Public Health Genomics: From the Science of Discovery to the Science of Action

Muin J. Khoury MD, PhD
Outline

- The Promise of Genomics in Medicine and Public Health
  - Technology, technology……

- Phases of Genomics Translation
  - The Public Health Approach

- Genomics and Improving Population Health
  - Examples and Case Studies
Published by the CDC Office of Public Health Genomics, the weekly Update offers links to genomics news and publications relevant to population health and health care.

Access the complete issue

Highlights of the week

- Evidence matters in genomic medicine
- March 27 was diabetes day: does diabetes run in your family?
- Making universal Lynch syndrome screening a reality
- U.S. Supreme Court bounces BRCA gene patent case
- Should genomic test results be returned to participants in research involving biobanks?
- Genetic insight into severe influenza: why some people get hospitalized
- Water-testing genetic tool kit can detect dozens of dangerous pathogens
Genomics and Global Health: The Example of Podoconiosis


ORIGINAL ARTICLE

HLA Class II Locus and Susceptibility to Podoconiosis

Fasil Tekola Ayele, Ph.D., M.P.H., Adebowale Adeyemo, M.D., Chris Finan, Ph.D., Elena Hailu, M.Sc., Paul Sinnott, Ph.D., Natalia Diaz Burlinson, M.Sc., Abraham Aseffa, M.D., Ph.D., Charles N. Rotimi, Ph.D., M.P.H., Melanie J. Newport, M.D., Ph.D., and Gail Davey, M.D.

Using a “genomics tool” to develop disease prevention strategy in a low-income setting: lessons from the podoconiosis research project

Fasil Tekola Ayele • Adebowale Adeyemo • Charles N. Rotimi

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J Community Genet 2012
The human genome at ten

Nearly a decade on from the completion of the draft sequence of the human genome, researchers should work with the same intensity and focus to apply the results to health.

The race to complete the first human genome sequence had everything a story needs to keep its audience enthralled — right down to the final line (see page 670). Along the way, geneticists have discovered that even basic concepts such as 'gene' and 'gene regulation' are far more complex than people had imagined.
The Next DNA Disruptor?

February 17, 2012

My Twitter feed just exploded. Oxford Nanopore, long watch in the field of mapping DNA, just announced a USB thumb drive DNA sequencer that may be able to handle a human genome with no prep work.

“Game changer” is an understatement,” says George Church. (Church was one of the inventors on one of the Oxford Nanopore that led to the device.) He ticked the following.

The $1,000 genome, the $100,000 analysis?

Elaine R Mardis*

Having recently attended the Personal Genomes meeting at Cold Spring Harbor Laboratories (I was an organizer this year), I was struck by the number of talks that described the use of whole-genome sequencing and analysis to reveal the genetic basis of disease in patients. These patients included a child with irritable bowel syndrome and...
The Vision of Genomic Medicine

What do we do with Genes?

Primary Prevention
Smoking cessation

Secondary Prevention
Colon Ca Screening

Tertiary Prevention
Pharmacogenomics

Personalized or Precision Medicine?

Collins FC, NEJM 1999

A 23 year old man named John

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>GENES INVOLVED*</th>
<th>RELATIVE RISK</th>
<th>LIFETIME RISK (%)</th>
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<tbody>
<tr>
<td>Reduced risk</td>
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<td>Prostate cancer</td>
<td>HPC1, HPC2, HPC3</td>
<td>0.4</td>
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<td>Alzheimer’s disease</td>
<td>APOE, FAD3, XAD</td>
<td>0.3</td>
<td>10</td>
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<td>Elevated risk</td>
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<td>Coronary artery disease</td>
<td>APOB, CETP</td>
<td>2.5</td>
<td>70</td>
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<td>Colon cancer</td>
<td>FCC4, APC</td>
<td>4</td>
<td>23</td>
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<td>Lung cancer</td>
<td>NAT2</td>
<td>6</td>
<td>40</td>
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</table>

Collins FC, NEJM 1999
We Live in The Era of the “Ome”: The Human Genome is Just the Beginning

- Genome
- Transcriptome
- Epigenome
- Proteome
- Metabolome
- Nutrigenome
- Microbiome
- Exposome

The Incidentalome
A Threat to Genomic Medicine

Isaac S. Kohane, MD, PhD
Daniel R. Masys, MD
Russ B. Altman, MD, PhD

GENOMIC MEDICINE IS POISED TO OFFER A BROAD ARRAY OF NEW GENOME-SCALE SCREENING TESTS. HOWEVER, THESE TESTS MAY LEAD TO A PHENOMENON IN WHICH MULTIPLE ABNORMAL GENOMIC FINDINGS ARE DISCOVERED, ANALOGOUS TO THE “INCIDENTALOMAS” THAT ARE OFTEN DISCOVERED IN RADIOLOGICAL STUDIES. IF PRACTITIONERS PURSUE THESE UNEXPECTED GENOMIC FINDINGS WITHOUT THOUGHT, THERE MAY BE DISASTROUS CONSEQUENCES. FIRST, PHYSICIANS WILL BE OVERWHELMED BY THE COMPLEXITY OF PURSUING UNEXPECTED GENOMIC MEASUREMENTS. SECOND, PATIENTS WILL BE SUBJECTED TO UNNECESSARY FOLLOW-UP TESTS, CAUSING ADDITIONAL MORBIDITY. THIRD, THE COST OF GENOMIC MEDICINE WILL INCREASE SUBSTANTIALLY WITH LITTLE BENEFIT TO PATIENTS OR PHYSICIANS (BUT WITH GREAT FINANCIAL BENEFITS TO THE GENOMIC TESTING INDUSTRY), THUS THROWING THE OVERALL SOCIETAL BENEFIT OF GENOME-BASED MEDICINE INTO QUESTION.

In this article, we discuss the basis for these concerns and suggest several steps that can be taken to help avoid these substantive risks to the practice of genomically personalized medicine.

Diagnostic Testing and Incidental Findings
Physicians are generally trained to order tests carefully and only if such tests will result in a change in management. For this reason, much time is spent deciding if a renal panel with 7 blood measurements should be expanded to a comprehensive panel with 20 or more measurements. Physicians know that as the number of tests increases, the chance that a spurious abnormal test result will arise also increases. They also know that it is difficult to ignore abnormal findings.

