Emergence and Promise of Genomics and Precision Medicine

Why We Need Public Health for Genomics and Precision Medicine to Succeed

A Brief History of Public Health Genomics

Human Genomics in Public Health Practice: What’s Next?

Khoury MJ, et al. Genetics in Medicine, Dec 2017
The Genomic Testing Landscape is Growing Rapidly

- Increasing Number of genetic tests
- Whole-genome sequencing as tool in clinical and public health practice
- Increasing public awareness and interest
- Proliferation of direct-to-consumer genetic tests

NIH Genetic Testing Registry Search January 25, 2018: 54334 tests, 10999 conditions, 16419 genes, and 509 labs
The U.S. Precision Medicine Initiative Promises a New Era of Medicine and Public Health

Launched in 2015, includes two components:

- A focus on molecularly targeted treatment for cancer
- A national cohort of at least 1 million people (AllofUs)

What is precision medicine?

"An emerging approach for disease prevention and treatment that takes into account people’s individual variations in genes, environment, and lifestyle."

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.

The White House. The Precision Medicine Initiative. whitehouse.gov/precision-medicine
The Success of the Precision Medicine Initiative Requires Public Health Partnership

- Inclusion and generalizability
- Focus on prevention
- Implementing what we know
- Healthcare-public health partnerships

Challenges in Genomics and Precision Medicine Implementation That Require Public Health Leadership

- Population health impact
- Evidence-based policy
- Health system implementation issues
- Laboratory quality
- Provider and public education
- Health disparities
A Crucial Public Health Role is to Assess and Assure Population Health Impact 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 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
Mission: Enable and promote CDC efforts in integrating genomics and precision medicine applications into public health actions that prevent disease, save health care costs and reduce health disparities.

- Identify evidence-based genomic applications
- Inform and communicate
- Integrate into practice and programs

www.cdc.gov/genomics/
Public Health Genomics at CDC: A Brief History

- 1997: CDC Strategic Plan/Creation of OPHG
- 1998: First of 4 National Conferences
- 2001: Genomic Competencies for Public Health
- 2003: Model State Programs
- 2004: Family Health History Initiative
- 2004: EGAPP Initiative
- 2006: Seed Funding to CDC Programs
- 2012: New Plan with focus on 3 Conditions
- 2014: Advanced Molecular Detection
- 2014: Toolkit for Public Health, PHGKB
- 2016: Concept of “Precision Public Health”

Public Health Genomics at CDC: Publications 2012-2016

EGAPP and Public Health Genomics: No Shortcuts to Evidence-based Genomics!

The EGAPP initiative: lessons learned
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group

The Evaluation of Genomic Applications in Practice and Prevention Working Group was first convened in 2005 to develop and test evidence-based methods for the evaluation of genomic tests in transition from research to clinical and public health practice. Over the ensuing years, the Working Group has met 26 times, publishing eight recommendation statements, two methodological articles, and one outcomes paper, as well as planning and serving as technical experts on numerous associated systematic reviews. Evaluation of Genomic Applications in Practice and Prevention methods have evolved to address implications of the proliferation of genome-wide association studies and are currently expanding to face challenges expected from clinical implementation of whole genome sequencing tests. In this article, we review the work of the Evaluation of Genomic Applications in Practice and Prevention Working Group over the first 10 years of its existence with an emphasis on lessons learned throughout the process. It is hoped that in addition to the published methods of the Working Group, the lessons we have learned along the way will be informative to others involved in producing evidence and consumers of evidence-based guidelines in the field of genomics.

Keywords: evidence-based medicine; genetics; guidelines development; public health genomics; systematic review methods

The completion of the human genome project was heralded as the dawn of the era of genomic-based personalized medicine. Numerous factors, however, have complicated the translation of scientific findings into clinical genomic testing with measurable health outcomes. The responsible integration of genomics technology into medical care poses challenges to health-care providers, consumers, and other stakeholders. These emerging genomic applications to health care have been discovered by a sequestration of knowledge. In this article, we review the work of the Evaluation of Genomic Applications in Practice and Prevention Working Group over the first 10 years of its existence with an emphasis on lessons learned throughout the process. It is hoped that in addition to the published methods of the Working Group, the lessons we have learned along the way will be informative to others involved in producing evidence and consumers of evidence-based guidelines in the field of genomics.

