From Precision Medicine to Precision Public Health: Challenges and Opportunities

Muin J. Khoury MD, PhD

CDC Office of Public Health Genomics
NCI Division of Cancer Control and Population Sciences
Outline

- Genomics, Precision Medicine and Public Health
- Multilevel Causation in the Era of Big Data
- Public Health Approach to Realizing Potential of Genomics and Precision Medicine
- From Precision Medicine to Precision Public Health
An emerging approach for disease prevention and treatment that takes into account people’s individual variations in genes, environment, and lifestyle.
Precision Medicine Initiative: Two Components: Cancer & National Cohort

NATIONAL CANCER INSTITUTE
PRECISION MEDICINE IN CANCER TREATMENT

Discovering unique therapies that treat an individual’s cancer based on the specific genetic abnormalities of that person’s tumor.

Patient Partnerships
EHRs
Technologies
Genomics
Data Science

The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine
National Precision Medicine Cohort: What is Early Success?

- “… a hypothetical 50 year woman with suboptimal diabetes control… Within 2 Years: enrolls, WGS, implant chip, smartphone, upload data-Using these data she changes her diet and medication dose…Within 5 Years: new drug based on molecular understanding of T2D, adjust dose to genotype”

- Francis Collins, NIH Director
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 contention for more than a century. This debate has taken on renewed importance as the scientific leadership at the National Institutes of Health (NIH), National Academy of Medicine, and U.S.

Seven Questions for Personalized Medicine

Personalized or precision medicine maintains that medical care and public health will be radically transformed by prevention and treatment programs more closely targeted to the individual patient. These interventions will be developed by sequencing more genomes, creating bigger biobanks, and linking biological information to health data in electronic medical records (EMRs) or obtained by monitoring technologies. Yet the assumptions underpinning personalized medicine have largely escaped questioning. In this Viewpoint, we seek to stimulate a more balanced debate by posing 7 questions for the advocates of personalized medicine.

Does the Human Genome Contribute to Disease Risk Prediction?

Personalized medicine builds on the Human Genome Project, which was forecasted to revolutionize disease risk prediction, with projected relative risks as high as 6 for gene variants linked to specific diseases. However, the relative risks for the vast majority of gene variants are offered enhanced screening and preemptive surgery. In the 25 years since BRCA1/2 was discovered, breast cancer mortality in the United States has declined by nearly one-third; however, little of this decline stems from the discovery of BRCA1/2. Moreover, BRCA1/2 is a unique story because the gene variants account for such a substantial amount of the variance in outcome for a limited number of patients.

In CF, 2 drugs (ivacaftor and lumacaftor) have recently been developed based on the CF transmembrane conductance regulator gene (CFTR), but they are useful only in patients with specific CFTR mutations, in whom they increase, singly or in combination, maximum forced expiratory volume (FEV1) by 5% to 10% and improve weight gain. However, since the discovery of this gene in the 1980s, CF survival has improved substantially as a result of strict adherence to clinical management guidelines originating in pulmonary physiology and infectious diseases, but not genomics.

Although well-deserved recognition has accompanied advances in precision medicine, these developments have also faced criticism for their cost, inequity, and potential for harm. In this Viewpoint, we ask whether personalized medicine can be made more inclusive and equitable, and whether countries can afford the costs.
Medicine & Public Health:
Health Impact Pyramid

Socioeconomic factors

Changing the context
To make individuals’ default decisions healthier

Long-lasting protective interventions

Clinical interventions

Counseling & education

Examples

Poverty, education, housing, inequality

Fluoridation, 0g trans fat, iodization, smoke-free laws

Immunizations, brief intervention, cessation of treatment, colonoscopy

Medication for high blood pressure, high cholesterol, diabetes

Eat healthy, be physically active

TR Frieden, AJPH 2010
Spectrum of Health & Strategies to Improve It: Personalized and Population Approaches

Fielding, J. E. et al. JAMA 2011;305:2110-2111
"Your Zip Code is More Important for Your Health than Your Genetic Code"

Living in the Southeast is bad for your health.

There is a huge range in the death rates across American states, driven by public policy, regional habits and socioeconomics, Tom Frieden, the director of the Centers for Disease Control and Prevention, said Thursday.

"Your longevity and health are more determined by your ZIP code than they are by..."
In the United States, the 5 leading causes of death are heart disease, cancer, chronic lower respiratory diseases, cerebrovascular diseases (stroke), and unintentional injuries. On May 2, 2014, the Centers for Disease Control and Prevention released an MMWR report on the annual number of potentially preventable deaths from these 5 causes in the United States. The data suggest that at least a third of those deaths every year are potentially preventable. The analysis compared the number of observed deaths in each state with an expected number that is based on average death rates for the three states with the lowest rates for each cause. States in the Southeast had the highest number of potentially preventable deaths. Therefore, potentially a large health impact may be achieved if states with higher rates were able to reduce the prevalence of risk factors for leading causes of death to the
Is Genomics Widening the Schism Between Medicine and Public Health

Posted on August 21, 2014 by Muin J Khoury, Director, Office of Public Health Genomics, Centers for Disease Control and Prevention

In 2007, we published a paper entitled: “Will genomics heal or widen the schism between medicine and public health?” We explored the long standing split between medicine and public health and how the emergence of genomics and other technologies can affect it. The “schism” was identified by Kerr White in his 1991 book in which he described a growing gap between individual- and population-based approaches to improving health in the 20th century. Kerr stated “today, the two cultures “medicine and “public health” seem to live in different, often unfriendly worlds”. Advances in genomics are fueled by the investigation of biological mechanisms of
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Big Data: From Association to Prediction

How about Causation?

