Implementation of Genomic Medicine: 
A Public Health Approach

Muin J. Khoury MD, PhD
Office of Public Health Genomics, CDC
Outline

- What’s public health got to do with genomic medicine?
- Public health genomics: 15 years on
- What are the priorities for public health genomics, 2012-2017?
What is Public Health?

“An effort organized by society to protect, promote, and restore the people’s health”

3 Essential Functions

- Assessment
- Policy Development
- Assurance
CDC Priorities

- Improving health security at home and around the world
- Better preventing the leading causes of illness, injury, disability, and death
- Strengthening public health – health care collaboration
CDC “Winnable Battles”: 6 key areas where public health can have a substantial impact

- Tobacco
- Obesity, Nutrition, Physical Activity and Food Safety
- Healthcare-Associated Infections
- Motor Vehicle Injuries
- Teen and Unintended Pregnancy
- HIV
Public Health Assessment Function

What Gets Measured Gets Done: Genomics, Surveillance Indicators and Healthy People 2020

Categories: genomics

September 13th, 2012 3:00 pm ET - Muin J Khoury, Director, Office of Public Health Genomics, Centers for Disease Control and Prevention
Katherine Kolor, Office of Public Health Genomics, Centers for Disease Control and Prevention

Public health surveillance indicators, such as those developed for the Healthy People initiative are useful for monitoring the development of genomic medicine in the United States. For several decades, Healthy People has established health benchmarks that are considered important metrics for tracking progress in health and healthcare in the United States.

The Healthy People objectives adopted in 2010 (HP 2020) introduced a new topic area to address the use of genomic testing in clinical and public health practice. HP 2020 includes two objectives related to genetic counseling and testing for hereditary cancer syndromes.

“The single most important thing that Public Health can do is to increase the degree to which decisions are made using good data” Tom Frieden, Jan 1, 2010
The best research will not save lives if it’s not used...we have to invest in programs”

Tom Frieden, CDC Director, May 2013
Outline

- What’s public health got to do with genomic medicine?
- Public health genomics 15 years on
- What are the priorities for public health genomics, 2012-2017?
CDC Public Health Genomics Movement

- 1997- Office of Public Health Genomics
- 1998- First National Conference
- 2000- Genomic Competencies for Public Health
- 2001- “Model” State Public Health Programs
- 2002- Family History Public Health Initiative
- 2003- NHANES Genomics initiative
- 2005- EGAPP Initiative
- 2006- GRaPHInt global public health genomics
- 2008- Model Translation Research and Programs
- 2009- GAPPNNet collaboration
- 2010- Fourth National Conference
- 2011- A New Beginning
The Public Health Genomics Model for Genomics Implementation

- Bench (base pairs, etc)
- Bedside (promising tests and interventions)
- Population Health
- Healthcare Systems & Prevention Programs
- Evidence based Recommendation or Policy
- Knowledge Integration

Development

T1

Discovery
T0

Evaluation
T2

Implementation
T3

Effectiveness & Outcomes
T4

Khoury MJ et al, AJPH, 2012
Limited Translational Research in Genomics: Beyond Bench to Bedside

2% of published genomics research in T2 – T4

Multiple clinical and population scientific disciplines involved

Translational Research in Cancer Genetics: The Road Less Traveled


Division of Cancer Control and Population Sciences and Office of Workforce Development, National Cancer Institute, Bethesda, Md., Division of Etiology, Department of Population Sciences, City of Hope, Duarte, Calif., and Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, Ga.
Utilization of epidermal growth factor receptor (EGFR) testing in the United States: a case study of T3 translational research

Julie A. Lynch, PhD, RN¹,², Muin J. Khoury, MD, PhD², Ann Borzecki, MD, MPH³, Jerry Cromwell, PhD⁴, Laura L. Hayman, PhD, RN⁵, Pat Reid Ponte, D.N.Sc., RN⁶, Glenn A. Miller, PhD⁷,⁸ and Christopher S. Lathan, MD, MPH⁶

Purpose: We examined hospital use of the epidermal growth factor receptor assay in patients with lung cancer in the United States. Our goal was to inform the development of a model to predict phase 3 translation of guideline-directed molecular diagnostic tests.