There is a rich literature in radiology on the “incidentaloma,” which is a finding (most commonly a mass) found on computed tomography or magnetic resonance imaging studies ordered for symptoms or concerns totally unrelated to the gland in which the mass is found. The workup of an incidentaloma is complicated by concerns that it may be associated with malignant disease and, at least initially, the lack of good data on the prevalence of malignant disease in the general population. Incidentalomas occur because imaging modalities do not report on the areas directly, not in the field of view.

This phenomenon of possible incidental genomic findings—the incidentalome—threatens to undermine the promise of molecular medicine. In particular, the application of comprehensive genotype and functional genomic measurements across the general population is likely to yield unexpected incidental findings for nearly everyone. Of course, there are important differences in the interpretation of genomic data and radiological data (e.g., discovering incidentalomas may be lifesaving), but the potential similarity is that the clinician and patient are confronted with results that they did not anticipate when the test was ordered.

The sequencing of the human genome has brought increasing interest in the use of genome-scale technologies to measure individual variation in the human genome. A variety of technologies have emerged that make it economically attractive to assess the structure and function of hundreds of thousands of genes simultaneously. Although all humans share more than 99.8% of their genome DNA sequence, the remaining 0.2% (along with environmental exposures) is responsible for much of the variation in risk of disease and response to therapies. Recent reports indicate that more than 300,000 single-nucleotide polymorphisms...
Integrative Personal “Omics” Profile?

- Integrative personal “omics” profile (iPOP) analysis on a healthy person over a 14-months period
- Combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles
- “Analysis showed various medical risks, including type 2 diabetes. It also uncovered extensive, dynamic changes in biological pathways across healthy and disease states”


The Rise of the Narcissome!!
Emerging "Genomic Tests"

<table>
<thead>
<tr>
<th>Disease/Disorder</th>
<th>Test to be Assessed</th>
<th>Target Population</th>
<th>Intended Use</th>
<th>Entered Date</th>
<th>Detail</th>
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<tbody>
<tr>
<td>Staphylococcus aureus infections</td>
<td>Mass spectrometry (mass spec)-based test involving nitrogen-15 (heavy nitrogen) labeled bacteriophage (phage); liquid chromatography (LC) and tandem mass spec analysis of peptides generated by trypsin digestion of phage proteins</td>
<td>Not specified</td>
<td>Detecting staphylococcus infections in a variety of situations, especially when large numbers of people need rapid testing</td>
<td>02/28/2012</td>
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<td>Down syndrome and Edwards Syndromes</td>
<td>Trisomy 21 and trisomy 18 testing of maternal blood for fetal DNA; Digital Analysis of Selected Regions (DANSR(TM)) assay reduces DNA sequencing by 10-fold as compared with massively parallel shotgun sequencing (MPSS)-based approaches; Fetal-fraction Optimized Risk of Trisomy Evaluation (FORTE(TM)) algorithm includes consideration of age-related risks and percentage of fetal DNA in the sample to generate individualized risk score for trisomy</td>
<td>Not specified</td>
<td>Non-invasive prenatal testing</td>
<td>02/28/2012</td>
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<tr>
<td>Mood disorders, mood disturbances, including depression and anxiety</td>
<td>Combination of proprietary biomarker test panels and an analytical report; assessment of variants/SNPs in: serotonin transporter (SLC6A4), gated calcium channel, dopamine receptor (DRD2), catechol methyl transferase (COMT), methylenetetrahydrofolate reductase</td>
<td>Patients with mood disorders, memory disorders</td>
<td>Tool to help health care providers understand patient genotype and help understand potential responses to medications</td>
<td>02/28/2012</td>
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<tr>
<td>Gene</td>
<td>Genetic Alteration</td>
<td>Tumor Type</td>
<td>Therapeutic Agent</td>
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<td><strong>Receptor tyrosine kinase</strong></td>
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<td>EGFR</td>
<td>Mutation, amplification</td>
<td>Lung cancer, glioblastoma</td>
<td>Gefitinib, erlotinib</td>
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<td>ERBB2</td>
<td>Amplification</td>
<td>Breast cancer</td>
<td>Lapatinib</td>
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<td>FGFR1</td>
<td>Translocation</td>
<td>Chronic myeloid leukemia</td>
<td>PKC412, BIBF-1120</td>
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<td>FGFR2</td>
<td>Amplification, mutation</td>
<td>Gastric, breast, endometrial cancer</td>
<td>PKC412, BIBF-1120</td>
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<td>FGFR3</td>
<td>Translocation, mutation</td>
<td>Multiple myeloma</td>
<td>PKC412, BIBF-1120</td>
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<td>PDGFRA</td>
<td>Mutation</td>
<td>Glioblastoma, gastrointestinal stromal tumor</td>
<td>Sunitinib, sorafenib, imatinib</td>
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<td>PDGFRB</td>
<td>Translocation</td>
<td>Chronic myelomonocytic leukemia</td>
<td>Sunitinib, sorafenib, imatinib</td>
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<td>ALK</td>
<td>Mutation or amplification</td>
<td>Lung cancer, neuroblastoma, anaplastic large-cell lymphoma</td>
<td>Crizotinib</td>
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<td>c-MET</td>
<td>Amplification</td>
<td>Gefitinib-resistant non–small-cell lung cancer, gastric cancer</td>
<td>Crizotinib, XL814, SU11274</td>
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<td>IGF1R</td>
<td>Activation by insulin-like growth factor II ligand</td>
<td>Colorectal, pancreatic cancer</td>
<td>CP-751, 871, AMG479</td>
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<td>c-KIT</td>
<td>Mutation</td>
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<td>FLT3</td>
<td>Internal tandem duplication</td>
<td>Acute myeloid leukemia</td>
<td>Lestaurnitinib, XL999</td>
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<td>RET</td>
<td>Mutation, translocation</td>
<td>Thyroid medullary carcinoma</td>
<td>XL184</td>
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<td><strong>Non–receptor tyrosine kinase</strong></td>
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<td>ABL</td>
<td>Translocation (BCR-ABL)</td>
<td>Chronic myeloid leukemia</td>
<td>Imatinib</td>
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<td>JAK2</td>
<td>Mutation (V617F), translocation</td>
<td>Chronic myeloid leukemia, myelo-proliferative disorders</td>
<td>Lestaurnitinib, INCB018424</td>
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<td>SRC</td>
<td>Overexpression</td>
<td>Non–small-cell lung cancer; ovarian, breast cancer; sarcoma</td>
<td>KX2–391, dasatinib, AZD0530</td>
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<td><strong>Serine–threonine–lipid kinase</strong></td>
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<td>BRAF</td>
<td>Mutation (V600E)</td>
<td>Melanoma; colon, thyroid cancer</td>
<td>SB-590885, PLX-4032, RAF265, XL281</td>
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<td>Aurora A and B kinases</td>
<td>Overexpression</td>
<td>Breast, colon cancer, leukemia</td>
<td>MK-5108 (VX-689)</td>
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<td>Polo-like kinases</td>
<td>Overexpression</td>
<td>Breast, lung, colon cancer; lymphoma</td>
<td>BI2536, GSK461164</td>
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<td>MTOR</td>
<td>Increased activation</td>
<td>Renal-cell carcinoma</td>
<td>Temsirolimus (CCI-779), BEZ235</td>
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<td>PI3K</td>
<td>PIK3CA mutations</td>
<td>Colorectal, breast, gastric cancer; glioblastoma</td>
<td>BEZ235</td>
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<td><strong>DNA damage or repair</strong></td>
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<tr>
<td>BRCA1 and BRCA2</td>
<td>Mutation (synthetic lethal effect)</td>
<td>Breast, ovarian cancer</td>
<td>Olaparib, MK-4827 (PARP inhibitors)</td>
<td></td>
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</tbody>
</table>