- Association
- Replication
- Classification
- Prediction
- ?CAUSATION

- Does Big Data care about “Causation”?
- Intervention is based on cause-effect relationships
The Promises of Genomics & Big Data

Automated hypothesis generation

Computer says “try this”

A new type of software helps researchers decide what they should be looking for

Oct 4th 2014 | Santa Barbara | From the print edition

GIGO!!!
Causation, Ecologic Fallacies & Hubris
A Case Study: Searching for Needles in the Haystack- The CDC HuGE Navigator

http://www.hugenavigator.net/HuGENavigator/home.do
Text Mining Tool To Find HuGE Articles in Published Literature

- PubMed Signal/Noise ratio very low
- Support Vector Machine (SVM) tool generated in 2008
- Based on >3800 words in text, extensively validated
- Sensitivity & specificity >97%
- Since 2008, genetic epidemiology literature has changed considerably
- Performance of SVM model was significantly reduced (60%)
- In 2014, Retrained SVM now using > 4500 words pushed sensitivity and specificity to >90%

Yu W et al. BMC Bioinformatics, 2008
Application of Data Mining in the Prediction of Type 2 Diabetes in the United States

- 1999-2004 National Health and Nutrition Examination Survey
- Developed and validated SVM models for diabetes, undiagnosed diabetes & prediabetes using numerous variables in survey
- Discriminative abilities Using area under ROC curve of 84% and 73%
- Validated known risk factors for diabetes
- Not clear what best models, what best variables to use and how applicable to other populations
- Proof of concept only

Yu W et al. BMC Medical Informatics 2010
The Challenges of Reproducibility

Today's Random Medical News

From the New England Journal of Panic-Inducing Garbage

Can Cause
- Hypothermia
- A Feeling of Well-Being
- Sexual Intimacy
- Depression
- Glaucoma

In
- Two-Income Families
- Men 25-40
- More Weight Smokers
- Rats
- Twins
- Children
- Adults
- 7 out of 10 Women

According to a report released today...

Jim Borgman
The Cincinnati Enquirer
King Features Syndicate
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Genomics Translation: Beyond Bench to Bedside

What Does it Take?

- Exploring all types of applications beyond diagnostics & therapeutics, some may not be at “bedside”
- Having the evidence, policies, education, and resources to act
- The need for multidisciplinary research (basic, clinical and population sciences)
Emergence of “Public Health Genomics”

Multidisciplinary field concerned with the effective and responsible translation of genome-based knowledge and technologies to improve population health

Bellagio statement 2006

Populations, Prevention, Policy
The Expanded Genomics Translation: Research Cycle

- **Population Health**
- **Discovery**
- **Application**
- **Knowledge Integration**
- **Evidence based Recommendation or Policy**
- **Health care & Prevention Programs**
- **Evaluation**

- Basic, Clinical & Population Sciences  T0
- Development  T1
- Implementation Science  T3
- Effectiveness & Outcomes Research  T4
- Khoury MJ et al, AJPH, 2012
Horizon Scanning for Genomic Applications

ORIGINIAL RESEARCH ARTICLE

Horizon scanning for translational genomic research beyond bench to bedside

Mindy Clyne, Marta Gwi

Purpose: The dizzying increase in the number of genomic studies provide a method for horizonal research beyond bench implementation, and out

Methods: We compiled specific publications

<1% of all genomic research T2+

Genetic test or other health application indication

Risk assessment  Diagnostic  Therapeutic  Prognostic  Combination or other

Other  Cancer
A Public Health Approach to Realizing Promises of Genomics

1. Use a Strong Epidemiologic Foundation

- Human Genome Epidemiology: Beyond Gene Discovery
- Study Design - Value of Representative Cohorts
- Embedding RCTs in Observational Cohorts
- Analysis & Interpretation
- Dealing with Confounding
- Minimizing Biases
- Can be extended to big Data
Editorial

Cancer Epidemiology in the 21st Century

Note from the Editor-in-Chief: This is the first in a series of commentaries that have arisen from an initiative of the National Cancer Institute to advance epidemiological science in the 21st century

Transforming Epidemiology for 21st Century Medicine and Public Health

Muin J. Khoury1,5, Tram Kim Lam1, John P.A. Ioannidis6, Patricia Hartge2, Margaret R. Spitz7, Julie E. Buring8, Stephen J. Chanock2, Robert T. Croyle1, Katrina A. Goddard12, Geoffrey S. Ginsburg13, Zdenko Herceg14, Robert A. Hiatt15, Robert N. Hoover2, David J. Hunter10, Barnet S. Kramer3, Michael S. Lauer4, Jeffrey A. Meyerhardt9, Olufunmilayo I. Olopade16, Julie R. Palmer11, Thomas A. Sellers17, Daniela Seminara1, David F. Ransohoff18, Timothy R. Rebbeck19, Georgia Tourassi20, Deborah M. Winn1, Ann Zauber21, and Sheri D. Schully1

