Will Precision Medicine Improve Population Health? (Yes, If…)

Muin J. Khoury, MD, PhD

March 16, 2018

Office of Public Health Genomics
Centers for Disease Control and Prevention

Outline: 4 Themes

- **Biological and Social Determinants of Disease Require Both Medical and Public Health Interventions**
- As Medicine Becomes More Precise (or Personalized), We Need Public Health to Ensure Its Population Health Benefits
- There is an Important Role for Public Health Sciences to Develop and Implement New Knowledge
- The Era of "Precision Public Health" is Upon Us!

Will Precision Medicine Improve Population Health?

Announcement of the precision medicine initiative has led to a variety of responses, ranging from enthusiastic expectations[1] to explicit skepticism,[2] about potential health benefits, limitations, and return on investment. This Viewpoint discusses whether precision medicine is unlikely or likely to improve population health, aiming to forge a consensus that bridges disparate perspectives on the issue. The potential of precision medicine to improve the health of individuals or small groups of individuals is not addressed here because it involves a different question with different metrics.

Precision Medicine Is Unlikely to Improve Population Health

There are 3 fundamental reasons why precision medicine might not improve the health of populations. First, disease pathogenesis, especially for common noncommunicable diseases, is extraordinarily complex. Abundant evidence has demonstrated this for the association between the multiplicity of specific genes and conditions, including obesity, hypertension, or certain cancers. Additionally, it is known that genetic associations have, in most instances, small effect sizes in contrast with more robust contributions of behavioral and social factors.

First, the United States faces extraordinary challenges to the health of its population. Over the past 30 years, the United States has fallen behind other high-income peer nations in health attainment on many metrics, including life expectancy and infant mortality, and there are persistent gaps in health outcomes by income and race/ethnicity.[4] The solution to these challenges is probably not an increased focus on the individual, but rather involves focusing on the social, economic, and structural drivers of population health that are ubiquitous and inevitably linked to health achievement as a country. The centrality of the precision medicine effort to the US national health research agenda may distract from efforts to remedy the foundational causes of ill health such as poverty, obesity, and education. Without addressing these causes, there will be little, if any, success in reversing the trends of poor achievement in US population health.

Second, precision medicine could (and to some extent has) led to a shift from which projects are funded by health research agencies. Funding for grants with a population health or public health goal has declined over the past 10 years at the National Institutes of Health, whereas funding for *-omic* research has increased substantially. This shift in funding may lead to an emerging

Khoury MJ and Galea S, JAMA 2016.

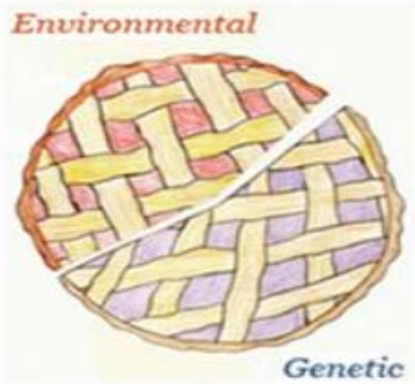
Nature vs. Nurture? Please, Not Again!

Are we products of nature or nurture? Science answers age-old question

Twin studies collated over the past 50 years reveal human traits and disease are almost equally determined by genetic and environmental factors

Researchers collated 2,748 studies involving more than 14.5 million pairs of twins and found the average variation for human traits and disease is 49% due to genetic factors and 51% due to environmental factors. Photograph: Alamy

Let's have stew not pie!



https://www.theguardian.com/science/2015/may/19/are-we-products-of-nature-or-nuture-science-answers-age-old-question
https://blogs.cdc.gov/genomics/2011/08/11/shall-we-have-pie-or-stew/

Human Diseases Result From Gene-Environment Interaction

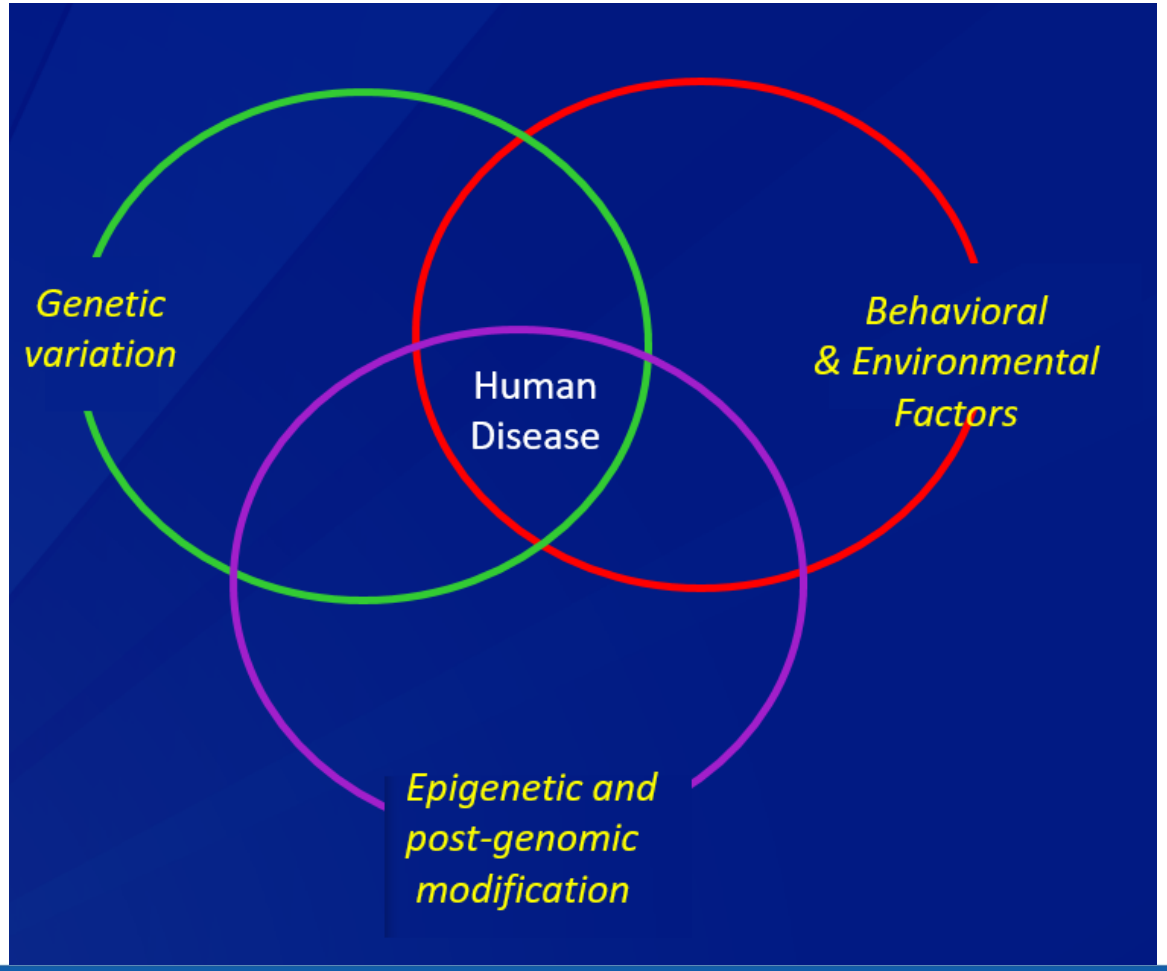
Genetic Diseases: 7000+ conditions, individually rare but collectively common

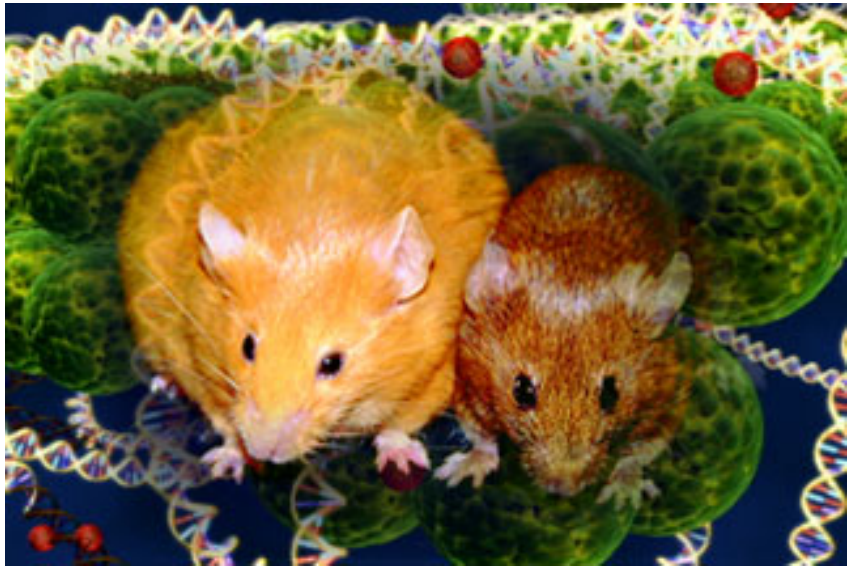
"Complex" Common Diseases: heart disease, cancer, diabetes

Many Genomes Interact

-Inherited (germ)
-Acquired (somatic) (e.g. cancer)
-Symbiotic (microbiome)
-Genomes of vectors

Interactions Are Getting More Complex
Epigenetics: Life Course and Intergenerational Effects