* PARP denotes poly(adenosine diphosphate–ribose) polymerase.
Table of Pharmacogenomic Biomarkers in Drug Labels

Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labels may contain information on genomic biomarkers and can describe:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

The table below lists FDA-approved drugs with pharmacogenomic information in their labels. Relevant sections of the label with such information are noted in the last column of the table. Biomarkers may include gene variants, functional deficiencies, expression changes, chromosomal abnormalities, and others. Please note that the table columns can be sorted. Pharmacogenomic information can appear in different sections of the label. For more information on the relevance of information in various parts of the drug label (e.g. Indications and Usage, Dosage and Administration, Boxed Warning, etc.), please go to the relevant labeling guidance. For information on the FDA's initiative to improve prescription drug labels, please visit the FDA/CDER Learn website.
Outline

■ The Promise of Genomics in Medicine and Public Health
  ■ Technology, technology……

■ Phases of Genomics Translation
  ■ The Public Health Approach

■ Genomics and Improving Population Health
  ■ Examples and Case Studies
Charting a course for genomic medicine from base pairs to bedside

Eric D. Green, Mark S. Guyer & National Human Genome Research Institute

Since the end of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence, genomic medicine has become mainstream of biomedical research. The scientific community's foresight in launching this ambitious project is evident in the broad range of scientific advances that the HGP has enabled, as shown in Fig. 1 (see foldout). Optimism about the potential contributions of genomics for improving human health has been fueled by new insights about cancer, the molecular basis of inherited diseases (http://www.ncbi.nlm.nih.gov/omim and http://www.genome.gov/GWASudies) and the role of structural variation in disease, some of which have already led to new therapies.

Although genomics has already begun to improve diagnostics and treatments in a few circumstances, profound improvements in the effectiveness of healthcare cannot realistically be expected for many years (Fig. 2). Achieving such progress will depend not only on research, but also on new policies, practices and other developments. We have illustrated the kind of achievements that can be anticipated with a few examples (Box 2) where a confluence of need and opportunities should lead to major accomplishments in genomic medicine in the coming decade. Similarly, we note three cross-cutting areas that are broadly relevant and fundamental across the entire spectrum of genomics and may have implications far beyond genomics.
The Genomics Evidence Gap

The Evidence Dilemma In Genomic Medicine

We need a roadmap for the appropriate integration of genomic discoveries into clinical practice.

by Muin J. Khoury, Al Berg, Ralph Coates, James Evans, Steven M. Teutsch, and Linda A. Bradley

ABSTRACT: An ongoing dilemma in genomic medicine is balancing the need for scientific innovation with appropriate evidence thresholds for moving technology into practice. The current low threshold allows unsubstantiated technologies to enter into practice, with the potential to overwhem the health system. Alternatively, establishing an excessively high threshold for evidence could slow the integration of genomics into practice and present disincentives for investing in research and development. Also, variable coverage and reimbursement policies contribute to the dilemma of genomics practice.

Perspective

The Human Genome And Translational Research: How Much Evidence Is Enough?

Given the lack of a robust translational infrastructure, conflict between those developing new technologies and those who must use or pay for them seems inevitable.

by Janet Woodcock

ABSTRACT: Multiple new genomic diagnostic tests are currently under development. Given the lack of an efficient translational infrastructure, it is not clear how, or whether, robust evidence for their clinical value will be generated. [Health Affairs 27, no. 6 (2008): 1616–1618; 10.1377/hlthaff.27.6.1616]

Closing the Evidence Gap in the Use of Emerging Testing Technologies in Clinical Practice

Kathryn A. Phillips, PhD

There is no consensus about optimal testing methods. Guidelines recommend using either immunohistochemistry, with indeterminate results confirmed by fluorescence in situ hybridization (FISH), or FISH to determine HER2 status. Although FISH is a better predictor of response to treatment, immunohistochemistry costs substantially less and is more easily performed in community laboratories.

Despite the clinical success of mastuzumab, there are concerns about the best methods for selecting patients for treatment. The accuracy and interpretation of HER2 tests have been validated, but their optimal performance remains to be established.

Perspective

The Health Benefits Of Genomics: Out With The Old, In With The New

We must dispense with old models of research support and regulatory guidance designed for the pre–Human Genome Project world.

by Kathy Hudson
“Spending on Genetic Tests is Forecast to Rise Sharply by 2021” LA Times, March 12, 2012

- In 2010, the cost of genetic and molecular testing was about $500 million.
- 40 percent: testing for infectious diseases, 16 percent for cancer, and the rest for various conditions.
- Three-quarters of doctors surveyed believe that genetic testing allows for more personalized therapy.
- 56 percent think that new genetic tests will increase health care costs, compared with 19 percent who think it will reduce health care costs.
“One view is that genomics is a form of new technology and it is well established that new technologies increase health care costs”

- HER2/neu gene and the development of trastuzumab

But, “reducing the use of interventions that will have little to no benefit could have an important effect on the cost curve, particularly when the intervention is common or very costly”

- Gene expression profiling among women with breast cancer

“Given the right policy decisions, genomics has the potential to improve health care value by ensuring that the most effective treatment is used in the most appropriate patients”
In 2006, Duke University researchers claimed that genomics-based tests were predictors of which chemotherapy would be most effective for specific cancer patients.