Abstract

In 2012, the National Cancer Institute (NCI) engaged the scientific community to provide a vision for cancer epidemiology in the 21st century. Eight overarching thematic recommendations, with proposed corresponding actions for consideration by funding agencies, professional societies, and the research community emerged from the collective intellectual discourse. The themes are (i) extending the reach of epidemiology beyond discovery and etiologic research to include multilevel analysis, intervention evaluation, implementation, and
# Epidemiology in the Era of Big Data

## Volume, Variety, Velocity

<table>
<thead>
<tr>
<th>Name</th>
<th>Meaning</th>
<th>Examples</th>
<th>Opportunities and Challenges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>Datasets with more observations</td>
<td>National electronic health record databases, social media datasets</td>
<td>Power to precisely measure unexpected associations, though potentially without substantive relevance</td>
</tr>
<tr>
<td>Variety</td>
<td>Datasets with variables from different sources; more variables per observation</td>
<td>-omics data, neighborhood data added to a phone survey</td>
<td>Capacity to assess complex interactions, but more complicated variable selection</td>
</tr>
<tr>
<td>Velocity</td>
<td>Data collected and analyzed in real time</td>
<td>Medication adherence intervention messaging adapted to subject response pattern</td>
<td>Potential to design dynamic interventions</td>
</tr>
</tbody>
</table>

Mooney S. et al, Epidemiology March 2015
A Public Health Approach to Realizing Promises of Genomics & Big Data

2. Develop a Robust Knowledge Integration Process
A Public Health Approach to Realizing Promises of Genomics & Big Data

2. Develop a Robust Knowledge Integration Process

Three articles in this issue of Genetics in Medicine describe examples of “knowledge integration,” involving methods for generating and synthesizing rapidly emerging information on health-related genomic technologies and engaging stakeholders around the evidence. Knowledge integration, the central process in translating genomic research, involves three closely related, iterative components: knowledge management, knowledge synthesis, and knowledge translation. Knowledge management is the ongoing process of obtaining, organizing, and displaying evolving evidence. For example, horizon scanning and “infoveillance” use emerging technologies to scan databases, registries, publications, and cyberspace for information on genomic applications. Knowledge synthesis is the process of conducting systematic reviews using a priori rules of evidence. For example, methods including meta-analysis, decision analysis, and modeling can be used to combine information from basic, clinical, and population research. Knowledge translation refers to stakeholder engagement and brokering to influence policy, guidelines and recommendations, as well as the research agenda to close knowledge gaps. The ultrarapid production of information requires adequate public and private resources for knowledge integration to support the evidence-based development of genomic medicine.

Key Words: evidence-based medicine; genomic medicine; knowledge integration; management; synthesis; translation
Clinical Genome Resource (ClinGen)

ClinGen
Launched in 2013 and supported by the National Institutes of Health, ClinGen is intended to be an authoritative central resource that defines the clinical relevance of genomic variants for use in precision medicine and research.

Critical Questions of the Program
- Is this gene associated with a disease? *Clinical validity*
- Is this variant causative? *Pathogenicity*
- Is this information actionable? *Clinical usefulness*

Building a Genomic Knowledge Base
ClinVar and Other Resources
ClinGen is developing several resources for the community. The first is ClinVar, which is a database at the National Center for Biotechnology Information that archives information submitted about variants with medical relevance. It is an integral part of ClinGen and serves as its public portal for the deposition and retrieval of variants and the interpretation of their clinical significance.

Improved Patient Care through Genomic Medicine

3. Use (and not avoid) Principles of Evidence-based Medicine and Population Screening

Schully et al, Genet Med 2014

Evidence synthesis and guideline development in genomic medicine: current status and future prospects

Sheri D. Schully, PhD, Tram Kim Lam, PhD, MPH, W. David Dotson, PhD, Christine Q. Chang, MPH, Naomi Aronson, PhD, Marian L. Birkeland, PhD, Stephanie Jo Brewster, MS, Stefania Bocci, PhD, Adam H. Buchanan, MS, Ned Calonge, MD, MPH, Kathleen Galzone, MSN, RN, Benjamin Djulbegovic, MD, PhD, Katrina A. Goddard, PhD, Roger D. Klein, MD, Teri E. Klein, PhD, Joseph Lau, MD, Rochelle Long, PhD, Gary H. Lyman, MD, MPH, Rebecca L. Morgan, MPH, Christina G.S. Palmer, CGC, PhD, Mary V. Relling, PharmD, Wendy S. Rubinstein, MD, PhD, Jesse J. Swen, PharmD, PhD, Sharon F. Terry, MA, Marc S. Williams, MD, FAAP, FACMG and Muin J. Khoury, MD, PhD.

Purpose: With the accelerated implementation of genomic medicine, healthcare providers will depend heavily on professional guidelines and recommendations. Because genomics affects many diseases across the lifespan, no single professional group covers the entirety of this rapidly developing field.

Methods: To pursue a discussion of the minimal elements needed to develop evidence-based guidelines in genomics, the Centers for Disease Control and Prevention and the National Cancer Institute jointly held a workshop to engage representatives from 35 organizations with interest in genomics (13 of which make recommendations). The workshop explored methods used in evidence synthesis and guideline development and initiated a dialogue to compare these methods and to assess whether they are consistent with the Institute of Medicine report “Clinical Practice Guidelines We Can Trust.”