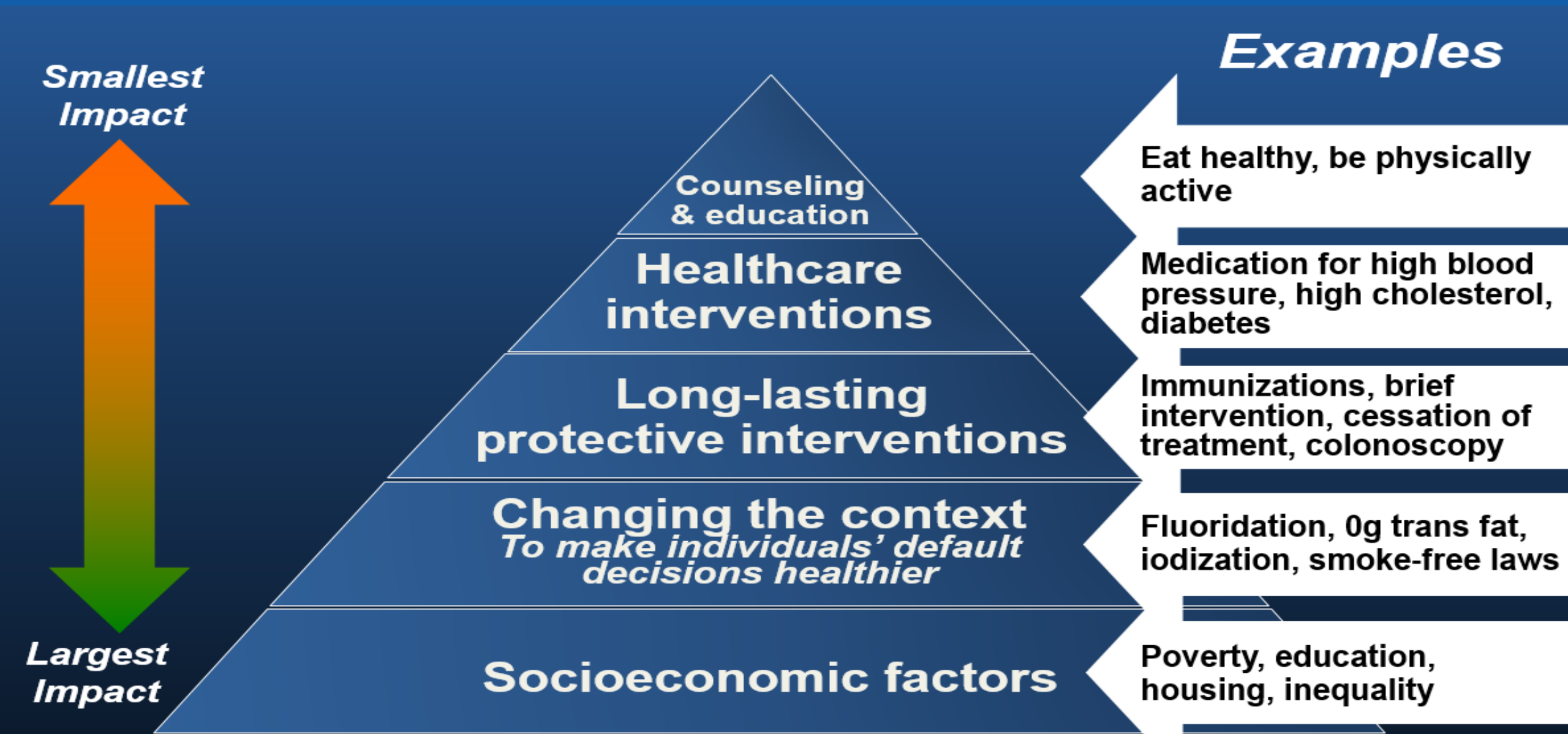




The Agouti Mouse and Impact of Epigenetics

http://blogs.cdc.gov/genomics/2014/10/09/epigenetics/

Almost All Health Problems Require Population and Individual Level Interventions Even Though Individual Interventions Have Less Impact



Precision Medicine vs Public Health: A False Dichotomy

Public Health in the Precision-Medicine Era

Ronald Bayer, Ph.D., and Sandro Galea, M.D., Dr.P.H.

That clinical medicine has contributed enormously to our ability to treat and cure sick people is beyond contention. But whether and to what extent medical care has transformed morbidity and mortality patterns at a population level and what contribution, if any, it has made to the well-being and life expectancy of the least-advantaged people have been matters of conten-

N ENGL J MED 373;6 NEJM.ORG AUGUST 6, 2015

The New England Journal of Medicine

"We worry that an unstinting focus on precision medicine… is a mistake — and a distraction from the goal of producing a healthier population."

Precision Medicine vs. Public Health: a False Dichotomy?

Posted on September 28, 2015 by Ron Zimmern, PHG Foundation and Muin J. Khoury, Office of Public Health Genomics, Centers for Disease Control and Prevention

The recent focus on precision medicine has attracted criticism from the public health community that firmly believes that health is determined by far more than health care, and that more sophisticated medical technologies may not adequately address important determinants of population health. There is no argument that a focus on the wider environmental, structural and social determinants of health is of the greatest importance for improving the health of populations and addressing health disparities. However, we wonder whether a contrast between public health practice and precision medicine is a false dichotomy. Improving the health of populations requires a multifaceted approach that includes access to quality health care and diverse disease prevention efforts. Already public health programs are using the power of genomics and molecular tools in the investigation and control of infectious disease outbreaks. For common chronic diseases, evidence is accumulating for targeting preventive actions that incorporate genomics.

Khoury and Zimmern, 2015

Bayer and Galea, NEJM 2015

Outline: 4 Themes continues

- Biological and Social Determinants of Disease Require Both Medical and Public Health Interventions
- **As Medicine Becomes More Precise (or Personalized), We Need Public Health to Ensure Its Population Health Benefits**
- There is an Important Role for Public Health Sciences to Develop and Implement New Knowledge
- The Era of "Precision Public Health" is Upon Us!

A Public Health Perspective on a National Precision Medicine Cohort

Balancing Long-term Knowledge Generation With Early Health Benefit

The new US precision medicine initiative[1] has been made possible by improvement and price reduction in genome sequencing, as well as advances in multiple sectors of biotechnology. The initiative includes 2 components: a focus on cancer intended to spur development of new targeted cancer treatments, and a proposal for establishing a national cohort of at least 1 million people to explore genetic and environmental determinants of health and disease. The success of this initiative requires a public health perspective to help ensure generalizability, assess methods of implementation, focus on prevention, and provide an appropriate balance between generation of long-term knowledge and short-term health gains.

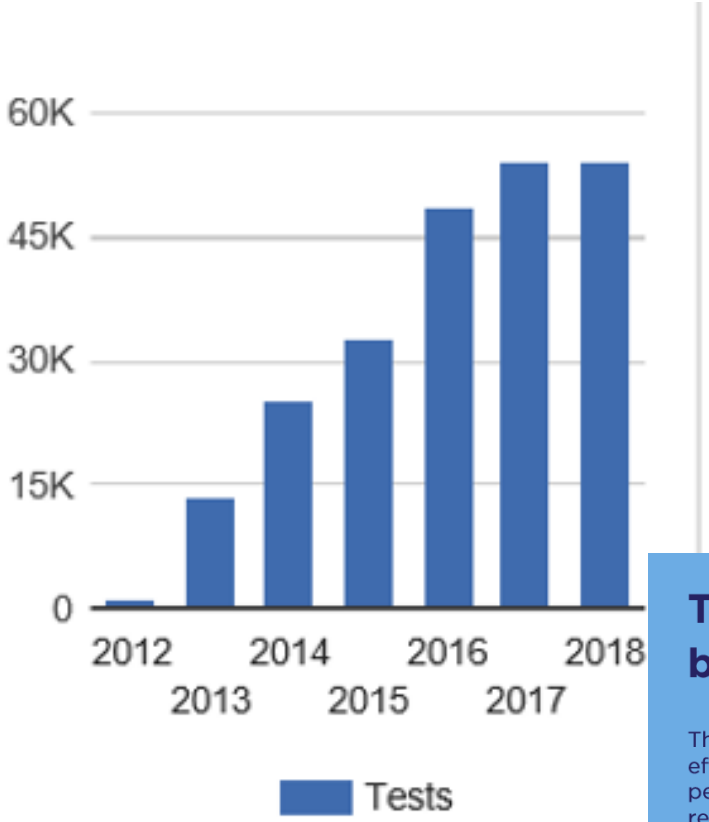
efit. For example, improving access to smoking cessation assistance is a component of the highly successful public health efforts that have resulted in reductions in smoking over the past few decades. Recent data suggest that using genetically informed biomarkers of the speed with which people metabolize nicotine[2] could lead to personalized smoking cessation. Another example of precision prevention is changes in recommended screening schedules for people at increased risk of cancer, identified either by acquisition of family health history or through detection of those individuals who carry pathogenic mutations in high-risk cancer genes.

The proposed long-term investment in precision medicine comes at a time of increasing fiscal restraint and

Khoury MJ and Evans JP, JAMA 2015.

The Genomic Testing Landscape is Growing Rapidly

- Increasing number of genetic tests
- Across lifespan (preconception to adults)
- Across continuum (prevention-treatment)
- Whole-genome sequencing as tool in clinical and public health practice
- Increasing public awareness and interest
- Proliferation of direct-to-consumer genetic tests
- Adoption by some healthcare systems
- Precision Medicine Initiative (AllofUs)



The future of health begins with All of Us

The *All of Us* Research Program is a historic effort to gather data from one million or more people living in the United States to accelerate research and improve health. By taking into account individual differences in lifestyle, environment, and biology, researchers will uncover paths toward delivering precision medicine.

NIH Genetic Testing Registry Search January 25, 2018: 54334 tests, 10999 conditions, 16419 genes, and 509 labs
https://allofus.nih.gov/

A Crucial Public Health Role is to Ensure Population Health Benefits of Genomics and Precision Medicine

- **Identifying applications that are supported by evidence for their use**
- **Assessing the population health impact of genomics and precision medicine**
  - Quantifying burden of preventable disease
  - Assessing Impact of interventions in terms of lives saved, disease prevented or detected earlier
  - Quantifying and modeling healthcare costs and savings
  - Assessing barriers and facilitators to implementation
  - Documenting and addressing health disparities
  - Assessing Laboratory practice

Opinion

VIEWPOINT

No Shortcuts on the Long Road to Evidence-Based Genomic Medicine

Muin J. Khoury, MD, PhD
Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, Georgia.

Rapid advances in genomics have led to a new era of precision medicine, resulting in a substantial increase in the number of genetic tests available for research and clinical practice. As of April 27, 2017, the Genetic Testing Registry,[1] maintained and updated by the National Institutes of Health, contained information on 49 521 tests conducted at 492 laboratories for 10 733 disease conditions involving 16 223 genes. These tests cover a wide variety of diseases, rare and common, for different types of applications such as diagnosis, treatment, and prevention.

For 2 decades, there have been ongoing discussions of the importance of a strong evidentiary foundation for genetic testing. Several advisory groups, including the Task Force on Genetic Testing[2] and the Secretary's Advisory Committee on Genetic Testing,[3] made a number of recommendations to strengthen the evidence base for genomic medicine. The key element of the discussion is the need to have answers to a number of scientific questions that are relevant to establishing the analytic validity of genomic tests (the ability of tests to be accurate),

> With the recent proliferation of direct-to-consumer genetic testing, the need for evidence in genomic medicine is more important than ever.

along with clinical validity (showing an association with disease end points) and clinical utility (showing effectiveness in improving health outcomes).[2]

What Is the Status of the Evidence Base In Genomic Medicine?

ence in genomic medicine. In 2014, 283 published articles evaluated implementation of genomic medicine. Most studies described uptake of genomic tests or preferences for use by clinicians and patients. Key study design elements, such as the racial/ethnic composition of study populations, were underreported in studies. Few studies incorporated implementation science theoretical frameworks, sustainability measures, or capacity-building measures. Most studies focused on patient factors associated with implementation rather than macro-level factors (eg, health systems, policies, education, financing). Only a few studies attempted to develop and evaluate evidence-based strategies that can improve implementation of genomic medicine. The authors concluded that "the current knowledge base around implementation science to turn the promise of genomic medicine into reality is severely limited."[5]

Moving Forward: A New Evidence Framework?

In March 2017, the National Academies of Sciences, Engineering, and Medicine released a study report titled "An Evidence Framework for Genetic Testing."[6] A special committee composed of a multidisciplinary group of experts examined the scientific literature to evaluate the evidence base for different types of genetic tests and "to develop a framework for decision making regarding the use of genetic tests in clinical care."[6] The committee focused on clinical applications and utility of genetic tests and examined how evidence is generated, evaluated, and synthesized. The committee reviewed several available methods for assessing the analytic validity, clinical validity, and clinical utility of genetic tests. These included the

Khoury MJ, JAMA, 2017.