Problems with key data and computational methods.

Inappropriate enrollment of patients in clinical trials, premature launch of companies, and retraction of dozens of research papers.

Five years after they were first made public, the tests were acknowledged to be invalid.
U. S. System of Oversight of Genetic Testing
Secretary’s Advisory Committee on Genetics, Health and Society, 2008

Figure 2.1: Map of the U.S. Oversight System for Genetic Testing
Omics-based Test Development Process

Discovery and Test Validation Stage

Discovery Phase
- Candidate Test Developed on Training Set, Followed by Lock-Down of All Computational Procedures
- Confirmation of Candidate Omics-Based Test Using:
  1. An Independent Sample Set if Available (Preferred); OR
  2. A Subset of the Training Set NOT Used During Training (Less Preferred)

Test Validation Phase
- IRB Approval and Consultation with the FDA
- Define Clinical Test Method
- Analytical Validation
- Clinical/Biological Validation Using Blinded Sample Set
- Defined, Validated, and Locked Down Test (Intended Use, Assay, Computational Procedures, and Interpretation Criteria)

BRIGHT LINE

Evaluation for Clinical Utility and Use Stage

Three Potential Pathways (IRB Approval and FDA Consultation)
- Prospective/Retrospective Study with Archived Specimens
- Prospective Clinical Trial; Test Does NOT Direct Patient Management
- Prospective Clinical Trial; Test Directs Patient Management

IDE Needed?
- No
- No
- Yes

FDA Approval/Clearance or LDT Process for Clinical Test
- Additional High-Quality Evidence to Evaluate Clinical Utility of the Test
- Practice Guidelines and Reimbursement
- Clinical Use

IOM Report
March 2012
Models for Genomics Translation into Population Health Benefits

- Premature translation
- “Lost in translation”
- Public health genomics: finding the right balance
Model 1: Premature Translation:
Lots of New Genomic Tests-Personal genome profiles
DTC Movement
Genomics Translation Highway: Bench to Bedside

Model 2: “Lost in Translation”
The practice of medicine

Will genomics widen health disparities?
Model 3: “Public Health Genomics”

Finding the right balance

- A multidisciplinary field concerned with the effective and responsible translation of genome-based knowledge and technologies to improve population health (Bellagio, 2006)
  - Understanding the drivers of population health (social and biological)
  - The knowledge, policies and resources to act
3 Essential Public Health Functions
1. Assessment
2. Policy development
3. Assurance and evaluation

“The single most important thing that Public Health can do is to increase the degree to which decisions are made using good data”

Dr. Tom Frieden, CDC Director, Jan 1, 2010

**Genomics Translation Highway**

**The Public Health Genomics Model: Beyond Bench to Bedside**

- **Bench** (base pairs, etc)
- **Bedside** (promising tests and interventions)
- **Population Health**
- **Evidence based Recommendation or Policy**

Knowledge Integration

- **Development**
  - T1
- **Evaluation**
  - T2
- **Implementation Science**
  - T3
- **Effectiveness & Outcomes Research**
  - T4

Khoury MJ et al, AJPH, 2012
The Public Health Genomics Model: Multidisciplinary Clinical and Population Sciences

Khoury MJ et al. Genetics in Medicine (August 2009)

<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>
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<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>
Limited Translational Research in Genomics
*Post 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 Epidemiology, Department of Population Sciences, City of Hope, Duarte, Calif.; and Office of Federal Health Information Policy, Health Resources and Services Administration.

Bar chart showing numbers of cases:
- T0: 827
- T1: 174
- T2: 9
- T3: 8
- T4: 1
Genomics Translation Highway: The Public Health Genomics Model

Population Health

Bench (base pairs, etc)

Bedside (promising tests and interventions)

Knowledge Integration

Genetic Epi With a Capital E

Discovery

T0

Effectiveness & Outcomes Research

T4

Healthcare Systems & Prevention Programs

T3

Very Few Evidence based Recommendations

Implementation Science

To RCT or not RCT?

Evaluation

Khoury MJ et al, AJPH, 2012
Human Genome Epidemiology (HuGE) (AKA Genetic Epidemiology with a Capital “E”)

- Applications of epidemiologic methods and approaches in evaluating the impact of human genome variation on health and disease in various populations and how to use this information to improve health and prevent disease
- Focus on Population-based Research
- Focus on Joint Effects of Genes and the Environment
- Incorporation of Underlying Biology

1st E: Environment
2nd E: Evaluation
HuGE: 1st E (Environment) 
Characterization of Genetic and Environmental Effects 
(Place, Person and Time)

- Prevalence
- Disease burden
  - Relative risk
  - Absolute risk
  - Attributable fraction
- Gene-gene and gene-environment interaction
Gene-Environment Interaction in Common Diseases: It is Getting More Complex....
HuGE Navigator (version 2.0)
An integrated, searchable knowledge base of genetic associations and human genome epidemiology.

10/05/2010 - If you want to keep informed including our Curator's weekly recommended HuGE articles, the alert for new weekly HuGE article additions, new features and services and others, please join us on Facebook and follow us on Twitter.

HuGE Navigator is a continuously updated knowledge base in human genome epidemiology, including population prevalence of genetic variants, genetic associations... more

To be informed any new updates on the site, please join us on Facebook and follow us on Twitter.

PhenoPedia: Look up genetic associations and human genome epidemiology summaries by disease.

Genopedia: Look up genetic associations and human genome epidemiology summaries by gene.

HuGE Literature Finder: Find published articles in genetic associations and human genome epidemiology.

GWAS Integrator: Explore published GWAS and relevant information.

HuGE Watch: Track the evolution of published literature in human genome epidemiology.

Gene Prospector: A gateway for evaluating genes in relation to disease and risk factors.