Results: The participating organizations that develop guidelines or recommendations all had policies to manage guideline development and group membership, and processes to address conflicts of interest. However, there was wide variation in the reliance on external reviews, regular updating of recommendations, and use of systematic reviews to assess the strength of scientific evidence.

Conclusion: Ongoing efforts are required to establish criteria for guideline development in genomic medicine as proposed by the Institute of Medicine.

Key Words: evidence synthesis, genomic medicine; guideline development
‘The Scientific Method Itself is Growing Obsolete.’ (A. Butte, Sep 2014)

How can big data change science?
Here's how medical research traditionally works:

1. Come up with a question or hypothesis.
2. Design an experiment to test it. Wait for new data to come in.
3. Form your conclusion.

Big data changes step 2:
Online, searchable databases provide instant answers, speeding up research.

- Medical records
- Health apps
- Genetics tests
- Lab tests
- Wearables
- Census

“..implicit assumption that big data are a substitute for, rather than a supplement to, traditional data collection and analysis.”

CDC-Sponsored EGAPP Working Group

• Independent, multidisciplinary, non-federal panel established in 2004
• Established a systematic, evidence-based process to assess validity & utility of genomic tests & family health history applications.
  • New methods for evidence synthesis and modeling in 2013, including next generation sequencing and stratified cancer screening based on family history
• 10 recommendation statements to date:
  • Colorectal cancer, breast cancer, heart disease, clotting disorders, depression, prostate cancer, diabetes, and more
• Clinical Validity vs Clinical Utility
• Uncovered evidence gaps that require additional research
• Principles can be applied to other “Big Data”
### Assessment of Tests by Type of Application: Clinical Validity & Utility

<table>
<thead>
<tr>
<th>Application of test</th>
<th>Clinical validity</th>
<th>Clinical utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis (symptomatic patient)</td>
<td>Association of marker with disorder</td>
<td>Improved clinical outcomes(^a)—health outcomes based on diagnosis and subsequent intervention or treatment</td>
</tr>
<tr>
<td>Disease screening (asymptomatic patient)</td>
<td>Association of marker with disorder</td>
<td>Availability of information useful for personal or clinical decision-making</td>
</tr>
<tr>
<td>Risk assessment/susceptibility</td>
<td>Association of marker with future disorder (consider possible effect of penetrance)</td>
<td>End of diagnostic odyssey</td>
</tr>
<tr>
<td>Prognosis of diagnosed disease</td>
<td>Association of marker with natural history benchmarks of the disorder</td>
<td>Improved health outcomes based on prevention or early detection strategies</td>
</tr>
<tr>
<td>Predicting treatment response or adverse events (pharmacogenomics)</td>
<td>Association of marker with a phenotype/metabolic state that relates to drug efficacy or adverse drug reactions</td>
<td>Improved health outcomes or adherence based on drug selection or dosage</td>
</tr>
</tbody>
</table>

\(^a\)Clinical outcomes are the net health benefit (benefits and harms) for the patients and/or population in which the test is used.
# Evidence-based Classification of Genomic Applications in Practice

<table>
<thead>
<tr>
<th>Tier 1 (Green)</th>
<th>Tier 2 (Yellow)</th>
<th>Tier 3 (Red)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA label requires use of test to inform choice or dose of a drug</td>
<td>FDA label mentions biomarker*</td>
<td>FDA label cautions against use</td>
</tr>
<tr>
<td>CMS covers testing</td>
<td>CMS coverage with evidence development</td>
<td>CMS decision against coverage</td>
</tr>
<tr>
<td>Clinical practice guideline based on systematic review supports testing</td>
<td>Clinical practice guideline, not based on systematic review, supports use of test</td>
<td>Clinical practice guideline recommends against use of test</td>
</tr>
<tr>
<td></td>
<td>Clinical practice guideline finds insufficient evidence but does not discourage use of test</td>
<td>Clinical practice guideline finds insufficient evidence and discourages use of test</td>
</tr>
<tr>
<td></td>
<td>Systematic review, without clinical practice guideline, supports use of test</td>
<td>Systematic review recommends against use</td>
</tr>
<tr>
<td></td>
<td>Systematic review finds insufficient evidence but does not discourage use of test</td>
<td>Systematic review finds insufficient evidence and discourages use</td>
</tr>
<tr>
<td></td>
<td>Clinical practice guideline recommends dosage adjustment, but does not address testing</td>
<td>Evidence available only from published studies without systematic reviews, clinical practice guidelines, FDA label or CMS labels coverage decision</td>
</tr>
</tbody>
</table>

*Can be reassigned to Green or Red if one or more conditions in these categories apply

A Public Health Approach to Realizing Promises of Genomics & Big Data

- 4. Develop a Robust Translational Research Agenda beyond Bench to Bedside

Khoury et al., Genet Med 2009

Table 3 Multidisciplinary research needed for evaluating personal genomics to improve health and prevent disease