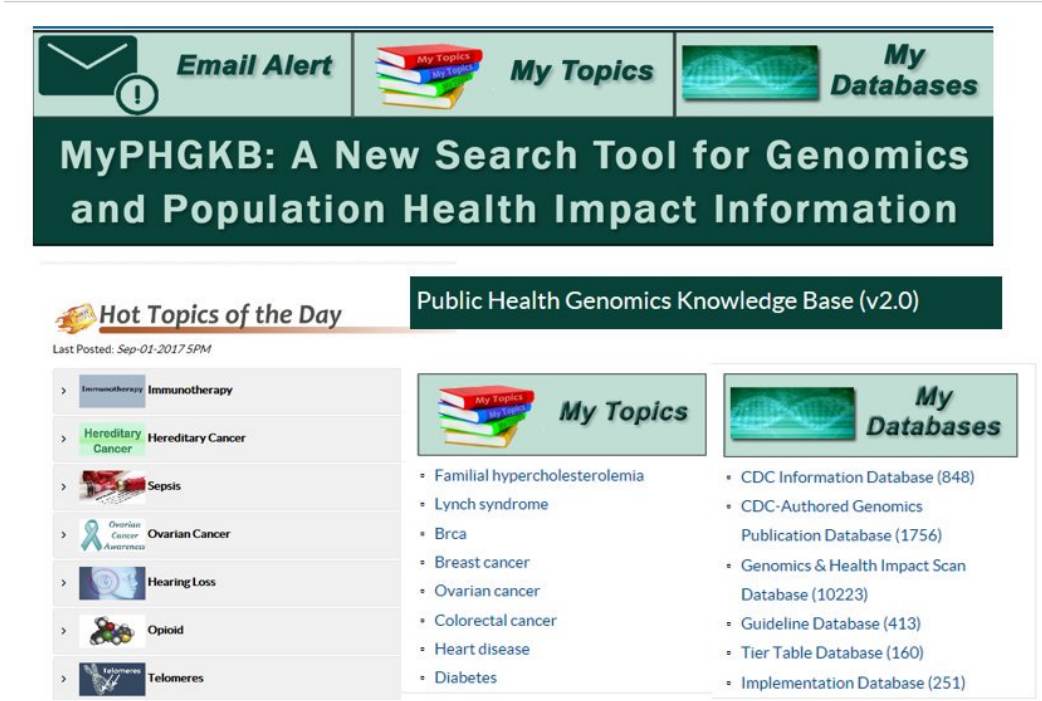
CDC Evidence-based Classification of Genomics and Precision Medicine Applications

Tier 1	Supported by a base of synthesized evidence for implementation in practice	e.g., newborn screening
Tier 2	Synthesized evidence is insufficient to support routine implementation in practice; may provide information for informed decision making	e.g., many pharmacogenomic tests
Tier 3	Evidence-based recommendations against use, or no relevant synthesized evidence identified; not ready for routine implementation in practice	e.g., direct-to-consumer personal genomic tests

Dotson WD, et al. *Clin Pharmacol Ther*. 2014

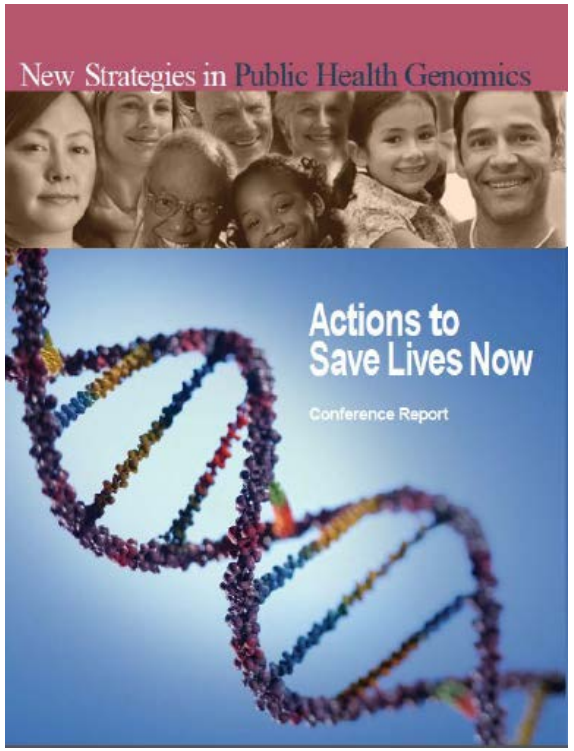
Evidence-based Genomic Tests Are Available in Practice and Can Save Lives Now!

- 68 Tier 1 tests, more than half are cancer related
- 107 Tier 2 tests, many pharmacogenomics
- Information on guidelines, programs, publications and tools can be searched using the Public Health Genomics Knowledge Base (PHGKB)
- Intended uses across the lifespan include screening, diagnosis, treatment, prognosis and risk assessment
- Weekly Update reaches ~70,000 subscribers



https://phgkb.cdc.gov/PHGKB/phgHome.action?action=home

Selected Tier 1 Genomic Applications Beyond Newborn Screening



2012

- Hereditary Breast and Ovarian Cancer (*BRCA1/2*)
- Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)
- Familial Hypercholesterolemia
- Collectively Affect ~2 Million People in US and Most Don't know it.
- Implementation of existing evidence-based guidelines can prevent cancer & heart disease, & save thousands of lives every year!
- Toolkit for public health departments
- Working with CDC programs and external partners

https://www.cdc.gov/genomics/implementation/toolkit/index.htm

Evidence-based Recommendations for Selected Hereditary Cancers

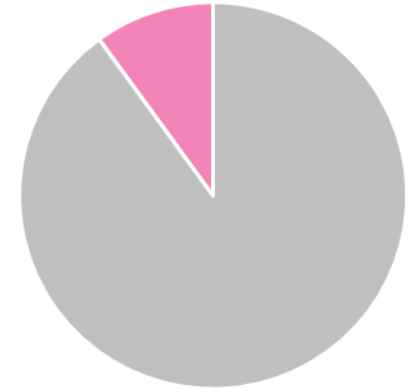
- **U.S. Preventive Services Task Force recommendation on *BRCA*-related cancer:**
  - Screening to identify family history associated with *BRCA1* or *BRCA2,* genetic counseling and *BRCA* testing
- **Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommendation for people with newly diagnosed colorectal cancer**
  - Access to genetic testing to identify Lynch syndrome to prevent cancer in their close relatives

Georgia Hurst, Lynch syndrome patient advocate and her son

Moyer VA. *Ann Intern Med.* 2014; 160(4):271–281.
Evaluation of Genomic Applications in Practice and Prevention Working Group. *Genet Med*. 2009 Jan;11(1):35–41.

Selected Cancers Associated with Hereditary Cancer Syndromes

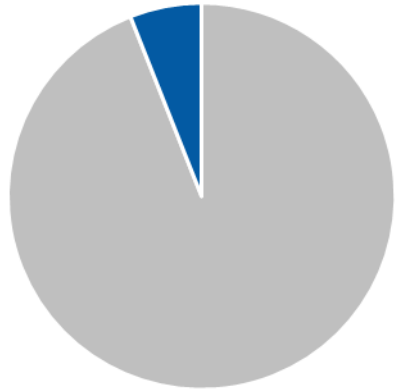
HBOC Syndrome



5% or approximately 22,000 cases of breast cancer each year

10% or approximately 2,000 cases of ovarian cancer each year

Lynch Syndrome



3% or approximately 4,000 cases of colorectal cancer each year

Campeau PM, et al. *Human Genetics.* 2008.
Pal T, et al. *Cancer.* 2005
Kaz AM, Brentnall TA. Nature Clin Pract Gastro & Hepa 2006.

CDC Public Health Genomics Activities in Cancer Control

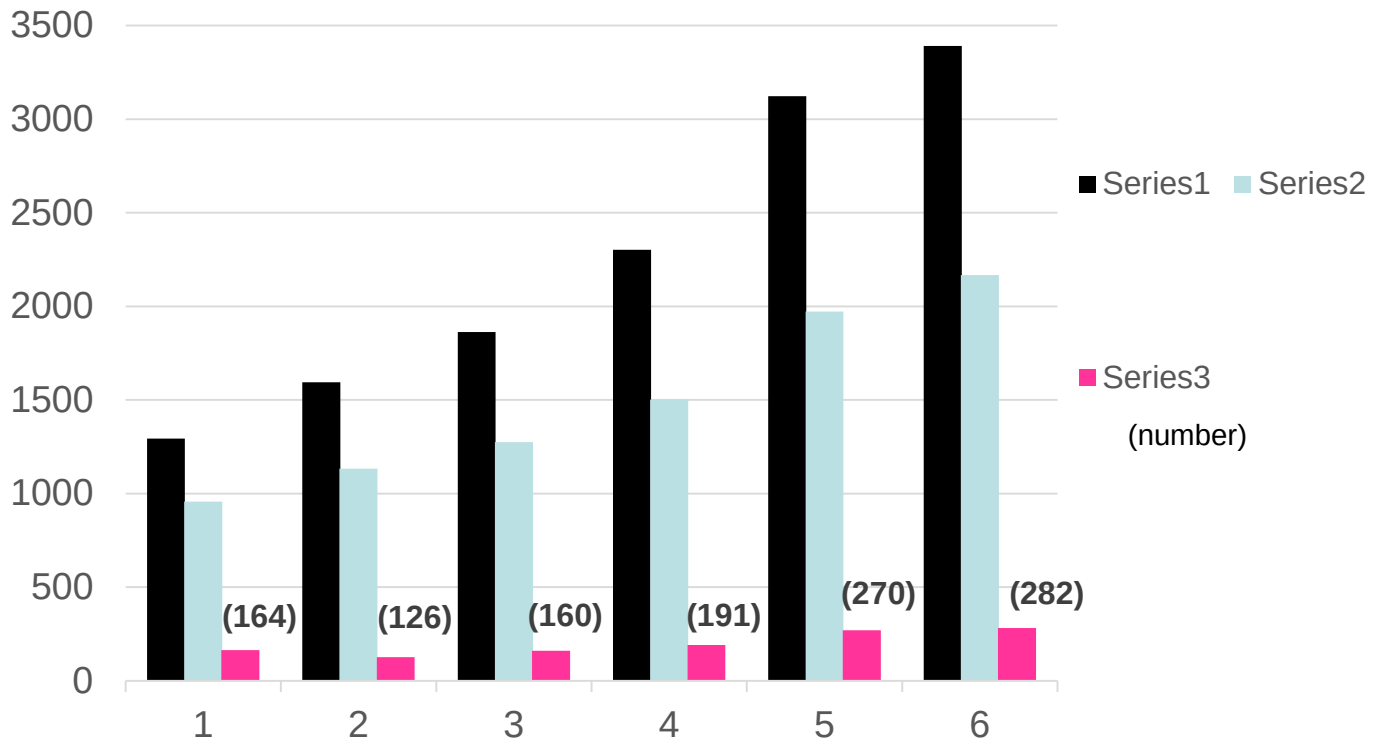
- **Builds capacity for cancer genomics activities in state public health departments**
  - Implement education, surveillance, and policy or systems change activities
  -
- **Currently funding programs in five states**
  - Colorado
  - Connecticut
  - Michigan
  - Oregon
  - Utah