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

Recent 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® maintained and updated by the National Institutes of Health, contained information on 49,537 tests conducted at 492 laboratories for 10,733 disease conditions involving 56,733 genes. These tests cover a wide variety of diseases, rare and common, for different types of applications such as diagnosis, treatment, and prevention.

For 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 and the Secretary’s Advisory Committee on Genetic Testing, made a number of recommendations to strengthen the evidence base for genomic medicine. Key elements of the discussions included the need to have answers to a number of scientific questions that are relevant to establishing the analytic validity of genetic 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 than ever.

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.” 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. The committee focused on clinical applications and utility of genetic tests and examined how evidence is generated, evaluated, and synthesized. The committee concluded that a new evidence framework for genetic testing is needed to address the rapid pace of advances in the field.
## 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
Newborn Screening Remains the Largest Public Health Genetics Program in the World

- More than 5 decades in the US started with PKU
- State run public health program that screens 4 million newborns every year
- Identifies more than 10,000 babies with 30+ genetic, metabolic & other disorders
- Complex system & policy issues (public health, healthcare, laboratories, costs, etc…)
- Residual blood spots have been used for other purposes

https://www.cdc.gov/newbornscreening/index.html
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
Selected Cancers Associated with Hereditary Cancer Syndromes

**HBOC Syndrome**
- **5% or approximately 22,000 cases of breast cancer each year**

**Lynch Syndrome**
- **3% or approximately 4,000 cases of colorectal cancer each year**
- **10% or approximately 2,000 cases of ovarian cancer each year**

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*


CDC Public Health Cancer Genomics Program

- Provides leadership and builds capacity for cancer genomics activities in state public health departments
  - Implement education, surveillance, and policy or systems change activities that will translate and implement national recommendations for cancer genomics

- Funded programs currently in five U.S. states
  - Colorado
  - Connecticut
  - Michigan
  - Oregon
  - Utah

CDC Awards Funding to Support Cancer Genomics. cdc.gov/cancer/breast/what_cdc_is_doing/genomics_foa.htm
Michigan Illustrates State Public Health Activities in Cancer Genomics

- Improved health outcomes and an enhanced quality of life for the people of Michigan through appropriate use of genetic information, technology, and services
- Increase availability of cancer-related genetic information to the Michigan public and decrease barriers to risk-appropriate services
Michigan Successes Related to BRCA Counseling Access and Referrals

Racial/ethnic and geographic disparities were present.
BRCA testing in young women with breast cancer: underutilization in Black and Hispanic women

Probability of BRCA testing (Hazard Ratio)

Race/ethnicity

Public Health Genomics and Health Disparities: Rural-Urban Disparities

BRCA Genetic Testing Among Women Aged 18-64 Years with Employer-Sponsored Health Insurance in Nonmetropolitan and Metropolitan Areas - United States, 2009-2014.

Kolor K et al, MMWR, September 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-care partnerships

Katherine Wilemon, President of The FH Foundation and her daughter

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

Priority Areas For Human Genomics in Public Health Practice for the Coming 5 Years

- Expanding and integrating the CDC tier 1 List
- Developing an evidence-based approach to genome sequencing in health systems
- Exploring pharmacogenomics as a tool for public health
- Exploring genomics as a tool for risk assessment and stratification to enhance screening and prevention for a wide variety of common diseases
- Developing a public health approach to rare diseases
- Preparing the workforce and the public
Ascertaining Persons with BRCA mutations and Lynch Syndrome using Current Evidence-based Guidelines Will Miss Most Cases Even with Cascade Testing