<table>
<thead>
<tr>
<th>Field</th>
<th>Scientific research</th>
<th>Current issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Genotype prevalence, calculating risks associated with genetic variants, gene–gene, and gene environment interactions</td>
<td>Data currently lacking on magnitudes of risks especially for joint effects of genes and environment</td>
</tr>
<tr>
<td>Clinical evaluation</td>
<td>Quantify added value of personal genomics in reclassifying risks compared traditional risk factors</td>
<td>Data currently suggest weak discriminatory ability of personal genomics compared with other factors. It is not yet clear what are the net health benefits versus harms in using personal genomics in prevention and clinical care</td>
</tr>
<tr>
<td>Behavioral and social sciences</td>
<td>Assess how genome profiles affect behavior of individuals, families and populations</td>
<td>Data from other fields suggest that behavior change is difficult. It is not clear if genome information matters</td>
</tr>
<tr>
<td>Communication sciences</td>
<td>Study communication and education strategies for using genomic information to improve health</td>
<td>Provider and consumers are not equipped to deal with this type of information</td>
</tr>
<tr>
<td>Health services research &amp; Public health surveillance</td>
<td>Assess impact of genome info health outcomes in the real world, health disparities, and economic indicators</td>
<td>Expensive technology when applied in populations; unknown health benefits and potential harms</td>
</tr>
</tbody>
</table>
A Public Health Approach to Realizing Promises of Genomics & Big Data
(Hint: Use Implementation Science)

Genomics and Health Impact Blog

Precision Medicine, Implementation Science and Public Health: How Do We Scale Up From 1 Million to 300 Million?

Posted on August 24, 2015 by Muin J Khoury, Director, Office of Public Health Genomics, Centers for Disease Control and Prevention

Planning for the 2015 Presidential Precision Medicine Initiative is in full swing. After the initial announcement in January 2015, several workshops were held to help in design and execution of the longitudinal cohort study of 1 million persons. The workshops covered important topics including a Building a Precision Medicine Research Cohort, Scientific Opportunities, Digital Health Data, Participant Engagement and Health Equity, and Mobile and Personal Technologies.

If the vision of precision medicine is to have our genome sequence available for use in disease prevention and health care, we have a unique opportunity through this initiative not only to make new discoveries but to learn how to implement and scale up this endeavor from where we are now to a million person cohort, and ultimately 300 million people. Can we build an infrastructure that can support both scientific discoveries and scalable implementation at a national level? Can we design a million person cohort that allows us to learn from the interaction of individuals in the cohort with families, communities, health care systems, public health and policy contexts? There are two key components to ensure long term success of a precision medicine cohort: implementation science and public health-healthcare partnerships.
Selected Emerging Tier 1 Genomic Applications

- Hereditary Breast and Ovarian Cancer (BRCA)
  - USPSTF 2013

- Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)
  - EGAPP 2009

- Familial Hypercholesterolemia
  - NICE 2008
Selected Tier 1 Genomic Applications: What’s in Common?

- Autosomal dominant disorders with adult onset
- Relatively common (collectively 2 million people in the USA)
- Most not ascertained or managed by health care
- Effective interventions that reduce mortality
- Evidence based recommendations
- Involves family history and cascading interventions
- Can be integrated into public health programs (Cancer and Heart Disease Programs)
- Could serve as models for similar genomic applications
Underutilization of BRCA1/2 testing to guide breast cancer treatment: Black and Hispanic women particularly at risk

Douglas E. Levy, PhD1,2,3, Stacey D. Byfield, PhD, MPH4, Catherine B. Comstock, MPH5, Judy E. Garber, MD, MPH3,6, Sapna Syngal, MD, MPH3,6,7, William H. Crown, PhD4, and Alexandra E. Shields, PhD1,2,3

**Purpose:** Women with early-onset (age ≤40 years) breast cancer are at high risk of carrying deleterious mutations in the BRCA1/2 genes; genetic assessment is thus recommended. Knowledge of BRCA1/2 mutation status is useful in guiding treatment decisions. To date, there has been no national study of BRCA1/2 testing among newly diagnosed women. **Methods:** We used administrative data (2004–2007) from a national sample of 14.4 million commercially insured patients to identify newly diagnosed, early-onset breast cancer cases among women aged 20–40 years (n = 1474). Cox models assessed BRCA1/2 testing, adjusting for covariates and differential lengths of follow-up. **Results:** Overall, 30% of women aged 40 years or younger received BRCA1/2 testing. In adjusted analyses, women of Jewish ethnicity were significantly more likely to be tested (hazard ratio = 2.83, 95% confidence to assess risk of hereditary breast and ovarian cancer (HBOC) is among the most established genetic tests in clinical use.1–3 Guidelines and commercial testing for BRCA1/2 mutations have been available for more than a decade,4 and most health insurers now reimburse at least partially for these tests in individuals at high risk for mutations.5 National guidelines recommend that women diagnosed with early-onset breast cancer receive BRCA1/2 testing to guide treatment decisions.6 Among patients newly diagnosed with cancer, a positive test result will often prompt more aggressive surgical treatment (e.g., bilateral salpingo oophorectomy or prophylactic contralateral mastectomy) with the goal of minimizing the potential for second primary cancers.3,7,8 A positive test result may also prompt consideration...
Cost-effectiveness of Universal BRCA1/2 Screening Evidence-Based Decision Making

Elisa F. Long, PhD
Anderson School of Management, University of California, Los Angeles.

Of the 233,000 breast cancers diagnosed annually in the United States, 5% to 10% are attributable to mutations in the BRCA1 or BRCA2 genes.1 Breast cancers in BRCA mutation carriers are characterized by younger age at onset, bilateral occurrence, and more aggressive behavior. In contrast, screening women of Ashkenazi Jewish descent—among whom 1 out of every 50 women carries a mutation—generates cost savings with Myriad’s less expensive test for 3 founder mutations. Another study3 has shown similarly favorable cost-effectiveness estimates.