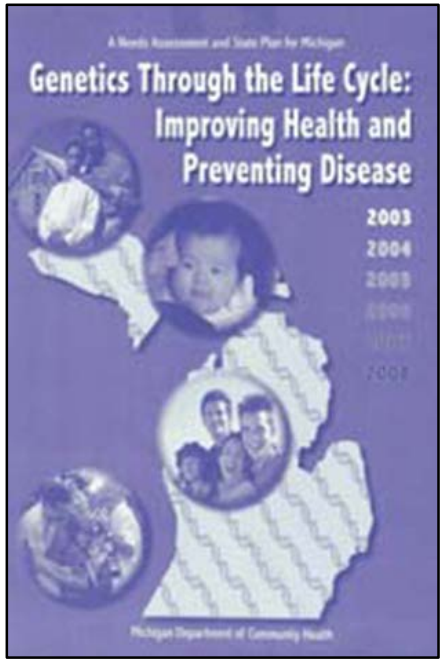
CDC Awards Funding to Support Cancer Genomics.
cdc.gov/cancer/breast/what_cdc_is_doing/genomics_foa.htm
St Pierre J, et al, Prev Chron Disease, 2014

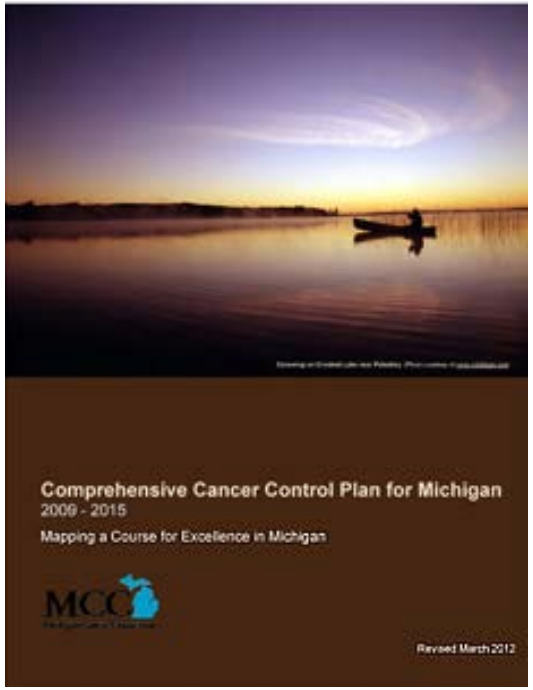
Box 1. Program Activities Supported by Cooperative Agreements in Public Health Genomics Through the Centers for Disease Control and Prevention, 2003–2008

- Develop or expand leadership capacity in public health genomics.
- Develop and implement population-based assessments and incorporate genomics into disease-specific data collection through surveillance and registries.
- Implement or expand the use of genomics in program activities.
- Educate the health care workforce, policy makers, and the public about the importance and role of family health history and genetic risk factors in disease etiology and prevention.
- Prepare the chronic disease workforce for using genomic tools to reduce the burden of specific diseases, and teach them the benefits and limitations of genetic tests.

Public Health Genomics: BRCA Testing in Michigan

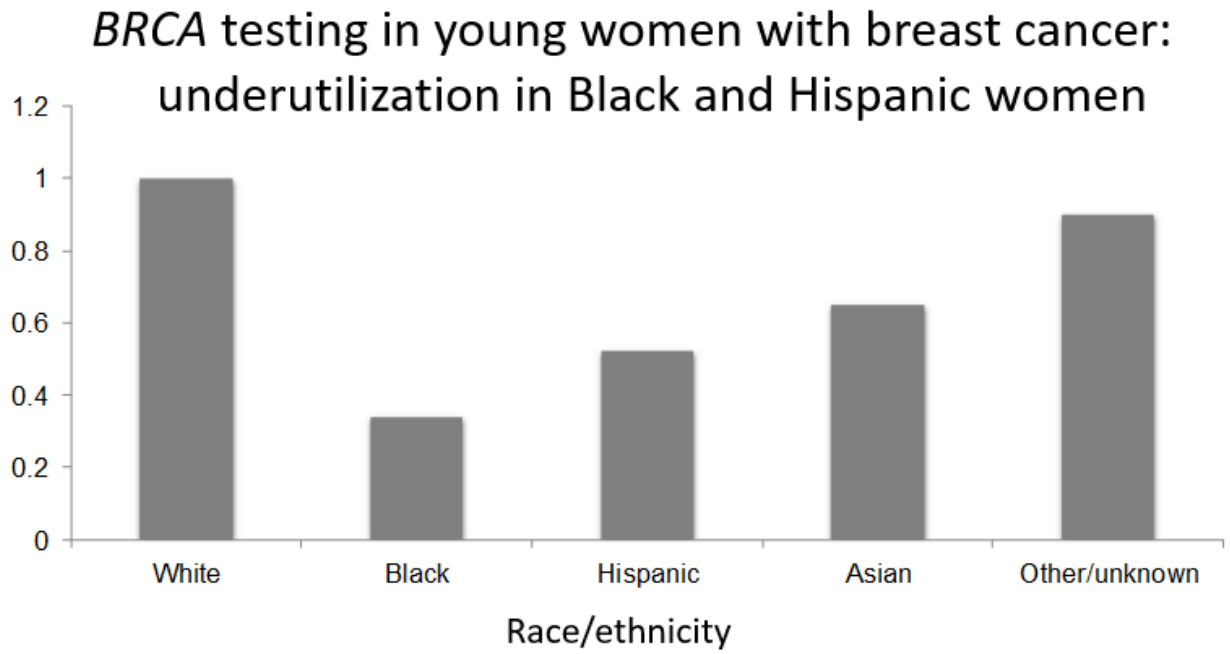




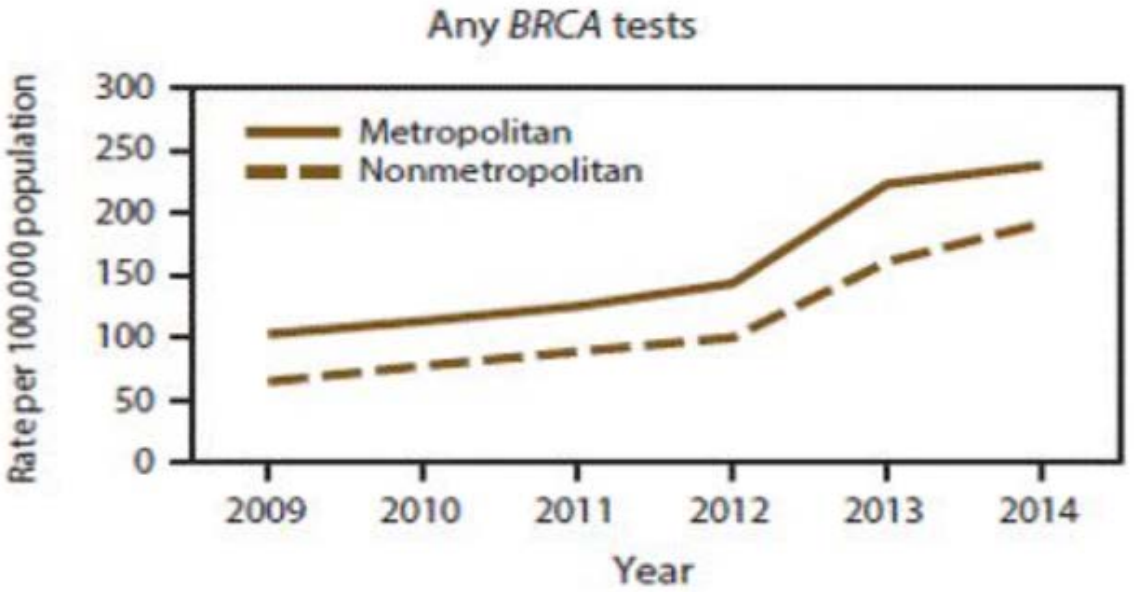


D Duquette, CDC Public Health Grand Rounds, April 2016
State of Michigan Cancer and Genetics Plans

Public Health Genomics and Health Disparities: BRCA Testing



Racial/Ethnic Differences



Rural-Urban Differences

Levy DE, et al. *Genet Med.* 2011
Kolor K et al, MMWR, 2017

Familial Hypercholesterolemia: A Missed Opportunity for Preventing Early Heart Attacks

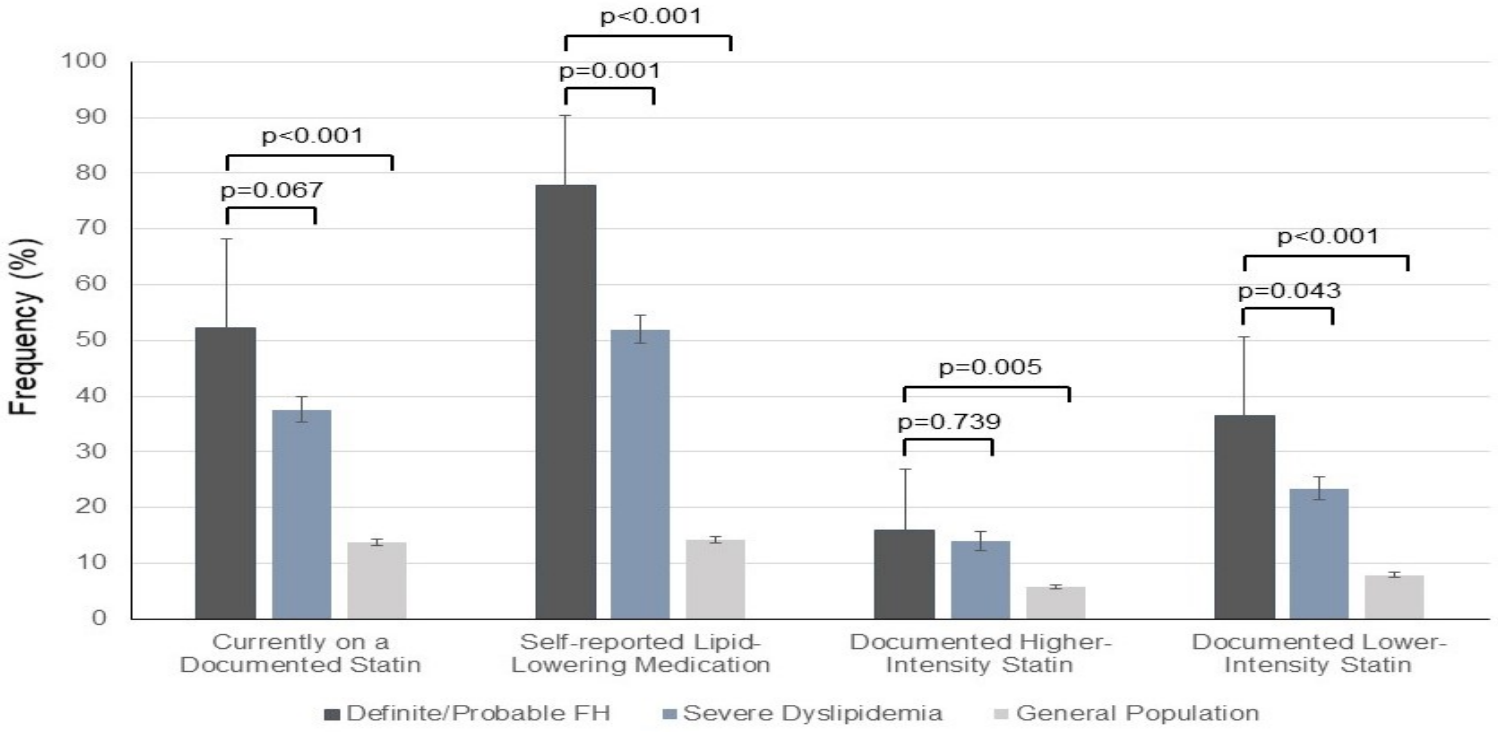
- **Common autosomal dominant condition (1/250) associated with premature death from heart disease**
- **Evidence-based recommendation for aggressive cholesterol reduction and cascade screening in relatives**
- **Highly underdiagnosed and undertreated**
- **Racial and ethnic disparities in diagnosis and management**
- **Missed opportunities for public health-health care partnerships**