Cancer GAMAdb: Database of cancer genetic associations from meta analyses and GWAS.

Variant Name Mapper: Map common names and rs numbers of genetic variants.
Trends in HuGE Published Literature 2000-2010 (HuGE Navigator)
Trends in Reported Gene-Environment Interaction

- In 2001
  - 2509 HuGE articles
    - 340 with E in abstract (13.6% of total)
      - 100 pharmacogenomics (29.4% of E)

- In 2010
  - 9112 HuGE articles (3.6 fold increase)
    - 1826 with E in abstract (20% of total)
      - 950 pharmacogenomics (52.0% of E)
HuGE 2nd E (Evaluation)  
Knowledge Synthesis  
and Evidence based Recommendations

- Independent multi disciplinary groups
- Evidence-based, transparent, and publicly accountable
- Systematic reviews
- Develop and disseminate recommendations

Evidence to Practice
EGAPPI
Evaluation of Genomic Applications in Practice and Prevention

U.S. Preventive Services Task Force (USPSTF)

The AHRQ Prevention and Care Management Portfolio fulfills AHRQ’s Congressionally mandated role to support the U.S. Preventive Services Task Force (USPSTF). The USPSTF is an independent panel of non-Federal experts in prevention and evidence-based medicine and is composed of primary care providers (such as internists, pediatricians, family physicians, gynecologists/obstetricians, nurses, and health behavior specialists).
Each intended use

ACCE Framework

Four components with multiple questions

- Analytic Validity (AV)
- Clinical Validity (CV)
- Clinical Utility (CU)
- ELSI
## Categories of Genomic Tests: Difference Between Validity and Utility

<table>
<thead>
<tr>
<th>Application of test</th>
<th>Clinical validity</th>
<th>Clinical utility</th>
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<tbody>
<tr>
<td>Diagnosis (symptomatic patient)</td>
<td>Association of marker with disorder</td>
<td>Improved clinical outcomes—health outcomes based on diagnosis and subsequent intervention or treatment</td>
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<tr>
<td></td>
<td></td>
<td>Availability of information useful for personal or clinical decision-making</td>
</tr>
<tr>
<td></td>
<td></td>
<td>End of diagnostic odyssey</td>
</tr>
<tr>
<td>Disease screening (asymptomatic patient)</td>
<td>Association of marker with disorder</td>
<td>Improved health outcome based on early intervention for screen positive individuals to identify a disorder for which there is intervention or treatment, or provision of information useful for personal or clinical decision making</td>
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<tr>
<td>Risk assessment/susceptibility</td>
<td>Association of marker with future disorder</td>
<td>Improved health outcomes based on prevention or early detection strategies</td>
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<tr>
<td></td>
<td>(consider possible effect of penetrance)</td>
<td></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, or outcomes of value to patients, based on changes in patient management</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>

*Clinical outcomes are the net health benefit (benefits and harms) for the patients and/or population in which the test is used.*

Outline

- The Promise of Genomics in Medicine and Public Health
  - Technology, technology……..

- Phases of Genomics Translation
  - The Public Health Approach

- Genomics and Improving Population Health
  - Examples and Case Studies
Using Genomics to Improve Health: Case Studies and Examples

- Universal screening for Lynch syndrome in newly diagnosed colorectal cancer
  - Cascade screening
- Genetic testing for Clopidogrel dosing
  - Pharmacogenomics
- Genetic testing for prostate cancer
  - Screening
- Genetic prediction of type 2 diabetes
  - Primary prevention
Lynch Syndrome

- In the U.S., ~141,000 individuals are diagnosed with CRC each yr
- ~4,200 (1-5%) are attributable to Lynch syndrome, an autosomal dominant disorder
- MMR gene mutations confer a lifetime risk of CRC of 20-65%
- In 2009, EGAPP WG recommended genetic testing of CRC patients and relatives of patients identified with Lynch to benefit relatives because screening colonoscopy can reduce CRC risk by 60%
- There are more than 800,000 people with Lynch syndrome in the US. Most are not diagnosed by the healthcare system. First degree relatives have a 50% likelihood of having the condition
“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.
# EGAPP Evidence Review at a Glance

<table>
<thead>
<tr>
<th>Testing Strategy</th>
<th>Application</th>
<th>QUALITY OF EVIDENCE Adequacy of information to address:</th>
<th>Overall Recommendation*</th>
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<tbody>
<tr>
<td>DNA analysis of mismatch repair (MMR) genes: (MLH1, MSH2, MSH6, PMS2)</td>
<td>Diagnostic Testing</td>
<td>Analytical Validity: Adequate</td>
<td>Sufficient evidence to recommend use for the benefit of relatives</td>
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<tr>
<td>Microsatellite Instability (MSI)</td>
<td><em>Preliminary</em> (Screening) Test</td>
<td>Clinical Validity: Convincing</td>
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<tr>
<td>Immunohistochemistry (IHC)</td>
<td><em>Preliminary</em> (Screening) Test</td>
<td>Clinical Utility: Adequate</td>
<td></td>
</tr>
<tr>
<td>Methylation Status (BRAF V600E mutation)</td>
<td><em>Preliminary</em> (Screening) Test (Supplemental to IHC)</td>
<td></td>
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</tbody>
</table>
Challenges to Implementation

- Lack of provider knowledge of Lynch syndrome and testing issues
- Question of informed consent
- Availability of genetic services
- Cost and coverage
- Psychosocial impact
- Informing relatives – who is responsible?
- Patient and provider compliance
- Infrastructure needs
- Testing limitations (e.g. IHC accuracy by site)
Implementing screening for Lynch syndrome among patients with newly diagnosed colorectal cancer: summary of a public health/clinical collaborative meeting

Cecelia A. Bellcross, PhD, MS1,2, Sara R. Bedrosian, BA, BFA1, Elvan Daniels, MD, MPH3, Debra Duquette, MS4, Heather Hampel, MS5, Kory Jasperson, MS6, Djenaba A. Joseph, MD, MPH7, Celia Kaye, MD, PhD8, Ira Lubin, PhD9, Laurence J. Meyer, PhD, MD10, Michele Reyes, PhD, MS1, Maren T. Scheun, MD, MPH11, Sheri D. Schully, PhD12, Leigha Senter, MS5, Sherri L. Stewart, PhD7, Jeanette St. Pierre, MA, MPH1, Judith Westman, MD5, Paul Wise, MD13, Vincent W. Yang, MD, PhD14 and Muin J. Khoury, MD, PhD1

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 this recommendation, the Centers for Disease Control and Prevention convened a multidisciplinary working group meeting in September 2010. This article reviews background that widespread implementation will present substantial challenges, and additional data from pilot studies will be needed. However, evidence of feasibility and population health benefits and the advantages of considering a public health approach were acknowledged. Lynch syndrome can potentially serve as a model to facilitate the development and 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.
Debate About Implementation

Point: Justification for Lynch Syndrome Screening Among All Patients With Newly Diagnosed Colorectal Cancer

Heather Hampel, MS, CGC, Columbus, Ohio

Counterpoint: Implementing Population Genetic Screening for Lynch Syndrome Among Newly Diagnosed Colorectal Cancer Patients—Will the Ends Justify the Means?