Table. Cost-effectivenessa of Breast Cancer Testing Strategies in the United States

<table>
<thead>
<tr>
<th>Source</th>
<th>Testing Strategy</th>
<th>Age Range of Female Population, y, and Risk Factor</th>
<th>Cost-effectiveness Ratio ($/QALY), $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plevritis et al,5 2006</td>
<td>Annual mammography</td>
<td>25-69, BRCA1&lt;br&gt;25-69, BRCA2</td>
<td>19,000&lt;br&gt;28,400</td>
</tr>
<tr>
<td></td>
<td>Annual mammography + MRI</td>
<td>35-54, BRCA1&lt;br&gt;35-54, BRCA2</td>
<td>55,400&lt;br&gt;130,700</td>
</tr>
<tr>
<td></td>
<td>Semiannual mammography + MRI</td>
<td>35-54, BRCA1&lt;br&gt;35-54, BRCA2</td>
<td>176,400&lt;br&gt;481,800</td>
</tr>
<tr>
<td>Grann et al,4 2011</td>
<td>Annual mammography</td>
<td>30-65, BRCA2</td>
<td>88,100</td>
</tr>
<tr>
<td></td>
<td>Annual mammography + MRI</td>
<td>30-65, BRCA2</td>
<td>247,600</td>
</tr>
<tr>
<td>Schousboe et al,6 2011</td>
<td>Biennial mammography</td>
<td>40-49, BI-RADS 1-2&lt;br&gt;40-49, BI-RADS 3-4</td>
<td>140,000-362,700&lt;br&gt;74,500-87,800</td>
</tr>
<tr>
<td></td>
<td>Annual mammography</td>
<td>50-79, BI-RADS 1-2&lt;br&gt;50-79, BI-RADS 3-4</td>
<td>63,700-208,700&lt;br&gt;21,400-51,000</td>
</tr>
<tr>
<td>Moore et al,7 2009</td>
<td>Annual MRI</td>
<td>High-risk women</td>
<td>179,600</td>
</tr>
<tr>
<td>Current study</td>
<td>BRCA mutation screening</td>
<td>&gt;30, Universal&lt;br&gt;30, Universal&lt;br&gt;30, Ashkenazi Jewish</td>
<td>1.7 million (Myriad)&lt;br&gt;920,000 (Ambry Genetics)&lt;br&gt;53,000 (Color Genomics)&lt;br&gt;Cost-saving</td>
</tr>
</tbody>
</table>

Abbreviations: BI-RADS, Breast Imaging-Reporting and Data System category; MRI, magnetic resonance imaging; QALY, quality-adjusted life-year.

a Incremental cost-effectiveness ratios are relative to the comparator strategy; cost-saving implies that the strategy increases QALYs while saving money.
“The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group found sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer (CRC) to reduce morbidity and mortality in relatives.
Implementing screening for Lynch syndrome among patients with newly diagnosed with colorectal cancer: Summary of a public health/clinical collaborative meeting

Cecelia A. Bellcross, PhD, MS\textsuperscript{1,2}, Sara R. Bedrosian, BA, BFA\textsuperscript{1}, Elvan Daniels, MD, MPH\textsuperscript{3}, Debra Duquette, MS\textsuperscript{4}, Heather Hampel, MS\textsuperscript{5}, Kory Jasperson, MS\textsuperscript{6}, Djenaba A. Joseph, MD, MPH\textsuperscript{7}, Celia Kaye, MD, PhD\textsuperscript{8}, Ira Lubin, PhD\textsuperscript{9}, Laurence J. Meyer, PhD, MD\textsuperscript{10}, Michele Reyes, PhD, MS\textsuperscript{1}, Maren T. Scheunener, MD, MPH\textsuperscript{11}, Sheri D. Schully, PhD\textsuperscript{12}, Leigha Senter, MS\textsuperscript{5}, Sherri L. Stewart, PhD\textsuperscript{7}, Jeanette St. Pierre, MA, MPH\textsuperscript{1}, Judith Westman, MD\textsuperscript{5}, Paul Wise, MD\textsuperscript{13}, Vincent W. Yang, MD, PhD\textsuperscript{14}, and Muin J. Khoury, MD, PhD\textsuperscript{1}

Abstract: Lynch syndrome is the most common cause of inherited colorectal cancer, accounting for approximately 3\% of all colorectal cancer cases in the United States. In 2009, an evidence-based review process conducted by the independent Evaluation of Genomic Applications in Practice and Prevention Working Group resulted in a recommendation to offer genetic testing for Lynch syndrome to all individuals with newly diagnosed colorectal cancer, with the intent of reducing morbidity and mortality in family members. To explore issues surrounding implementation of population-level programs for evidence-based genomic medicine applications involving follow-up testing of at-risk relatives. Such endeavors will require multilevel and multidisciplinary approaches building on collaborative public health and clinical partnerships. Genet Med 2011:XX(X):000–000.

Key Words: genetic screening, colorectal cancer, Lynch syndrome, HNPCC, genetic testing
Cascade genetic testing in Lynch syndrome: room for improvement

Kory Jasperson

Genetic testing in relatives of individuals with Lynch syndrome is of utmost importance for targeted screening and prevention. A recent systematic review suggests that the uptake of testing in at-risk relatives is inadequate and therefore the cost-effectiveness of Lynch syndrome testing is questionable. The results:

The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Work Group (EWG) in 2009 established that there was “sufficient evidence to recommend offering genetic testing for Lynch syndrome to individuals with newly diagnosed colorectal cancer.”