http://www.medped.org/index.html

Knowles J et al, JAMA, 2017

Familial Hypercholesterolemia is Common and Undertreated in the United States

Prevalence of documented statin and self-reported lipid lowering medication use

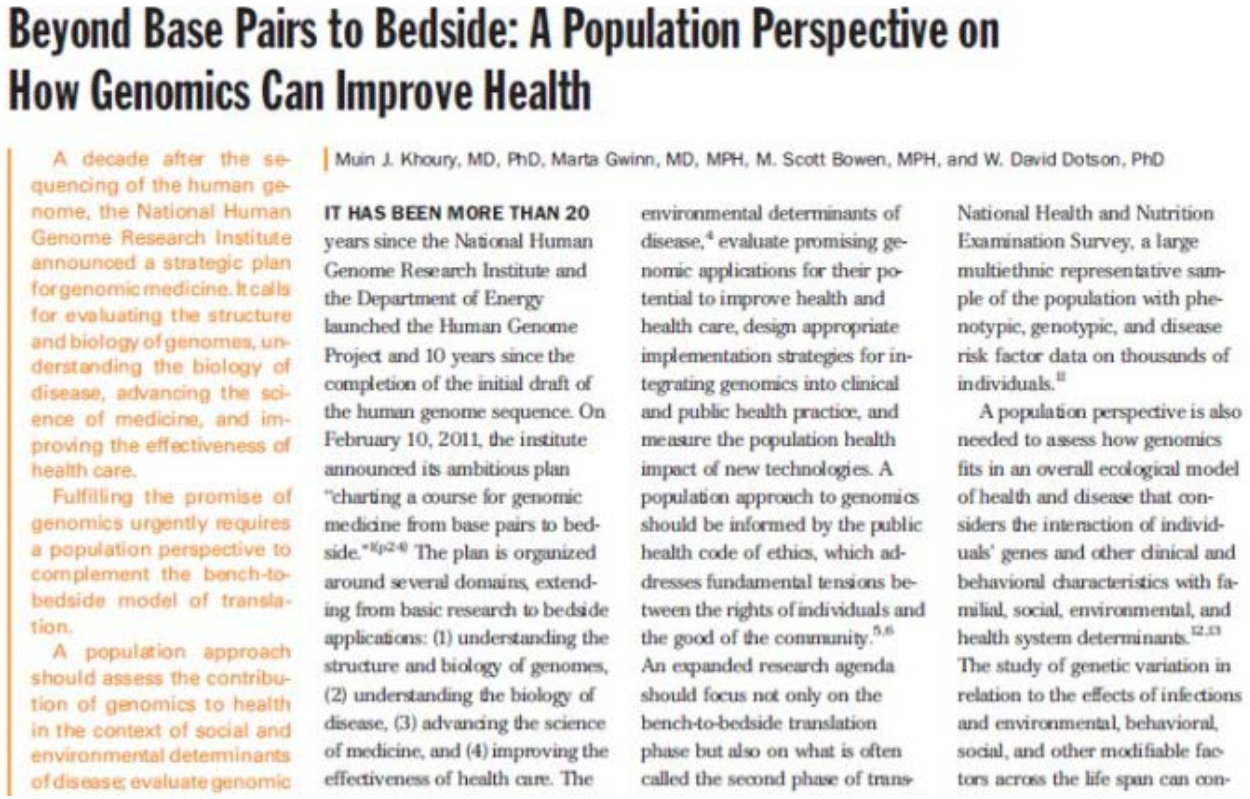


Young and uninsured patients are at the highest risk for under treatment

Bucholz, EM et al. Circulation (in press)

Outline: 4 Themes continued

- Biological and Social Determinants of Disease Require Both Medical and Public Health Interventions
- As Medicine Becomes More Precise (or Personalized), We Need Public Health to Ensure Its Population Health Benefits
- **There is an Important Role for Public Health Sciences to Develop and Implement New Knowledge**
- The Era of "Precision Public Health" is Upon Us!



Beyond Base Pairs to Bedside: A Population Perspective on How Genomics Can Improve Health

A decade after the sequencing of the human genome, the National Human Genome Research Institute announced a strategic plan for genomic medicine. It calls for evaluating the structure and biology of genomes, understanding the biology of disease, advancing the science of medicine, and improving the effectiveness of health care.

Fulfilling the promise of genomics urgently requires a population perspective to complement the bench-to-bedside model of translation.

A population approach should assess the contribution of genomics to health in the context of social and environmental determinants of disease; evaluate genomic

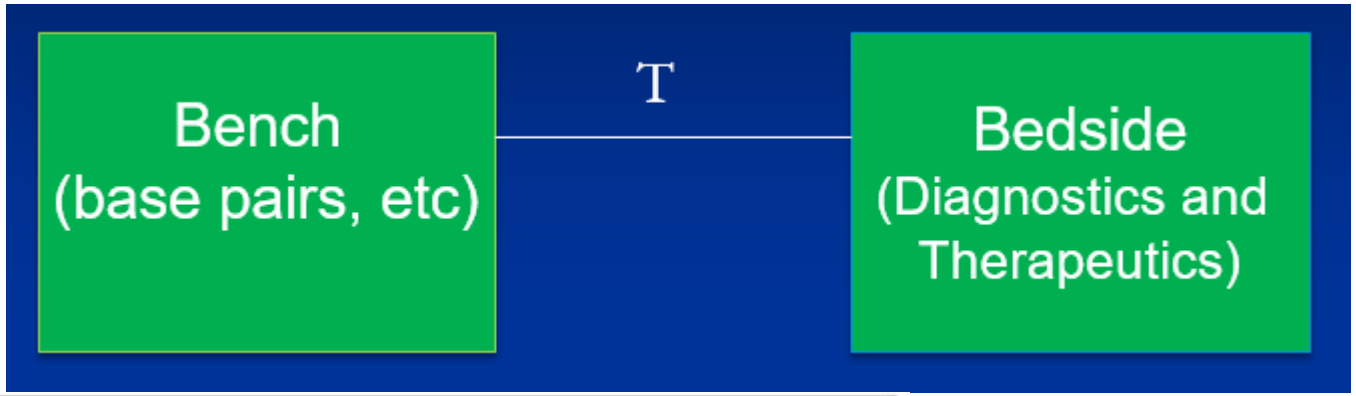
Muin J. Khoury, MD, PhD, Marta Gwinn, MD, MPH, M. Scott Bowen, MPH, and W. David Dotson, PhD

IT HAS BEEN MORE THAN 20 years since the National Human Genome Research Institute and the Department of Energy launched the Human Genome Project and 10 years since the completion of the initial draft of the human genome sequence. On February 10, 2011, the institute announced its ambitious plan "charting a course for genomic medicine from base pairs to bedside."[1(p2-4)] The plan is organized around several domains, extending from basic research to bedside applications: (1) understanding the structure and biology of genomes, (2) understanding the biology of disease, (3) advancing the science of medicine, and (4) improving the effectiveness of health care. The environmental determinants of disease,[4] evaluate promising genomic applications for their potential to improve health and health care, design appropriate implementation strategies for integrating genomics into clinical and public health practice, and measure the population health impact of new technologies. A population approach to genomics should be informed by the public health code of ethics, which addresses fundamental tensions between the rights of individuals and the good of the community.[5,6] An expanded research agenda should focus not only on the bench-to-bedside translation phase but also on what is often called the second phase of trans- National Health and Nutrition Examination Survey, a large multiethnic representative sample of the population with phenotypic, genotypic, and disease risk factor data on thousands of individuals.[11]

A population perspective is also needed to assess how genomics fits in an overall ecological model of health and disease that considers the interaction of individuals' genes and other clinical and behavioral characteristics with familial, social, environmental, and health system determinants.[12,13] The study of genetic variation in relation to the effects of infections and environmental, behavioral, social, and other modifiable factors across the life span can con-

Khoury MJ et al, AJPH, 2011.

Genomics Translation: Bench to Bedside



Charting a course for genomic medicine from base pairs to bedside

Eric D. Green[1], Mark S. Guyer[1] & National Human Genome Research Institute*

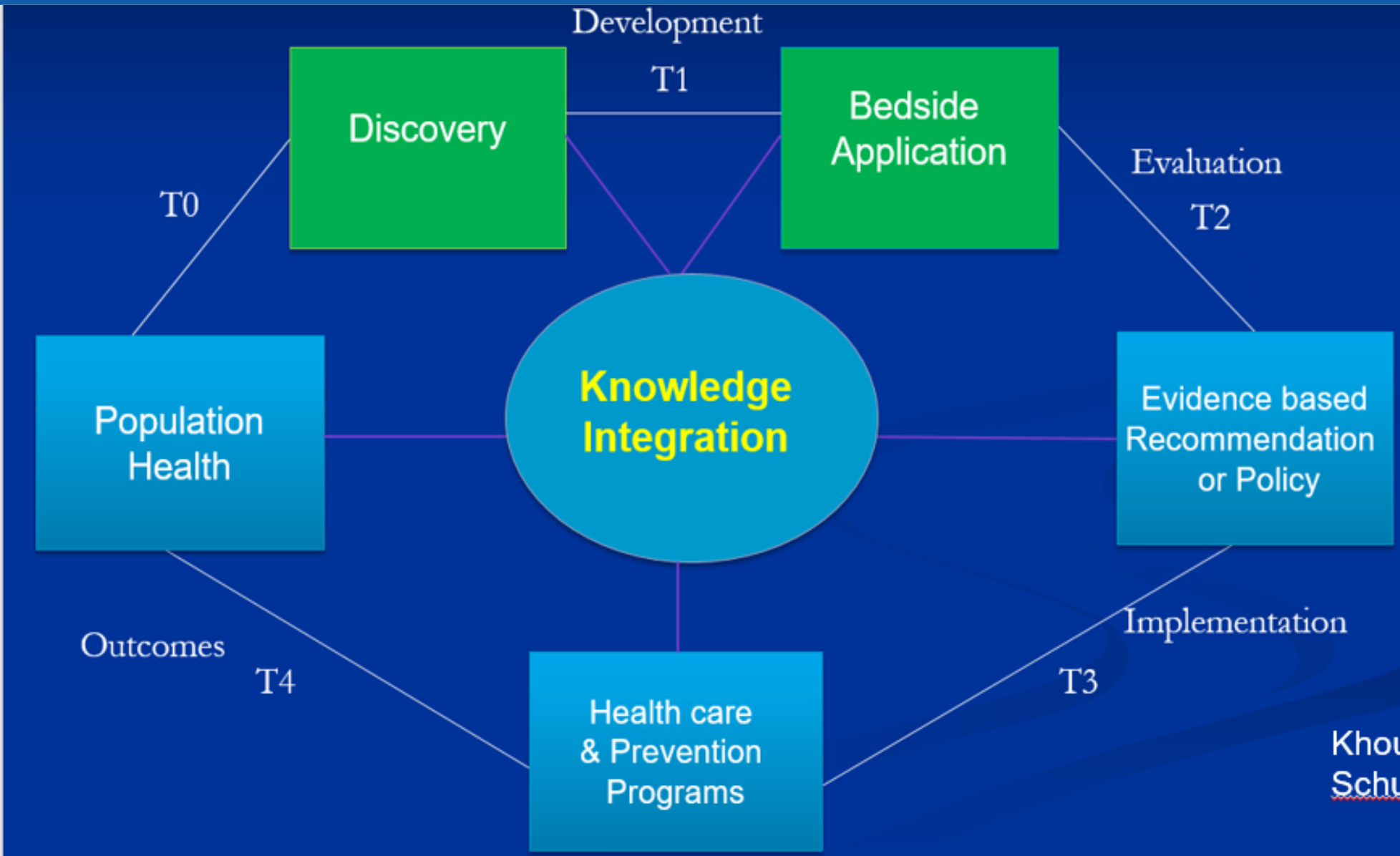
There has been much progress in genomics in the ten years since a draft sequence of the human genome was published. Opportunities for understanding health and disease are now unprecedented, as advances in genomics are harnessed to obtain robust foundational knowledge about the structure and function of the human genome and about the genetic contributions to human health and disease. Here we articulate a 2011 vision for the future of genomics research and describe the path towards an era of genomic medicine.