Michael J. Hall, MD, MS, Philadelphia, Pennsylvania

To Screen or Not To Screen for Lynch Syndrome

By Judy Peres
Genomics and Health Impact Blog
A blog devoted to discussing best practices and questions about the role of genomics in disease prevention, health promotion and healthcare.

Public Health Genomics > Genomics and Health Impact Blog

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...
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.
Genomics & Health Impact Update

Published by the Office of Public Health Genomics (OPHG), the Update offers links to genomics news and publications relevant to population health and health care. The Update highlights family health history and genomic tests, along with relevant data, policy, and legislation. Please send your comments to: genetics@cdc.gov.

Thursday, March 22, 2012      Volume 28      Number 12

Highlights of the Week:

Spotlight

March 22 is Lynch Syndrome Awareness Day

- New Blog Post: Making Universal Screening for Lynch Syndrome a Reality: The Lynch Syndrome Screening Network
- 33 State Governors declare March 22 Lynch Syndrome Awareness Day
- Genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives, EGAPP Recommendation
- Genetic Testing for Lynch Syndrome in Colorectal Cancer, CDC Podcast
Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial


Summary
Background Observational studies report reduced colorectal cancer incidence in carriers of Lynch syndrome, the major form of hereditary colorectal cancer, but none has directly assessed the impact of aspirin use on cancer risk.

Methods In the CAPP2 randomised trial, carriers of Lynch syndrome were randomised to daily aspirin 300 mg or placebo and followed for 5 years. The primary endpoint was colorectal adenomas, confirmed using endoscopy. Secondary endpoints included colorectal cancer incidence and other gastrointestinal outcomes.

Results In total, 1513 participants were randomised, with 754 in the aspirin group and 759 in the placebo group. During the trial, 38 participants in the aspirin group and 56 in the placebo group developed colorectal adenomas (risk ratio 0.66 [95% CI 0.49-0.89], p=0.006). There were no statistically significant differences in colorectal cancer incidence between the two groups (42 events in the aspirin group vs 51 in the placebo group, risk ratio 0.83 [95% CI 0.57-1.21], p=0.35).

Comment
Aspirin and colorectal cancer prevention in Lynch syndrome

More than 600 000 people worldwide die of colorectal cancer annually, and aspirin is the subject of a major report in The Lancet by John Burn and colleagues. In previous work, four placebo-controlled randomised trials showed that aspirin reduced risk of colorectal adenomas, precursor of all colorectal cancers, and in patients with a family history of colorectal cancer. A randomised trial in familial adenomatous polyposis suggested that aspirin may protect against adenoma development. A meta-analysis of long-term data from five randomised trials of cardiovascular prevention, aspirin reduced the 20-year risk of colorectal cancer by 24% and of associated mortality by 35%.

Although this collection of data is compelling, a definitive conclusion on aspirin efficacy requires a long-term, large-scale randomised controlled trial. In our study, short-term findings, colorectal cancer (not combined with adenoma) developed in fewer patients on aspirin (4%) than in those not on aspirin (7%; hazard ratio [HR] 0.53 [95% CI 0.35-0.81], p=0.001) in an intent-to-treat (ITT) analysis, and significantly fewer (HR 0.41 [95% CI 0.26-0.64], p=0.002) in a prespecified per-protocol analysis (in about 60% of long-term patients; aspirin treatment for ≥2 years ascertained by extrapolated tablet counts). Aspirin was associated with a reduced risk of colorectal cancer (incidence ratio 0.56, 95% CI 0.32-0.99, p=0.05) in ITT analyses accounting for multiple primary colorectal cancers in some individuals.

These results are compelling and consistent with aspirin’s preventive effect in sporadic neoplasias, although the study has limitations. For example, endpoint ascertainment was not standardised, and more intensive surveillance for colorectal cancer is needed in the future.
Clopidogrel

- Antiplatelet agent
- Used in patients with Acute Coronary Syndrome
- Decreases risk of MI, stroke, death
- Increases risk of bleeding
- Ingestion, intestinal absorption and hepatic biotransformation
- Genes involved: e.g. \textit{ABCB1}, \textit{CYP3A4}, \textit{CYP3A5}, \textit{CYP2C19}, \textit{P2RY12} and \textit{ITGB3}
**Review**

**Clopidogrel (Plavix)**

- CYP2C19 feno(gen)o type
  - PM (*2/*2)
  - EM (*1/*1)
  - UM (*17/*17)

**Bioactivated clopidogrel**

**Platelet aggregation**

- ADP-induced platelet aggr. (AU* min)
  - PM: 500
  - EM: 300
  - UM: 100

- Stent thrombosis (%)
  - PM: 2.5
  - EM: 0.5
  - UM: N/A

- Bleeding events (%)
  - PM: N/A
  - EM: 8
  - UM: 2

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*TRENDS in Pharmacological Sciences* February 2011, Vol. 32, No. 2
FDA Boxed Warning on Clopidogrel

Warning: Diminished Effectiveness in Poor Metabolizers

- Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19
- Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

PLAVIX (clopidogrel bisulfate) tablets PI.

FDA warnings on more than 80 gene-drug pairs
Recommendations for Use Are Usually Based on Clinical Utility

ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning". A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association

David R. Holmes, Jr, Gregory J. Dehmer, Sanjay Kaul, Dana Leifer, Patrick T. O'Gara and C. Michael Stein

Circulation published online Jun 28, 2010;

2. Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can considerations.