Methods: This was a retrospective observational study. Using logistic regression, we analyzed the association between hospitals’ institutional and regional characteristics and the likelihood that an epidermal growth factor receptor assay would be ordered.

Results: Significant institutional predictors included affiliation with an academic medical center (odds ratio, 1.48; 95% confidence interval, 1.20–1.83), participation in a National Cancer Institute clinical research cooperative group (odds ratio, 2.66, 1.66–2.55), and availability of positron emission tomography scan (odds ratio, 1.44, 1.07–1.94) and cardiothoracic surgery (odds ratio, 1.90, 1.52–2.37) services. Significant regional predictors included metropolitan county (odds ratio, 2.08, 1.48–2.91), population with above-average education (odds ratio, 1.46, 1.09–1.96), and population with above-average income (odds ratio, 1.46, 1.04–2.05). Distance from a National Cancer Institute cancer center was a negative predictor (odds ratio, 0.996, 0.995–0.998), with a 34% decrease in likelihood for every 100 miles.

Conclusion: In 2010, only 12% of US acute-care hospitals ordered the epidermal growth factor receptor assay, suggesting that most patients with lung cancer did not have access to this test. This case study illustrated the need for: (i) increased dissemination and implementation research, and (ii) interventions to improve adoption of guideline-directed molecular diagnostic tests by community hospitals.

Genet Med advance online publication 28 February 2013

Key Words: dissemination and implementation; EGFR assay; equity in access; lung cancer genomics; T3 translation

Predictors of Use: Affiliation with academic center, participation in NCI cooperative group, metropolitan county, education, income
Knowledge Integration: EGAPP Working Group

• Independent, multidisciplinary, non-federal panel established by CDC 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 screening
• Six recommendation statements to date:
  • Colorectal cancer, breast cancer, heart disease, clotting disorders, depression
• New recommendations in 2013
  • Prostate cancer, diabetes, and more
• Uncovering major knowledge gaps
  • Setting a translational research agenda
What is GAPPNet?

- Collaboration of individuals and organizations interested in validating and translating genome-based applications into practice and prevention

- Vision: to realize the promise of genomics in treating and preventing disease, improving health and reducing health disparities
4 Domains of GAPPPNet

- Knowledge Synthesis & Dissemination
- Evidence-based Recommendations
- Network of Networks
- Implementation Programs
- Translation Research (T2-T4)
Determining and sharing what we know and what we don’t know and how we know it

Research to fill gaps and how to implement

Integrate into clinical and public health practice thru education, policy surveillance & evaluation

Linking evidence to practice In a credible and transparent way
Outline

- What’s public health got to do with genomic medicine?
- Public health genomics 15 years on
- What are the priorities for public health genomics, 2012-2017?
CDC Advanced Molecular Detection Initiative

- Improve pathogen identification & detection
- Adapt new diagnostics to meet public health needs
- Help states meet future reference testing needs
- Implement enhanced & integrated lab information systems
- Develop prediction, modeling, and better surveillance tools

The New England Journal of Medicine

Rapid Whole-Genome Sequencing for Investigation of a Neonatal MRSA Outbreak


Open Access - Freely available online

Routine Use of Microbial Whole Genome Sequencing in Diagnostic and Public Health Microbiology

Tier 1: Recommended for clinical use by evidence-based panels, based on systematic review of evidence of validity and utility.

Tier 2: May be useful for informed decision making, based on demonstrated validity, and promising utility.