Implementing genomic medicine in the clinic: the future is here

Teri A. Manolio, MD, PhD[1], Rex L. Chisholm, PhD[2], Brad Ozenberger, PhD[1], Dan M. Roden, MD[3], Marc S. Williams, MD[4,5], Richard Wilson, PhD[6], David Bick, MD[7], Erwin P. Bottinger, MD[8], Murray H. Brilliant, PhD[9], Charis Eng, MD, PhD[10], Kelly A. Frazer, PhD[11], Bruce Korf, MD, PhD[12], David H. Ledbetter, PhD[5], James R. Lupski, MD, PhD[13], Clay Marsh, MD[14], David Mrazek, MD[15], Michael F. Murray, MD[16], Peter H. O'Donnell, MD[17], Daniel J. Rader, MD[18], Mary V. Relling, PharmD[19], Alan R. Shuldiner, MD[20], David Valle, MD[21], Richard Weinshilboum, MD[22], Eric D. Green, MD, PhD[1] and Geoffrey S. Ginsburg, MD, PhD[23]

Nature, 2011; Genetics in Medicine, 2013

Genomics Translation: Beyond Bench to Bedside ("The Road Less Traveled")



Translational Research T2 and Beyond Involves multiple Clinical and population disciplines but is <2% total genomic publications

Khoury MJ, et al, AJPH, 2012
Schully S et al, PHG, 2010

Tier 1 Genomic Applications: Health Systems and Implementation Science

SYSTEMATIC REVIEW | Genetics inMedicine

The current state of implementation science in genomic medicine: opportunities for improvement

Megan C. Roberts, PhD[1], Amy E. Kennedy, PhD, MPH[1], David A. Chambers, DPhil[1] and Muin J. Khoury, MD, PhD[1,2]

Purpose: The objective of this study was to identify trends and gaps in the field of implementation science in genomic medicine.

Methods: We conducted a literature review using the Centers for Disease Control and Prevention's Public Health Genomics Knowledge Base to examine the current literature in the field of implementation science in genomic medicine. We selected original research articles based on specific inclusion criteria and then abstracted information about study design, genomic medicine, and implementation outcomes. Data were aggregated, and trends and gaps in the literature were discussed.

Results: Our final review encompassed 283 articles published in 2014, the majority of which described uptake (35.7%, $n = 101$) and preferences (36.4%, $n = 103$) regarding genomic technologies, particularly oncology (35%, $n = 99$). Key study design elements, such as racial/ethnic composition of study populations, were underreported in studies. Few studies incorporated implementation science theoretical frameworks, sustainability measures, or capacity building.

Conclusion: Although genomic discovery provides the potential for population health benefit, the current knowledge base around implementation to turn this promise into a reality is severely limited. Current gaps in the literature demonstrate a need to apply implementation science principles to genomic medicine in order to deliver on the promise of precision medicine.

Genet Med advance online publication 12 January 2017

Key Words: dissemination; genomic medicine; implementation; precision medicine; translational research

MyCode® results returned

533 patient-participants have received results*

For the latest results, see go.geisinger.org/results.

Geisinger mycode | 150,000+ PARTICIPANTS

December 1, 2017

Risk condition	Patients per risk condition	Gene	Patients per gene
CDC tier 1 conditions (click link)			
Hereditary breast and ovarian cancer (early breast, ovarian, prostate and other cancers)	203	*BRCA1*	68
		BRCA2	135
Familial hypercholesterolemia (early heart attacks and strokes)	86	*APOB*	31
		LDLR	55
Lynch syndrome (early colon, uterine and other cancers)	50	*PMS2*	18
		MSH6	23
		MSH2	6
		MLH1	3
Cardiovascular risk			
Cardiomyopathy (diseases of the heart muscle with dangerous complications)	52	*MYH7*	8
		MYBPC3	29
		TPM1	2
		TNNI3	3
		TNNT2	5
		MYL3	4
		LMNA	1

Robert M et al, Genetics in Medicine, 2017

Geisinger, MyCode project https://www.geisinger.org/mycode

Tier 2 Genomic Applications: Pharmacogenomics
Pockets of Success but Not Ready for Large Scale Implementation

JAMA | Original Investigation

Effect of Genotype-Guided Warfarin Dosing on Clinical Events and Anticoagulation Control Among Patients Undergoing Hip or Knee Arthroplasty

The GIFT Randomized Clinical Trial

Brian F. Gage, MD, MSc; Anne R. Bass, MD; Hannah Lin, BA; Scott C. Woller, MD; Scott M. Stevens, MD; Noor Al-Hammadi, MBChB, MPH; Juan Li, MPH; Tomás Rodríguez Jr, MS; J. Philip Miller, AB; Gwendolyn A. McMillin, PhD; Robert C. Pendleton, MD; Amir K. Jaffer, MD, MBA; Cristi R. King, BS; Brandi DeVore Whipple, BS; Rhonda Porche-Sorbet, MS; Lynnae Napoli, BS; Kerri Wesley Hollomon, MD, MBA; Robert L. Barrack, MD; Ryan M. Nunley, MD; Gerard

IMPORTANCE Warfarin use accounts for more medication-related er visits among older patients than any other drug. Whether genotype can prevent these adverse events is unknown.

OBJECTIVE To determine whether genotype-guided dosing improve initiation.

DESIGN, SETTING, AND PATIENTS The randomized clinical Genetic In Warfarin to Prevent Deep Vein Thrombosis included patients aged 6 warfarin for elective hip or knee arthroplasty and was conducted at Enrollment began in April 2011 and follow-up concluded in October

INTERVENTIONS Patients were genotyped for the following polymo *VKORC1-1639G>A, CYP2C9*2, CYP2C9*3,* and *CYP4F2 V433M.* In a 2 patients were randomized to genotype-guided (n = 831) or clinically dosing on days 1 through 11 of therapy and to a target international r either 1.8 or 2.5. The recommended doses of warfarin were open lab clinicians were blinded to study group assignment.

Polygenic Risk Score Identifies Subgroup With Higher Burden of Atherosclerosis and Greater Relative Benefit From Statin Therapy in the Primary Prevention Setting

Editorial, see p 2102

BACKGROUND: Relative risk reduction with statin therapy has been consistent across nearly all subgroups studied to date. However, in analyses of 2 randomized controlled primary prevention trials (ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm] and JUPITER [Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin]), statin therapy led to a greater relative risk reduction among a subgroup at high genetic risk. Here, we aimed to confirm this observation in a third primary prevention randomized controlled trial. In addition, we assessed whether those at high genetic risk had a greater burden of subclinical coronary atherosclerosis.

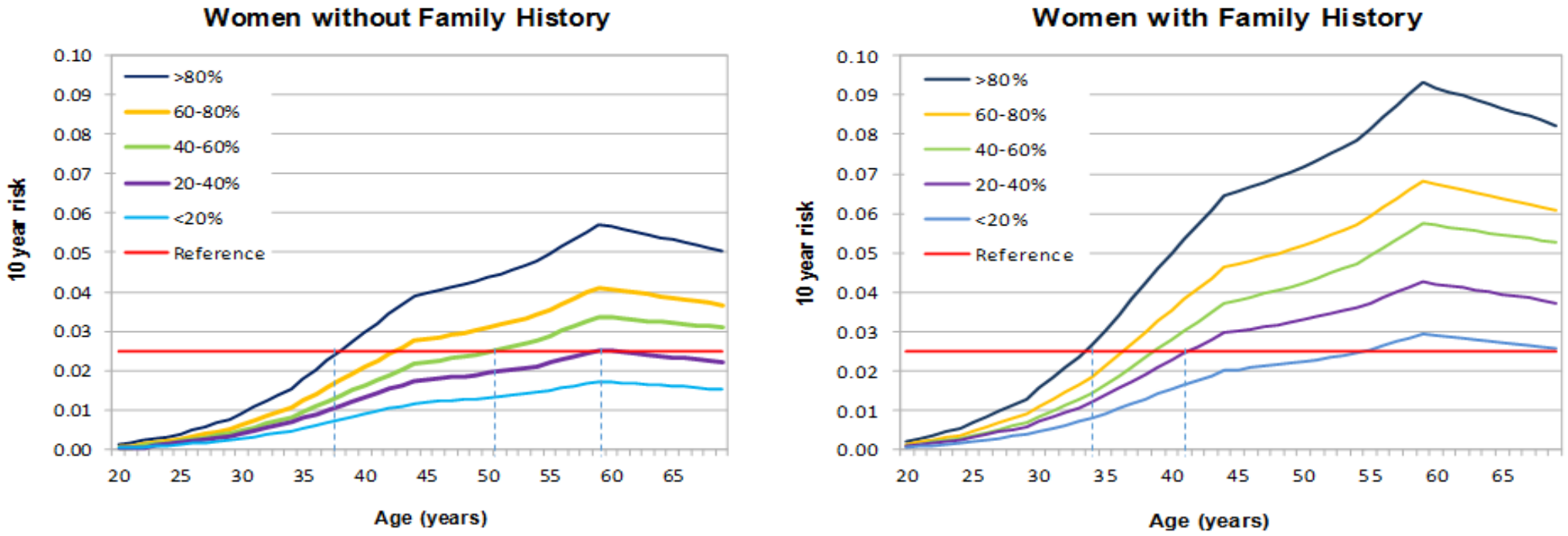
METHODS: We studied participants from a randomized controlled trial of primary prevention with statin therapy (WOSCOPS [West of Scotland Coronary Prevention Study]; n=4910) and 2 observational cohort studies (CARDIA [Coronary Artery Risk Development in Young Adults] and BioImage; n=1154 and 4392, respectively). For each participant, we calculated a polygenic risk score derived from up to 57 common DNA sequence variants previously associated with coronary heart