Population-Based Universal Screening for Lynch Syndrome: Ready, Set… How?

Joanne Ngeow and Charis Eng, Cleveland Clinic Genomic Medicine Institute, Cleveland, OH

See accompanying article on page 2554

Although the fields of health care and public health have many evidence-based innovations, the failure to implement health interventions that have been rigorously demonstrated to be cost effective hampers health care delivery. The identification of individuals who are at increased risk of hereditary cancer allows for the possibility of heightened surveillance and early cancer detection, resulting in decreased disease-specific mortality. Such data-driven identification and risk stratification to guide management is one of the foundations of value-based health care delivery. However, it is not always easy to identify those in the general population who may be at increased risk of hereditary colorectal cancer (CRC). The Genetic Counselors’ Oncology Network (GCON) was formed in 2004 to identify and provide resources to inherited cancer syndrome genes.

Ngs deficiency, defined as the presence of microsatellite instability (MSI) or loss of MMR protein expression (detected via immunohistochemistry [IHC]), which are the cellular hallmarks of this disorder. Ward et al explored a population-based approach by including all incident CRCs that were identified within their catchment area of 1.2 million residents in New South Wales, Australia. The study consisted of two phases. In the first phase, without obtaining patient consent, they identified all MMR-deficient cancers by IHC and assigned an a priori likelihood for LS as either low (both MLH1 loss and BRAF mutation) or high (all other cancers). Recommendations were sent to the treating physicians.
Making Universal Screening for Lynch Syndrome a Reality: The Lynch Syndrome Screening Network

Categories: colorectal cancer, genomics

March 22nd, 2012 11:35 am ET - Guest Blogger

Deb Duquette, MS, CGC, Sarah Mange, MPH- Michigan Department of Community Health
Cecelia Belcross, PhD, MS- Emory University
Heather Hampel, MS, CGC- The Ohio State University
Kory Jasperson, MS, CGC- Huntsman Cancer Institute

Authors are all from the Lynch Syndrome Screening Network (LSSN) Founding Board of Directors

Every day, about 400 people in the United States are diagnosed with colorectal cancer. Approximately twelve of them have Lynch syndrome, a hereditary condition that increases the risk of colorectal cancer and other cancers. Identifying people with Lynch syndrome could have substantial health
Outline

- Genomics, Precision Medicine and Public Health
- Multilevel Causation in the Era of Big Data
- Public Health Approach to Realizing Potential of Genomics and Precision Medicine
- From Precision Medicine to Precision Public Health
A New Era of “Precision Public Health”: It’s Not Just Genomics and Treatment!

- Targeting Prevention Efforts
- Pathogen Genomics
- Modernizing Surveillance, Informatics & Epidemiology
The Promises of Genomics & Big Data

- **Targeted Screening & Prevention**

<table>
<thead>
<tr>
<th>Routine/Guideline</th>
<th>When Introduced</th>
<th>When It Should Be Discontinued/Superseded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap Smear</td>
<td>1940s</td>
<td>2014</td>
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<tr>
<td>PSA</td>
<td>1987</td>
<td>2013</td>
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<tr>
<td>Mammography</td>
<td>1967</td>
<td>2014</td>
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<tr>
<td>Standard Prenatal Aneuploidy Screening</td>
<td>1970s</td>
<td>2014</td>
</tr>
<tr>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
<td>1952</td>
<td>2013</td>
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<tr>
<td>Annual Checkup</td>
<td>1920s</td>
<td>2013</td>
</tr>
<tr>
<td>Pelvic Exam</td>
<td>1940s</td>
<td>2014</td>
</tr>
<tr>
<td>Low Sodium Diet &lt; 2 mg</td>
<td>1980</td>
<td>2014</td>
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</table>

Population medicine: let’s get over it (E. Topol)

Nobody is average but the question is what to do about it?

Nobody is average but what to do about it? The challenge of individualized disease prevention based on genomics

Posted on July 2, 2014 by Muin J Khoury, Director, Office of Public Health Genomics, Centers for Disease Control and Prevention

Each week, Garrison Keillor shares with National Public Radio listeners the latest news from Lake Wobegon where "all the women are strong, all the men are good looking, and all the children are above average." The concept of "average" is deeply rooted in our scientific analysis of all health related traits such as height, weight and health indicators (such as blood sugar, cholesterol) and in assessing the likelihood of developing disease. There are several ways to measure average such as mean, median and mode that reflect different aspects of central tendency in a population.
Toward Risk-tailored Precision Screening

Risk-assessment
(using age, family history, genetic profile, etc.)

Q. What factors to include?

Stratify population into several groups

Q. How many?
Q. What thresholds?

Tailor screening to each risk group
(different screening modality, age for start / end of screening, inter-screening interval)

Q. Which interventions work for different risk groups?

Diagram adapted from: Burton et al. IJPH 2012: 9(4)

From N Pashayan
Genetic Susceptibility to Breast Cancer

- Common low penetrance variants, (currently known 94 loci), explain ~15% of excess Familial Relative Risk (FRR)
- Subtype specific

- Rare high penetrance alleles in BRCA1 and BRCA2 explain ~15% of FRR
- Rare moderate penetrance alleles in TP53, LKB1, CDH1, PTEN, BRIP1, PALB2, ATM and CHEK2 explain ~ 6% of the FRR

From N Pashayan
Age and Polygenic Score in Breast Cancer Screening?