5. The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. In

From David Veenstra
**CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events**  
A Systematic Review and Meta-analysis

Michael V. Holmes, MBBS, MSc  
Pablo Perel, PhD  
Tina Shah, PhD  
Aroon D. Hingorani, PhD  
Juan P. Casas, PhD

**Context**  
The US Food and Drug Administration recently recommended that CYP2C19 genotyping be considered prior to prescribing clopidogrel, but the American Heart Association and American College of Cardiologists have argued evidence is insufficient to support routine CYP2C19 genotype testing.

**Objective**  
To appraise evidence on the association of CYP2C19 genotype and clopidogrel response through systematic review and meta-analysis.

**Data Sources**  
PubMed and EMBASE from their inception to October 2011.

**Study Selection**  
Studies that reported clopidogrel metabolism, platelet reactivity or clinically relevant outcomes (cardiovascular disease [CVD] events and bleeding), and information on CYP2C19 genotype were included.

**Data Extraction**  
We extracted information on study design, genotyping, and disease outcomes and investigated sources of bias.

**Results**  
We retrieved 32 studies of 42,016 patients reporting 3545 CVD events, 579 stent thromboses, and 1412 bleeding events. Six studies were randomized trials (“effect-modification” design) and the remaining 26 reported individuals exposed to clopidogrel (“treatment-only” design). In treatment-only analysis, individuals with 1 or more CYP2C19 alleles associated with lower enzyme activity had lower levels of active clopidogrel metabolites, less platelet inhibition, lower risk of bleeding (relative risk [RR], 0.84; 95% CI, 0.75-0.94; absolute risk reduction of 5-8 events per 1000 individuals), and higher risk of CVD events (RR, 1.18; 95% CI, 1.09-1.28; absolute risk increase of 8-12 events per 1000 individuals). However, there was evidence of small-study bias (Hartford test \( P = .001 \)). When analyses were restricted to studies with 200 or more events, the point estimate was attenuated (RR, 0.97; 95% CI, 0.86-1.09). In effect-modification studies, CYP2C19 genotype was not associated with modification of the effect of clopidogrel on CVD endpoints or bleeding (\( P > .05 \) for interaction for both). Other limitations included selective outcome reporting and potential for genotype misclassification due to problems with the *a* allele nomenclature for cytochrome enzymes.

**Conclusion**  
Although there was an association between the CYP2C19 genotype and clopidogrel responsiveness, overall, there was no significant association of genotype with cardiovascular events.

JAMA. 2011;306(4):2704-2714  
www.jama.com
Case Study 1

48 year old white male in good health,
- father diagnosed with localized prostate cancer at age 68

Concerned, he got tested using deCODE Prostate Cancer Genetic Test: Relative risk = 1.88

- High risk prompted early PSA test by primary care
  - PSA – high normal at 2.0ng/ml

- High risk prompted urologist to perform TRUS-guided biopsy
  - Positive - Gleason score of 6
  - Radical prostatectomy with nerve sparing
Genetics and Prostate Cancer Screening

- Case Study 2

“Dr. Oz found out he's 30 percent less likely than the average man is of developing prostate cancer. Which means, he can be a little less diligent about scheduling regular prostate examinations. "Think of the trade-off," he says. "Thanks to this test, I don't have to have rectal exams"
## Selected Genetic Variants Associated with Prostate Cancer

<table>
<thead>
<tr>
<th>Locus</th>
<th>Risk-allele frequency</th>
<th>Risk ratio per allele</th>
<th>Variance</th>
</tr>
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<tbody>
<tr>
<td>2q31</td>
<td>0.94</td>
<td>1.30</td>
<td>0.008</td>
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<tr>
<td>2p15</td>
<td>0.19</td>
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<td>2p21</td>
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<td>3q21.3</td>
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From N. Pashayan (January, 2012)
The Debate About Prostate Cancer Screening

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Published at www.nejm.org March 18, 2009
(10.1056/NEJMoa0810696)

Screening and Prostate-Cancer Mortality in a Randomized European Study
Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Antonio Roncador, M.D., Liisa Määtänen, Ph.D., Chris H Bangma, Bert G.

Published at www.nejm.org March 18, 2009
(10.1056/NEJMoa0810084)

Screening for Prostate Cancer — The Controversy That Refuses to Die
Michael J. Barry, M.D.

Editor's note: Do the benefits of PSA screening outweigh the risks? Watch video of a roundtable discussion, participate in a poll, and contribute your comments in our Clinical Directions feature — Screening for Prostate Cancer. Commenting closes April 1, 2009.
“Participation in screening considerably increases the likelihood of having prostate cancer diagnosed; Yet, few of these men die of prostate cancer, and death rates are similar in screened and unscreened men.”

“The present estimates provide a sobering illustration of the frequency of harms men are likely to experience if they participate in PSA screening. The risk of having a false alarm rises strongly with age and with increasing familial risk.”
Screening for Prostate Cancer

This topic is in the process of being updated. Please go to the Update in Progress section to see the latest documents available.

This topic page summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on screening for prostate cancer.

Current Recommendation

Release Date: August 2008

- The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening in men younger than age 75 years.
  Grade: I Statement.
- The USPSTF recommends against screening for prostate cancer in men age 75 years or older.
  Grade: D Recommendation.
Evidence Review on Prostate Cancer Screening (2011)

Screening for Prostate Cancer: A Review of the Evidence for the U.S. Preventive Services Task Force

Roger Chou, MD; Jennifer M. Croswell, MD, MPH; Tracy Dana, MLS; Christina Bougatsos, BS; Ian Blazina, MPH; Rongwei Fu, PhD; Ken Gleitsmann, MD, MPH; Helen C. Koenig, MD, MPH; Clarence Lam, MD, MPH; Ashley Maltz, MD, MPH; J. Brin Rugge, MD, MPH; and Kenneth Lin, MD

Background: Screening can detect prostate cancer at earlier, asymptomatic stages, when treatments might be more effective.

Purpose: To update the 2002 and 2008 U.S. Preventive Services Task Force evidence reviews on screening and treatments for prostate cancer.

Data Sources: MEDLINE (2002 to July 2011) and the Cochrane Library Database (through second quarter of 2011).