Pradeep Natarajan, MD, MMSc*
Robin Young, PhD*
Nathan O. Stitziel, MD, PhD
Sandosh Padmanabhan, MD, PhD
Usman Baber, MD
Roxana Mehran, MD
Samantha Sartori, PhD
Valentin Fuster, MD, PhD
Dermot F. Reilly, PhD
Adam Butterworth, PhD
Daniel J. Rader, MD
Ian Ford, PhD†
Naveed Sattar, MD, PhD†
Sekar Kathiresan, MD†

JAMA 2016, 2017
Circulation, 2017

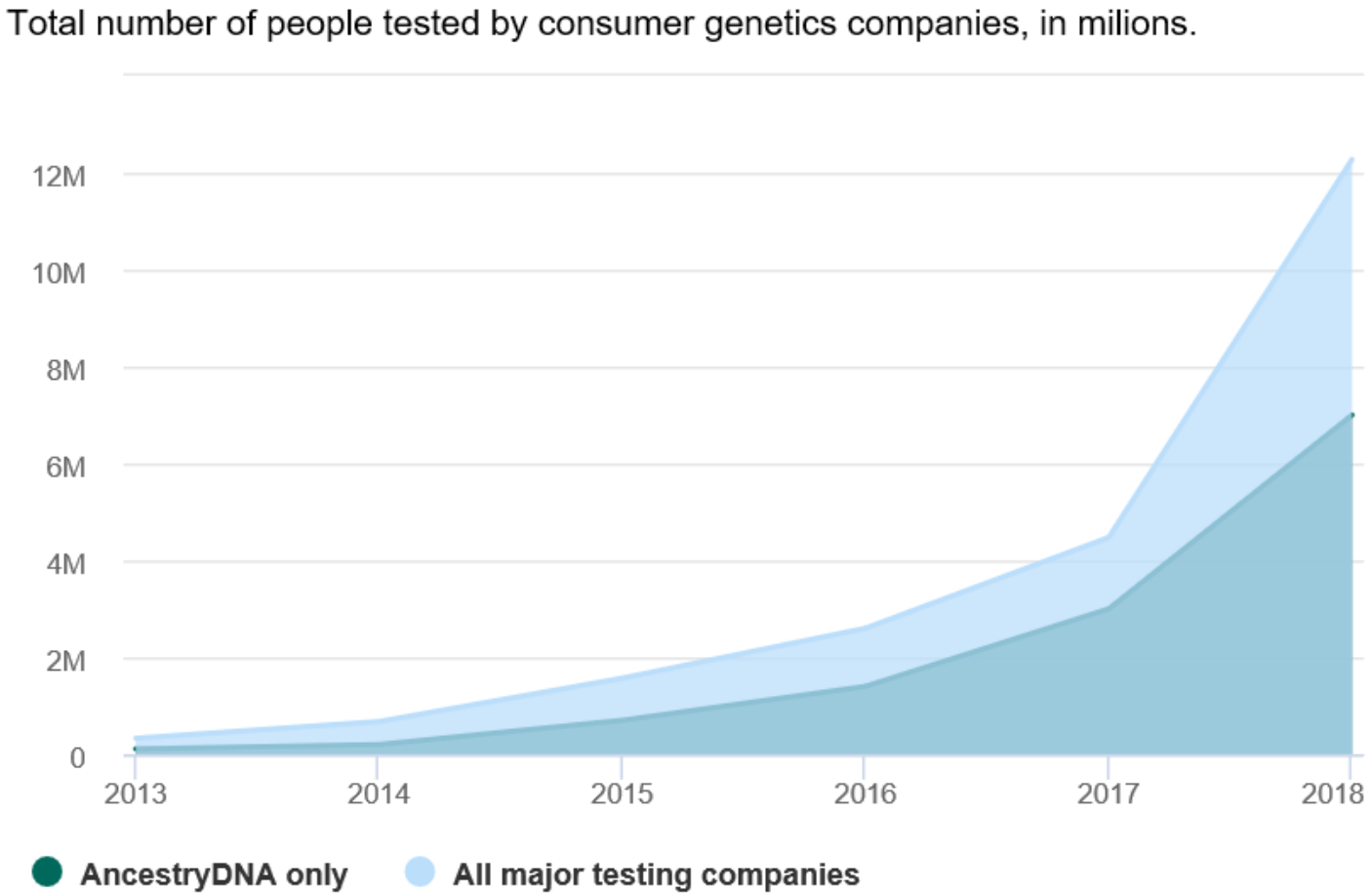
Tier 2 Genomic Applications: Genetic Risk Scores Example of Breast Cancer Screening

10-year absolute risk of developing breast cancer for women with and without family history by polygenic risk percentiles

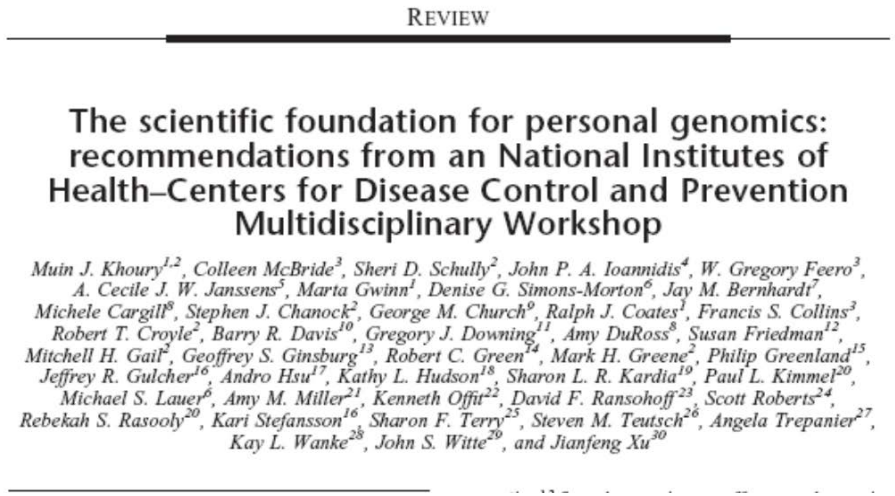


Mavaddat et al. JNCI 2015: 107(5)

Tier 3 Genomic Applications
Personal Direct to Consumer Genetic Tests



Think Before You Spit, 2017 Edition!



REVIEW

The scientific foundation for personal genomics: recommendations from an National Institutes of Health–Centers for Disease Control and Prevention Multidisciplinary Workshop

Muin J. Khoury[1,2], Colleen McBride[3], Sheri D. Schully[2], John P. A. Ioannidis[4], W. Gregory Feero[3], A. Cecile J. W. Janssens[5], Marta Gwinn[1], Denise G. Simons-Morton[6], Jay M. Bernhardt[7], Michele Cargill[8], Stephen J. Chanock[2], George M. Church[9], Ralph J. Coates[1], Francis S. Collins[3], Robert T. Croyle[2], Barry R. Davis[10], Gregory J. Downing[11], Amy DuRoss[8], Susan Friedman[12], Mitchell H. Gail[2], Geoffrey S. Ginsburg[13], Robert C. Green[14], Mark H. Greene[2], Philip Greenland[15], Jeffrey R. Gulcher[16], Andro Hsu[17], Kathy L. Hudson[18], Sharon L. R. Kardia[19], Paul L. Kimmel[20], Michael S. Lauer[6], Amy M. Miller[21], Kenneth Offit[22], David F. Ransohoff[23], Scott Roberts[24], Rebekah S. Rasooly[20], Kari Stefansson[16], Sharon F. Terry[25], Steven M. Teutsch[26], Angela Trepanier[27], Kay L. Wanke[28], John S. Witte[29], and Jianfeng Xu[30]

- Regalado A, MIT Technology Review, Feb 2018
- Khoury MJ et al, Genetics in Medicine, 2009

Outline: 4 Themes cont.

- Biological and Social Determinants of Disease Require Both Medical and Public Health Interventions
- As Medicine Becomes More Precise (or Personalized), We Need Public Health to Ensure Its Population Health Benefits
- There is an Important Role for Public Health Sciences to Develop and Implement New Knowledge
- **The Era of "Precision Public Health" is Upon Us!**

Precision Public Health for the Era of Precision Medicine

Muin J. Khoury, MD, PhD,[1,2] Michael F. Iademarco, MD, MPH,[1,3] William T. Riley, PhD[2]

The Precision Medicine Initiative[1] promises a new healthcare era. A proposed 1 million–person cohort could create a deeper understanding of disease causation. Improvements in quality of sequencing, reduction in price, and advances in "omic" fields and biotechnology promise a new era, variably labeled personalized or precision medicine. Although genomics is one driver of precision health care, other factors may be as important (e.g., health information technology).

Both excitement and skepticism met the announcement.[2] Public health experts are concerned about the disproportionate emphasis on genes, drugs, and disease, while neglecting strategies to address social determinants

evidentiary foundation for use. The following are examples of priority areas.