Tier 3: Not ready for clinical use, due to validity or utility not demonstrated, or systematic assessment finding harms outweigh benefits.

http://www.cdc.gov/genomics/gtesting/tier.htm
## Genomic Applications in Research and Practice, by Tier of Evidence

<table>
<thead>
<tr>
<th>Genomic Applications</th>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Established validity and utility + evidence Rx</td>
<td>Established Validity and promising utility</td>
<td>Unclear Validity &amp; Utility</td>
</tr>
<tr>
<td>Examples</td>
<td>Lynch, BRCA, FH, Newborn Screening</td>
<td>FDA pharmacogenomic drug labels; Whole Genome Sequence, personal genomic tests</td>
<td></td>
</tr>
<tr>
<td>Actions</td>
<td>Implement in general practice</td>
<td>Informed decision making in practice</td>
<td>Do not implement in general practice</td>
</tr>
<tr>
<td>Research</td>
<td>Implementation &amp; outcomes research (T3-T4)</td>
<td>Comp Effectiveness Res, Patient-centered OR, Trials (T2-T4)</td>
<td>Validity &amp; efficacy research (T1-T2)</td>
</tr>
<tr>
<td>Potential for disparities</td>
<td>High for disparities in implementation</td>
<td>High for both research &amp; implementation</td>
<td>High for research disparities</td>
</tr>
</tbody>
</table>
Selected Emerging Tier 1 Genomic Applications

- Hereditary Breast and Ovarian Cancer (BRCA)
- Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)
- Familial Hypercholesterolemia
Selected Tier 1 Genomic Applications: What’s in Common?

- Genetic autosomal dominant disorders with adult onset
- Relatively common (collectively 2 million people in the USA)
- Most not ascertained or managed by health care system
- Effective interventions that reduce morbidity and 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
- Only the tip of the iceberg
Underutilization of \textit{BRCA1/2} testing to guide breast cancer treatment: Black and Hispanic women particularly at risk

Douglas E. Levy, PhD\textsuperscript{1,2,3}, Stacey D. Byfield, PhD, MPH\textsuperscript{4}, Catherine B. Comstock, MPH\textsuperscript{5}, Judy E. Garber, MD, MPH\textsuperscript{3,6}, Sapna Syngal, MD, MPH\textsuperscript{3,6,7}, William H. Crown, PhD\textsuperscript{4}, and Alexandra E. Shields, PhD\textsuperscript{1,2,3}

\textbf{Purpose}: Women with early-onset (age \(\leq 40\) years) breast cancer are at high risk of carrying deleterious mutations in the \textit{BRCA1/2} genes; genetic assessment is thus recommended. Knowledge of \textit{BRCA1/2} mutation status is useful in guiding treatment decisions. To date, there has been no national study of \textit{BRCA1/2} testing among newly diagnosed women. \textbf{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 \textit{BRCA1/2} testing, adjusting for covariates and differential lengths of follow-up. \textbf{Results}: Overall, 30\% of women aged 40 years or younger received \textit{BRCA1/2} testing. In adjusted analyses, women of Jewish ethnicity were significantly more likely to be tested (hazard ratio = 2.83, 95\% confidence interval). To assess risk of hereditary breast and ovarian cancer (HBOC) is among the most established genetic tests in clinical use\textsuperscript{1–3}. Guidelines and commercial testing for \textit{BRCA1/2} mutations have been available for more than a decade\textsuperscript{4}, and most health insurers now reimburse at least partially for these tests in individuals at high risk for mutations\textsuperscript{5}. National guidelines recommend that women diagnosed with early-onset breast cancer receive \textit{BRCA1/2} testing to guide treatment decisions\textsuperscript{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\textsuperscript{3,7,8}. A positive test result may also prompt consideration...
Using Core Public Health Functions to Promote BRCA Best Practices among Health Plans

D. Duquette a, K. Lewis b, J. McLosky a, J. Bach a

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Key Words
BRCA • Cancer • Education • Genetic counseling • Genomics • Health plan • Policy • Public health • Surveillance

Conclusions: MDCH has implemented an effective approach to promote cancer prevention through health plan policies that federal and state agencies.

