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!

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.

Let’s have stew not pie!

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

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

Examples

- Eat healthy, be physically active
- Medication for high blood pressure, high cholesterol, diabetes
- Immunizations, brief intervention, cessation of treatment, colonoscopy
- Fluoridation, 0g trans fat, iodization, smoke-free laws
- Poverty, education, housing, inequality
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-

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

Khoury and Zimmern, 2015
Bayer and Galea, NEJM 2015
Outline: 4 Themes continues

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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)

NIH Genetic Testing Registry Search January 25, 2018: 54334 tests, 10999 conditions, 16419 genes, and 509 labs

[https://allofus.nih.gov/](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

### CDC Evidence-based Classification of Genomics and Precision Medicine Applications

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

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

- 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

2012

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

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

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

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.

CDC Awards Funding to Support Cancer Genomics.
cdc.gov/cancer/breast/what_cdc_is_doing/genomics_foa.htm
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

**BRCA testing in young women with breast cancer:**
underutilization in Black and Hispanic women

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**Racial/Ethnic Differences**

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Other/unknown</td>
</tr>
</tbody>
</table>

**Rural-Urban Differences**

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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)
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Genomics Translation: Bench to Bedside

Charting a course for genomic medicine from base pairs to bedside

Implementing genomic medicine in the clinic: the future is here

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

Schully S et al, PHG, 2010
# Tier 1 Genomic Applications: Health Systems and Implementation Science

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

Megan C. Roberts, PhD¹, Amy E. Kennedy, PhD, MPH¹, David A. Chambers, DPhil¹ and Muin J. Khoury, MD, PhD¹²

**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 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 = 100) regarding genomic technologies, particularly oncology (35.7%, n = 90). 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.

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**MyCode® results returned**

533 patient-participants have received results*

For the latest results, see [go.geisinger.org/results.](https://go.geisinger.org/results)

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<table>
<thead>
<tr>
<th>Risk condition</th>
<th>Patients per risk condition</th>
<th>Gene</th>
<th>Patients per gene</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hereditary breast and ovarian cancer</strong> (early breast, ovarian, prostate and other cancers)</td>
<td>203</td>
<td>BRCA1</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRCA2</td>
<td>135</td>
</tr>
<tr>
<td><strong>Familial hypercholesterolemia</strong>      (early heart attacks and strokes)</td>
<td>86</td>
<td>APOB</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LDLR</td>
<td>55</td>
</tr>
<tr>
<td><strong>Lynch syndrome</strong>                     (early colon, uterine and other cancers)</td>
<td>50</td>
<td>PMS2</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH6</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MSH2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MLH1</td>
<td>3</td>
</tr>
</tbody>
</table>

**Cardiovascular risk**

| Cardiomyopathy                          | 52                           | MYH7 | 8                 |
|                                         |                              | MYBPC3 | 29               |
|                                         |                              | TPM1 | 2                 |
|                                         |                              | TNNI3 | 3                |
|                                         |                              | TNNT2 | 5                |
|                                         |                              | MYL3 | 4                 |
|                                         |                              | LMNA | 1                 |
Tier 2 Genomic Applications: Pharmacogenomics

Pockets of Success but Not Ready for Large Scale Implementation

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

The GIFT Randomized Clinical Trial

Pockets of Success but Not Ready for Large Scale Implementation

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, analyses of 2 randomized controlled primary prevention trials (ASCOT-B additional Cardiovascular Outcomes Trial: Lipid-Lowering Arm and JUPITER (Justification for the Use of Statins in Primary 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 (WUSA/SPECS [Most of Scotland Coronary Prevention Study]; n=9970) and 2 observational cohort studies (CARDIA [Coronary Artery Risk Development in Young Adults] and BioMagnetics: 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...
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

Total number of people tested by consumer genetics companies, in millions.

Think Before You Spit, 2017 Edition!

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

Main J. Khoury1,2, Colleen McBride3, Sheri D. Schully4, John P. A. Ioannidou5, W. Gregory Feero3, A. Cecile J. W. Janssen1, Maria Gwirner1, Dennis G. Simons-Morton6, Jay M. Bernardi1, Michele Garfiff7, Stephen J. Chanock3, George M. Church8, Ralph J. Coates1, Francis S. Collins9, Robert T. Crengle10, Barry R. Davis11, Gregory J. Downey11, Amy Dukas12, Susan Friedman11, Mitchell H. Gail12, Geoffrey S. Ginsburg6, Robert C. Green8, Mark H. Grodetsky, Philip Greenland13, Jeffrey R. Gusco12, Andrea Hsu11, Kathy L. Hudson10, Sharon L. R. Kardia14, Paul L. Kimmie15, Michael S. Launer16, Amy M. Miller17, Kenneth Oft17, David F. Ranshoff18, Scott Roberts19, Rebekah S. Baswolf20, Kurt Stefansson20, Sharon P. Terry21, Steven M. Teutsch22, Angela Trepanier23, Kay L. Wanke20, John S. Witte20, and Jianfeng Xu20

- Regalado A, MIT Technology Review, Feb 2018
- Khoury MJ et al, Genetics in Medicine, 2009
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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, PhD2

The Precision Medicine Initiative1 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 of health. A framework is needed to provide an 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

“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

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

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

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