Role of Multidisciplinary Public Health Sciences

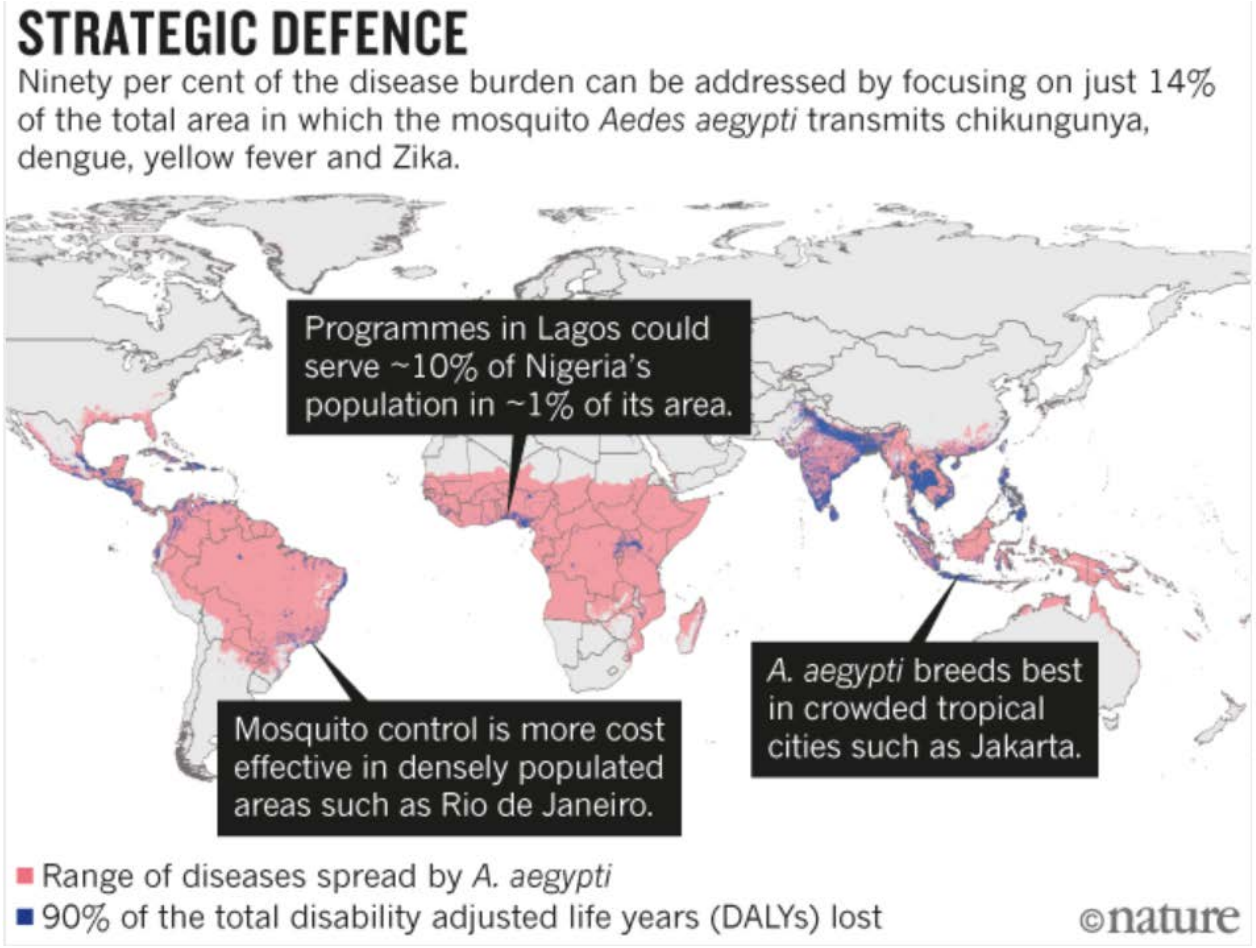
Though precision medicine focuses on individualized care, its success truly requires a population-based approach. To learn what interventions work for whom, data on each individual need to be compared with data from large, diverse numbers of people to identify population subgroups likely to respond differently to interventions. In addition, collecting information from

Khoury MJ et al, AJPM, 2016.

"Delivering the Right Intervention to the Right Population at the Right Time"

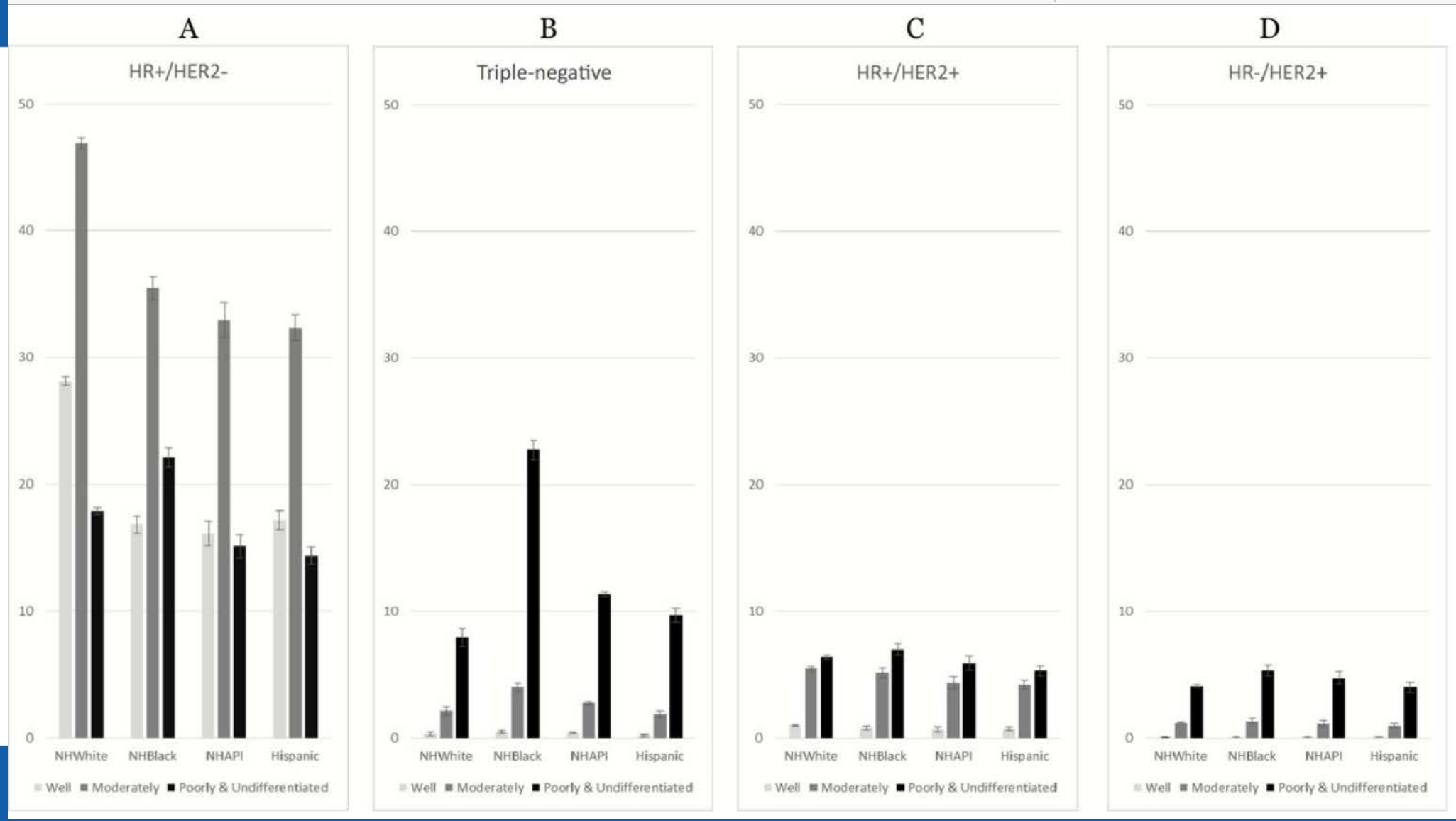
3 Core Public Health Functions

- Assessment
  - More "precision" in measuring population health (surveillance/monitoring/ tracking)
- Policy Development
  - More "precision" in developing appropriate policies and
- Assurance
  - More "precision" in delivering interventions & addressing health disparities



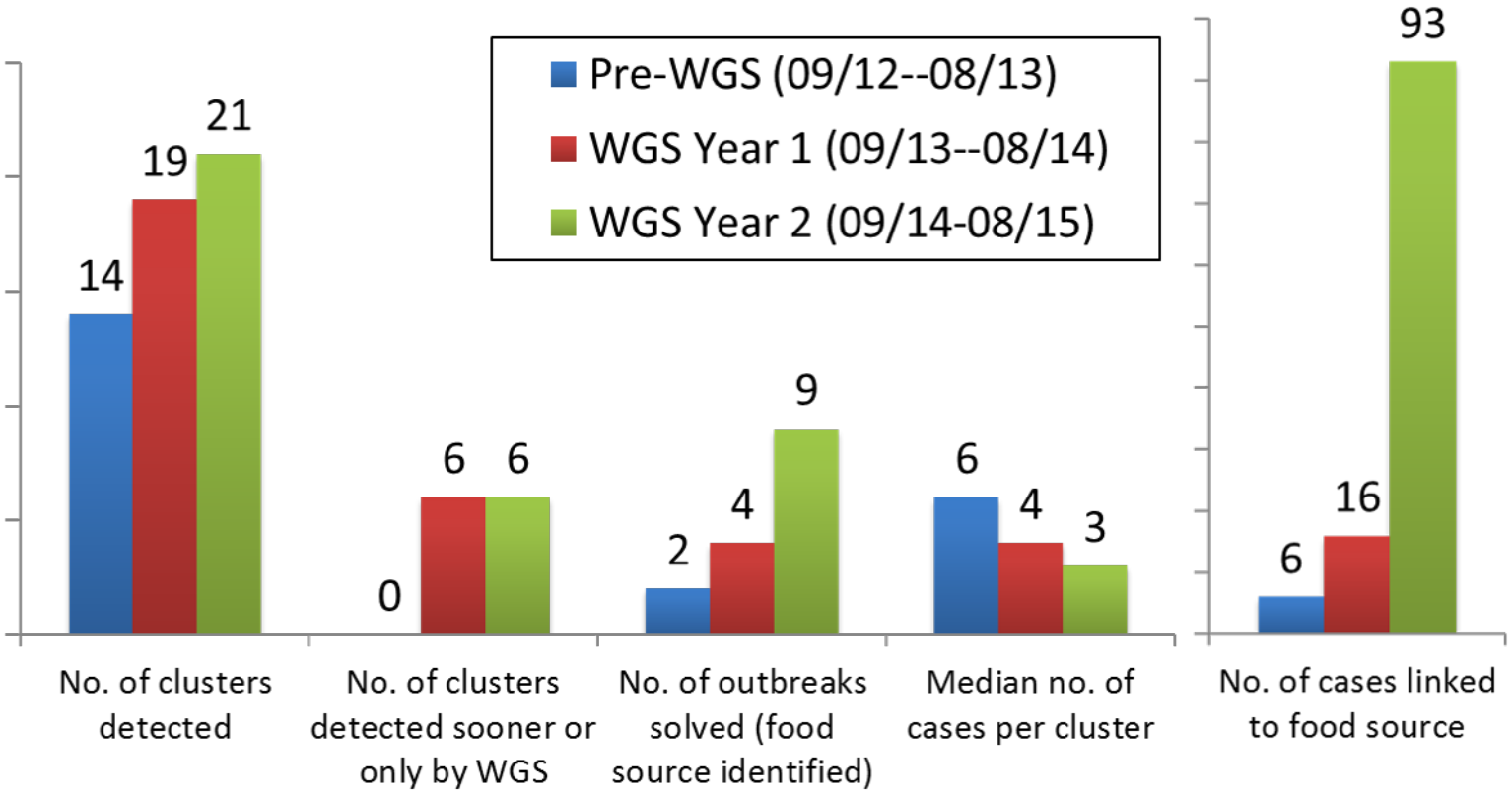
Dowell SF et al, Nature, 2016.

Using More "Precision" in Public Health Surveillance (e.g., Cancer SEER Program)



Annual Report to the Nation on the Status of Cancer, 1975-2011,, JNCI, 2015

CDC Advanced Molecular Detection Initiative
Using Whole Genome Sequencing in Tracking Listeria Outbreaks In the United States



Gwinn M et al, J Clin Microbiol 2017

Courtesy: Brendan Jackson, Enteric Diseases Epidemiology Branch

From Precision Medicine to Precision Public Health

- Biological and Social Determinants of Disease Require Both Medical and Public Health Interventions
- As Medicine Becomes More Precise (or Personalized), We Need Public Health to Ensure Its Population Health Benefits
- There is an Important Role for Public Health Sciences to Develop and Implement New Knowledge
- The Era of "Precision Public Health" is Upon Us!