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

- **Reference:** 2.5% 10-year absolute risk for developing breast cancer corresponds to risk of UK women aged 47, i.e. age of invitation to the UK NHS Breast Screening programme.

Mavaddat et al. JNCI 2015: 107(5): djv036

From N Pashayan
**Pathogen Genomics: CDC Advanced Molecular Detection Initiative**

Advanced Molecular Detection (AMD)

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**Un-locking the promise of technology to protect Americans**

---

Using molecular technologies to counter infections in patients and populations

<table>
<thead>
<tr>
<th>Application</th>
<th>Patient care</th>
<th>Public health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen identification</td>
<td>Rapid diagnosis</td>
<td>Outbreak detection</td>
</tr>
<tr>
<td>Antibiotic selection</td>
<td>Proper treatment</td>
<td>Effective antibiotic use guidelines</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Better protection</td>
<td>Reduced burden of disease</td>
</tr>
</tbody>
</table>
~48 million foodborne illnesses occur in the U.S. each year, resulting in ~128,000 hospital admissions and 3,000 deaths

Although most cases occur as part of unrecognized outbreaks, >1,000 outbreaks are reported each year

PulseNet, a national network of public health and food regulatory agency laboratories, has played a key role in identifying and stopping foodborne illness outbreaks

Pathogens/foods linked to most foodborne illnesses
- *Campylobacter* (poultry)
- *E. coli* O157 (ground beef, leafy greens, raw milk)
- *Listeria* (deli meats, unpasteurized soft cheeses, produce)
- *Salmonella* (eggs, poultry, meat, produce)
- *Vibrio* (raw oysters)
- *Norovirus* (common in many foods)
- *Toxoplasma* (meats)

From R. Khabbaz
Nationwide Listeriosis Surveillance Using WGS

- Collaboration with:
  - Federal Agencies – FDA, NCBI, USDA
  - All state public health laboratories
  - France, UK, Denmark, Australia, and Canada

- Analysis of all U.S. clinical cases of *Listeria monocytogenes* infection and some food/environmental sources

- Provides foundational infrastructure and methods for next generation PulseNet and a generalizable platform for genome-scale molecular epidemiologic surveillance


From R. Khabbaz
Listeria WGS

- **1718** patient isolates and **2495** food and environmental isolates sequenced as of Sept 22, 2015

- Compared with PFGE, WGS
  - Detected clusters faster and sped investigations
  - Excluded cases from PFGE clusters
  - Included isolates with different PFGE patterns in same cluster
  - Identified clusters not detected by PFGE
  - Strongly linked patient isolates with food and environmental isolates

- Successful pilot demonstrates WGS eventually can replace PFGE

From R. Khabbaz
Listeria Cluster Metrics Pre/Post WGS

From R. Khabbaz
Improving Precision in Public Health Surveillance
(Cancer SEER Program)

A
HR+/HER2-

B
Triple-negative

C
HR+/HER2+

D
HR-/HER2+

## Improving Disease Classification in Population Surveillance

- **Colorectal Cancer Consensus Classification**

<table>
<thead>
<tr>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI immune</td>
<td>Canonical</td>
<td>Metabolic</td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>14%</td>
<td>37%</td>
<td>13%</td>
<td>23%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Feature</th>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI, CIMP high, hypermutation</td>
<td>SCNA high</td>
<td>Mixed MSI status, SCNA low, CIMP low</td>
<td>SCNA high</td>
<td></td>
</tr>
<tr>
<td>BRAF mutations</td>
<td></td>
<td>KRAS mutations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune infiltration and activation</td>
<td>WNT and MYC activation</td>
<td>Metabolic deregulation</td>
<td>Stromal infiltration, TGF-β activation, angiogenesis</td>
<td></td>
</tr>
<tr>
<td>Worse survival after relapse</td>
<td></td>
<td></td>
<td>Worse relapse-free and overall survival</td>
<td></td>
</tr>
</tbody>
</table>
“As cholera swept through London in the mid-19th century, a physician named John Snow painstakingly drew a paper map indicating clusters of homes where the deadly waterborne infection had struck. In an iconic feat in public health history, he implicated the Broad Street pump as the source of the scourge—a founding event in modern epidemiology. Today, Snow might have crunched GPS information and disease prevalence data and solved the problem within hours”
Health Impact Pyramid for Genomics: Public Health-Healthcare Collaborations

- Socioeconomic factors
  - ELSI
  - Public health Programs
  - Clinical Interventions
  - Public Education

Examples

- Genomic health literacy
- Pharmacogenomics, diagnostics
- Population screening, infectious disease control
- Policies on protection, sharing, disparities, access etc
- Nonmedical uses of genomics
Summary

- Genomics, Precision Medicine and Public Health
  - Individual vs Population Approaches are Complementary, Not Competitive

- Big Data and Causation in the Era of Genomics
  - It’s Complicated!

- Public Health Approach to Realizing Potential of Genomics and Precision Medicine
  - Extending the Translation Continuum, Public Health-Healthcare Partnerships

- From Precision Medicine to Precision Public Health
  - Modernizing public health assessment & intervention