Fig. 2. Increase in number of health plans aligned with USPSTF Grade B Recommendation.
“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.
Practice: Survey: Of 24 NCI-designated comprehensive cancer centers, 71 percent reported that they routinely screened tumor samples from colorectal cancer patients. Only 15 percent of smaller community-based cancer programs reported doing so.
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 Bellcross, 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
HHS Healthy People 2020
Genomics Objectives

G-1: Increase the proportion of women with a family history of breast and/or ovarian cancer who receive genetic counseling

➔ U.S. Preventive Services Task Force Recommendation

G-2: Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing to identify Lynch syndrome

➔ Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group Recommendation
Realizing HP 2020 Objectives: State Genomics Programs

• Since 2008, CDC has supported state genomics programs in Michigan, Oregon, and more recently Georgia, to implement the evidence-based genomics recommendations underpinning the HP objectives.

States are:

• Identifying people targeted by the HP 2020 genomics objectives using cancer registries and educating health providers about evidence-based recommendations
• Implementing model payer policies to facilitate coverage consistent with the breast/ovarian cancer objective
• Developing and evaluating new data sources to measure progress toward these objectives
Cancer registry bidirectional reporting

- Identify relevant breast, ovarian, colorectal and other cancer cases reported to state cancer registry
- Inform reporting institutions of relevant cancer cases with informational materials about hereditary breast and ovarian cancer and Lynch syndrome
- Michigan reported back over 15,000 cases of cancer relevant to HP 2020 objectives (2007-2008 data).
- Connecticut reported back over 5000 cases of cancer through a Healthy People 2020 Action Award (2008-2009 data).
Current CDC OPHG Activities for Implementing Genomic Medicine

• Public health Genomics Implementation Tool Kit

• Clickable State Map of Genomics Activities

• Population Level Surveillance Indicators

• Refining Tier 1-3 Evidence Classification

• Online Genomics & Health Impact Weekly Update

• Training and Technical Assistance
How about Whole Genome Sequencing?
A Systematic Approach to WGS

- Whole Genome Sequencing is now being applied in research and has begun to permeate clinical medicine.

- Traditional models of test interpretation, reporting and patient counseling may be no longer feasible.

- Given the large amount and heterogeneous nature of data with which we must deal, a categorical approach represents a promising way forward.

- By categorizing genomic data within an *a priori* “binning” structure based upon current clinical knowledge and standards of care we can facilitate its use in practice.
Proposal for “Binning” the Whole Genome Sequence (Berg et al., GIM 2011)

<table>
<thead>
<tr>
<th>Criteria:</th>
<th>Clinical Utility</th>
<th>Clinical Validity</th>
<th>Unknown Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bins:</td>
<td>Bin 1 Medically actionable incidental information</td>
<td>Bin 2A Low risk incidental information</td>
<td>Bin 2B Medium risk incidental information</td>
</tr>
<tr>
<td>Examples:</td>
<td>BRCA1/2, MLH1, MSH2, FBN1, NF1</td>
<td>PGx variants and common risk SNPs</td>
<td>APOE Carrier status for recessive Mendelian disorders</td>
</tr>
<tr>
<td>Estimated number of genes/loci:</td>
<td>10s (eventually 100s – 1000s)</td>
<td>1000s</td>
<td>10s</td>
</tr>
</tbody>
</table>

### Alleles that would be reportable (YES) or not reportable (NO) in a clinical context

<table>
<thead>
<tr>
<th>Variants</th>
<th>Known deleterious</th>
<th>Presumed deleterious</th>
<th>VUS</th>
<th>Presumed benign</th>
<th>Known benign</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>YES</td>
<td>YES/NO¹</td>
<td>YES/NO¹</td>
<td>YES/NO¹</td>
<td>N/A²</td>
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<tr>
<td></td>
<td>YES</td>
<td>N/A³</td>
<td>YES/NO¹</td>
<td>YES/NO¹</td>
<td>NO⁴</td>
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<tr>
<td></td>
<td>NO</td>
<td>N/A³</td>
<td>NO</td>
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<td></td>
<td>NO</td>
<td>N/A³</td>
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<td>NO</td>
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Evidentiary and Ethical Issues around Return of Results in WGS Analysis