Study Selection: Randomized trials of prostate-specific antigen–based screening, randomized trials and cohort studies of prostatectomy or radiation therapy versus watchful waiting, and large observational studies of perioperative harms.

Data Extraction: Investigators abstracted and checked study details and quality using predefined criteria.

Data Synthesis: Of 5 screening trials, the 2 largest and highest-quality studies reported conflicting results. One found that screening was associated with reduced prostate cancer–specific mortality compared with no screening in a subgroup of men aged 55 to 69 years after 9 years (relative risk, 0.80 [95% CI, 0.65 to 0.98]; absolute risk reduction, 0.07 percentage point). The other found no statistically significant effect after 10 years (relative risk, 1.1 [CI, 0.80 to 1.5]). After 3 or 4 screening rounds, 12% to 13% of screened men had false-positive results. Serious infections or urine retention occurred after 0.5% to 1.0% of prostate biopsies. There were 3 randomized trials and 23 cohort studies of treatments. One good-quality trial found that prostatectomy for localized prostate cancer decreased risk for prostate cancer–specific mortality compared with watchful waiting through 13 years of follow-up (relative risk, 0.62 [CI, 0.44 to 0.87]; absolute risk reduction, 6.1%). Benefits seemed to be limited to men younger than 65 years. Treating approximately 3 men with prostatectomy or 7 men with radiation therapy instead of watchful waiting would each result in 1 additional case of erectile dysfunction. Treating approximately 5 men with prostatectomy would result in 1 additional case of urinary incontinence. Prostatectomy was associated with perioperative death (about 0.5%) and cardiovascular events (0.6% to 3%), and radiation therapy was associated with bowel dysfunction.

Limitations: Only English-language articles were included. Few studies evaluated newer therapies.

Conclusion: Prostate-specific antigen–based screening results in small or no reduction in prostate cancer–specific mortality and is associated with harms related to subsequent evaluation and treatments, some of which may be unnecessary.

Primary Funding Source: Agency for Healthcare Research and Quality.
Draft Recommendations of the USPSTF on Prostate Cancer Screening (2011)

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement
DRAFT

Summary of Recommendation and Evidence

The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)-based screening for prostate cancer. This is a grade D recommendation.

This recommendation applies to men in the U.S. population that do not have symptoms that are highly suspicious for prostate cancer, regardless of age, race, or family history. The Task Force did not evaluate the use of the PSA test as part of a diagnostic strategy in men with symptoms that are highly suspicious for prostate cancer. This recommendation also does not consider the use of the PSA test for surveillance after diagnosis and/or treatment of prostate cancer.

Rationale

Importance

Prostate cancer is the most commonly diagnosed non-skin cancer in men in the United States, with a lifetime risk of diagnosis currently estimated at 15.9%. Most cases of prostate cancer have a good prognosis, but some are aggressive; the lifetime risk of dying from prostate cancer is 2.8%. Prostate cancer is rare before age 50 years and very few men die of prostate cancer before age 60 years. The majority of deaths due to prostate cancer occur after age 75 years (1).

Detection

Contemporary recommendations for prostate cancer screening all incorporate the measurement of serum PSA levels; other methods of detection such as digital rectal examination or ultrasonography may be included. The evidence is convincing that PSA-based screening programs result in the detection of many cases of asymptomatic prostate cancer. The evidence is also convincing that the majority of men who have asymptomatic cancer detected by PSA screening have a tumor that meets histological criteria for prostate cancer, but the tumor either will not progress or is so indolent and slow-growing that it will not affect the man’s lifespan or cause adverse health effects, as he will die of another cause first. The terms “overdiagnosis” or “pseudodisease” are used to describe both of these situations. It is difficult to determine the precise magnitude of overdiagnosis associated with any screening and treatment program. The rate of overdiagnosis of prostate cancer increases as the number of men subjected to biopsy increases. The number of cancer cases that could be detected in a screened population is large; a single study in which men eligible for PSA screening underwent biopsy irrespective of PSA level detected cancer in nearly 25% of men (2). The rate of overdiagnosis will also depend upon the age at which diagnosis is made. Cancer diagnosis in older men with shorter life expectancies is much more likely to be overdiagnosis.

Benefits of Detection and Early Intervention

The primary goal of prostate cancer screening is to reduce deaths due to prostate cancer, and a reduction in either prostate cancer death or overall mortality was the primary outcome addressed in all prostate cancer screening studies assessed by the Task Force. The evidence is convincing that for men aged 70 years and older, screening has no mortality benefit. For men aged 50 to 69 years, the evidence is convincing that the reduction in prostate cancer mortality 10 years after screening is small to none. Screen-detected cancer can fall into one of three categories: cancer that results in death in spite of early diagnosis and treatment, cancer for which early diagnosis and treatment improves survival, and cancer for which the outcome would be good in the absence of screening due to indolent tumors. Ninety-five percent of men with PSA-detected cancer who are followed for 12 years do not die from that cancer, even in the absence of definitive treatment (3). The possibility is very small that death from prostate cancer is less likely in men

### Genetic Prediction of Type 2 Diabetes

Many Variants from GWAS or Candidate Genes Associated with Type 2 Diabetes

<table>
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<tr>
<th>SNP</th>
<th>Locus</th>
<th>Chr</th>
<th>Locus re Gene</th>
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Value-Added of Genome Score for Type 2 Diabetes?

What is the Clinical Utility of Testing for Susceptibility to Type 2 Diabetes?

Data from Diabetes Prevention Program (DPP)

RCT results stratified by genotype
In Summary

- **Genomics in Medicine and Public Health**
  - Technology-driven process holds great promise

- **Phases of Genomics Translation**
  - The public health approach is urgently needed for an orderly translation process. Multiple population disciplines needed to address the added value of genomics in improving population health

- **Genomics and Improving Population Health**
  - A few success stories today but much more to come with balanced investments and appropriate policy
Genomics Translation Highway: The Public Health Genomics Model

- **Bench (base pairs, etc)**
- **Bedside (promising tests and interventions)**
- **Knowledge Integration**
- **Very Few Evidence based Recommendations**

**T0**
- Discovery

**T1**
- Genetic Epi
- With a Capital E

**T2**
- Evaluation
  - To RCT or not RCT?

**T3**
- Implementation
  - Science

**T4**
- Effectiveness & Outcomes
- Research

Khoury MJ et al, AJPH, 2012