Diversity in
Research

Policies around Inclusion

Enhance Funding for Technology
Development and Data Science

Analyze Disparities in Genomic
Medicine

Increasing Access to
Precision Services

Increasing Education

Building Infrastructure

Many individuals in populations disproportionately burdened by disease are looking for answers.

To the extent that our research provides those answers **it is our duty to ensure clinical translation is equitable.**



Acknowledgements

FDA

NHGRI

Partner's Personalized Medicine

CAMD at BWH

Harvard Medical School

Genomes 2 People

Pgen Study Group

Center for Global Cancer Prevention at Harvard
School of Public Health

Tim Rebbeck

Nadya Ali

Heidi Rehm

Vence Bonham

David Williams

Robert Green

Daiva Nielsen

Alexis Carrere

J.Scott Roberts