April, 2013

American College of Medical Genetics and Genomics

ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing

Robert C. Green, MD, MPH1,2, Jonathan S. Berg, MD, PhD3, Wayne W. Grody, MD, PhD4,6, Sarah S. Kalia, ScM, CGC1, Bruce R. Korf, MD, PhD7, Christa L. Martin, PhD, FACMG8, Amy McGuire, JD, PhD9, Robert L. Nussbaum, MD10, Julienne M. O’Daniel, MS, CGC11, Kelly E. Ormond, MS, CGC12, Heidi L. Rehm, PhD, FACMG2,13, Michael S. Watson, MS, PhD, FACMG14, Marc S. Williams, MD, FACMG15, Leslie G. Biesecker, MD16

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Evidentiary and Ethical Issues around Return of Results in WGS Analysis: EGAPP Approach

Description and pilot results from a novel method for evaluating return of incidental findings from next-generation sequencing technologies

Katrina A.B. Goddard, PhD, Evelyn P. Whitlock, MD, MPH, Jonathan S. Berg, MD, PhD, Marc S. Williams, MD, Elizabeth M. Webber, MS, Jennifer A. Webster, MS, Jennifer S. Lin, MD, MCR, Kasmintan A. Schrader, MBBS, Doug Campos-Outcalt, MD, MPA, Kenneth Offit, MD, MPH, Heather Spencer Feigelson, PhD and Celine Hollombe, MPH

Purpose: The aim of this study was to develop, operationalize, and pilot a transparent, reproducible, and evidence-informed method to determine when to report incidental findings from next-generation sequencing technologies.

Methods: Using evidence-based principles, we proposed a three-stage process. Stage I “rules out” incidental findings below a minimal threshold of evidence and is evaluated using inter-rater agreement and comparison with an expert-based approach. Stage II documents criteria for clinical actionability using a standardized approach to allow experts to consistently consider and recommend whether results should be routinely reported (stage III). We used expert opinion to determine the face validity of stages II and III using three case studies. We evaluated the time and effort for stages I and II.

Results: For stage I, we assessed 99 conditions and found high inter-rater agreement (89%), and strong agreement with a separate expert-based method. Case studies for familial adenomatous polyposis, hereditary hemochromatosis, and α1-antitrypsin deficiency were all recommended for routine reporting as incidental findings. The method requires <3 days per topic.

Conclusion: We establish an operational definition of clinically actionable incidental findings and provide documentation and pilot testing of a feasible method that is scalable to the whole genome.

Key Words: clinical actionability; population screening; secondary findings; whole-exome sequencing; whole-genome sequencing
We screen newborns, don’t we?: realizing the promise of public health genomics

James P. Evans, MD, PhD¹, Jonathan S. Berg, MD, PhD¹, Andrew F. Olshan, PhD², Terry Magnuson, PhD¹ and Barbara K. Rimer, DrPH³

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.¹ However, the improvement of population health through such an approach has remained elusive.² 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.

In seeking to apply genomic technologies to public health, the traditional focus on common diseases is understandable. After all, even minor progress in risk reduction for diseases that are already common may represent an important public health advance. However, with the identification of more and more people carrying potentially disease-causing mutations, new questions about the long-term implications of this information have emerged.

To date, efforts to tailor prevention and care for individuals with a significantly increased risk for disease have focused on those who are already diagnosed with disease.³ Medical interventions are usually most beneficial when identified disease risks and potential benefits are high. Finally, efforts that aim for genomic risk stratification often are justified by the hope that simply informing individuals of their genetic risks for disease will induce beneficial behavioral changes.⁴ Thus far, this notion is largely contradicted by available evidence.⁵ 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.⁶

However, recent advances in sequencing technology provide a new opportunity to expand the focus of public health genomics in a way in which its promise can be realized. Millions of people have had their genomes sequenced, but how to interpret this information has been slow to develop.⁷ By shifting the focus of genomic research to the identification of rare disease-causing mutations, we can realize the promise of public health genomics.

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