<table>
<thead>
<tr>
<th>BRCA</th>
<th>U.S. Population Estimates (2014)</th>
<th>Estimated Number with BRCA or Lynch</th>
<th>% Identified by Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>~ 82 Million women ages 30-69 years</td>
<td>200,000 estimated BRCA carriers</td>
<td>&lt; 50% identified by family history</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>~ 200 Million people ages 20-69 years</td>
<td>450,000 estimated w/ Lynch syndrome</td>
<td>&lt; 10% Identified by cascading</td>
</tr>
</tbody>
</table>

Kolor K et al, in preparation
Health Systems Partnerships for Appropriate Use of Population Wide Genome Sequencing and Measuring its Public Health Impact

We screen newborns, don’t we?: realizing the promise of public health genomics

James P. Evans, MD, PhD; Jonathan S. Berg, MD, PhD; Andrew F. Olishan, PhD; Terry Magnuson, PhD; and Barbara K. Rimer, DrPH

Genomics and public health have been uneasy bedfellows for some time. Most efforts to improve population health through genomic approaches have focused on the assessment of risks for common diseases, with the aim of tailoring interventions and screening. However, the improvement of population health through such an approach has remained elusive. Now, rapid progress in affordable, robust DNA sequencing offers a promising opportunity. By expanding the field’s focus from common to rare diseases, it may be possible to realize the promise of public health genomics by identifying those millions of individuals who unknowingly carry mutations that confer a dramatic predisposition to preventable diseases.

population health risks; medical interventions are usually most beneficial when identified disease risks and potential benefits are high. Finally, efforts that aim for genomic risk stratification are justified by the hope that simply informing individuals of their genetic risks for disease will induce beneficial behavioral changes. Thus far, this notion is largely contradicted by available evidence. Although we already know how to lower risks for most common diseases, getting populations to eat properly, exercise, and give up unhealthy behaviors, especially without major policy changes, is challenging, and there is little evidence to suggest that genetic tweaking of risk will meaningfully augment these efforts.

MyCode® results returned
533 patient-participants have received results*

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

December 1, 2017

<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>Hereditary breast and ovarian cancer</td>
<td>203</td>
<td>BRCA1</td>
<td>68</td>
</tr>
<tr>
<td>Familial hypercholesterolemia (early heart attacks and strokes)</td>
<td>86</td>
<td>APOB</td>
<td>31</td>
</tr>
<tr>
<td>Lynch syndrome (early colon, uterine and other cancers)</td>
<td>50</td>
<td>PMS2</td>
<td>18</td>
</tr>
<tr>
<td>Cardiovascular risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy (diseases of the heart muscle with dangerous complications)</td>
<td>52</td>
<td>MYH7</td>
<td>8</td>
</tr>
</tbody>
</table>

Evans J et al, Genetics in Medicine, 2013
Trivedi BP, Science, October 2017
Progress in Pharmacogenomics for Public Health Impact: Pockets of Success but Not Ready for Large Scale Implementation

J Abbasi, JAMA, 2016
Example of Genetic Risk Stratification: Can We Use Age and “Genetic Risk Scores” in 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)
Rare Diseases, Genomics and Public Health: A Growing Intersection

- A rare disease affects < 200,000 people
- > 7000 rare diseases; 25 million people in the US
- 4300 “genetic” conditions with known molecular basis
- The “diagnostic odyssey”: Genome sequencing yield 25-50%
- More and more therapies found
- Assessing population burden of disease
- Assurance of health care and prevention needs

Valdez R et al, Genetics in Medicine, 2017
Preparedness, Preparedness, Preparedness!!

Genomic Workforce Competencies 2001

Genomic competencies for the public health workforce at any level in any program

A public health worker is able to:

- Demonstrate basic knowledge of the role that genomics plays in the development of disease
- Identify the limits of his/her genomic expertise
- Make appropriate referrals to those with more genomic expertise

THANK YOU!

https://www.cdc.gov/genomics/translation/competencies/index.htm