Public Health Genomics: Translating Genome Discoveries into Population Health

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Outline

- The phases of genomics translation
- Public health genomics: crucial role of clinical and population sciences in genomics translation
- Vision for the next decade: needs and opportunities
"I predict that comprehensive, genomics-based health care will become the norm with individualized preventive medicine and early detection of illnesses" (Zerhouni, 2006)
Two Challenges in Genomics Translation

Challenge 1: Premature Translation

Jan 17, 2008

Prostate Cancer Health Center

Prostate Cancer Gene Test Coming Soon

Test Screens for 5 Genetic Variants and Will Be Available in Months, Researchers Say

By Miranda Hitti

WebMD Medical News

Jan. 16, 2008 -- Scientists at the New England Journal of Medicine say they have developed a test that screens men's blood for five genetic variants that may signal an increased risk of prostate cancer. Once those blocks are detected, the test takes about a week.

Cumulative Association of Five Genetic Variants with Prostate Cancer

S. Lilly Zheng, M.D., Jielin Sun, Ph.D., FredrikWiklund, Ph.D., Shelly Smith, M.S., Pär Stattin, M.D., Ph.D., Ge Li, M.D., Hans-Olov Adami, M.D., Ph.D., Fang-ChiIou, Ph.D., Xi Zhu, B.S., KaterinaBalter, Ph.D.

Jan 17, 2008
Your genes offer a road map to optimal health

2007: 23andMe introduces the first Personal Genome Service. Unlock the secrets of your own DNA. Today.


Perspective

Letting the Genome out of the Bottle — Will We Get Our Wish?

David J. Hunter, M.B., B.S., Sc.D., M.P.H., Main J. Khoury, M.D., Ph.D., and Jeffrey M. Drazen, M.D.

It may happen soon. A patient, perhaps one you have known for years, who is overweight and...
"I am convinced that within five years every college-educated person in America is going to have a profile like this. You cannot afford not having this."

Kari Stefansson, DeCode Genetics-April 1, 2008
Genetic Testing as a Public Health Issue

Two Challenges in Genomics Translation

Challenge 2: “Lost in Translation”

C. Lenfant NEJM 2003;349:868

< 33% of patients with coronary artery disease are prescribed aspirin

“About a quarter of the cases of FH predicted were diagnosed routinely; most remained undiagnosed until middle age”

Two Challenges in Genomics Translation
Challenge 2: ”Lost in Translation”
C. Lenfant NEJM 2003;349:868

“Let's be realistic: If we didn't do it with aspirin, how can we expect to do it with DNA?”


“About a quarter of the cases of FH predicted were diagnosed routinely; most remained undiagnosed until middle age”
“Translational and Clinical Science—Time for a New Vision”
E. Zerhouni NEJM 2005;353:15
**Discovery to Candidate Health Application**

1. **Gene discovery**
   - Define health outcome & intended use
   - Evaluate gene/environment/disease associations
   - Describe gene-disease biology
   - Identify potential interventions
   - Establish analytic & clinical validity

2. **Candidate health application**

Courtesy: W. Burke
Based on Khoury et al. Genet Med 2007
The “Second” Phase of Translation

“The Roadmap Less Traveled” L. Green

T1: First block:
Translation from concept into first human studies

T2: Second block:
Translation from human studies into practice

Bench <-> Bedside <-> Population

IOM Clinical Research Roundtable, Sung et al JAMA, 2003

Courtesy: G Ginsberg
T2
Candidate Health Application to Evidence-based Practice Guidelines

- Establish clinical utility
- Evidence synthesis
  - Identify evidence gaps: uncertainties about benefits, costs, harms
- Stakeholder input
- Evidence-based process

Courtesy: W. Burke
Based on Khoury et al. Genet Med 2007
The “Third” Phase in Translation

Figure. “Blue Highways” on the NIH Roadmap

- **BENCH**
  - Basic Science Research
  - Preclinical Studies
  - Animal Research

- **T1**
  - Case Series
  - Phase 1 and 2 Clinical Trials

- **BEDSIDE**
  - Human Clinical Research
  - Controlled Observational Studies
  - Phase 3 Clinical Trials

- **T2**
  - Translation to Humans
  - Guideline Development
  - Meta-analyses
  - Systematic Reviews

- **PRACTICE**
  - Clinical Practice
  - Delivery of Recommended Care to the Right Patient at the Right Time
  - Identification of New Clinical Questions and Gaps in Care

- **T3**
  - Dissemination Research
  - Implementation Research

- **T2**
  - Translation to Patients
  - Phase 3 and 4 Clinical Trials
  - Observational Studies
  - Survey Research

- **T3**
  - Translation to Practice
T3
Practice Guidelines to Health Practice

Dissemination research
Implementation research
Diffusion research
Phase IV clinical trials/observation
Policy analysis: Identify policy options that support appropriate use

Courtesy: W. Burke
Based on Khoury et al/ Genet Med 2007
The “Fourth” Phase of Genomics Translation: Population Health Impact!

**T4**

*Health Practice to Population Health Impact*

- Define outcomes of interest
- Identify/develop appropriate metrics
- Implement surveillance
- Determine benefits and harms
- Re-evaluate guidelines and policies → Identify needed changes

*Courtesy: W. Burke*

*Based on Khoury et al. Genet Med 2007*
The Genomics Translation Highway: 2001-2006

- More than 350,000 published human genetics/genomics articles
  - Almost all discovery
  - ~2% Translation Research T2+
  - Only 2 evidence-based recommendations
    - BRCA1 (11 years post gene discovery)
    - HFE (10 years post gene discovery)

The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention?

Main J. Khoury, MD, PhD, Maria Gwinn, MD, MPH, Paula W. Yoon, PhD, MPH, Nicole Dowling, PhD, Cynthia A. Moore, MD, PhD, and Linda Bradley, PhD

October 2007 · Vol. 9 · No. 10

Advances in genomics have led to mounting expectations in regard to their impact on health care and disease prevention. In light of this fact, a comprehensive research agenda is needed to move human genome discoveries into health practice in a way that maximizes health benefits and minimizes harm to individuals and populations. We present a framework for the continuum of multidisciplinary translation research that builds on previous characterization efforts in genomics and other areas in health care and prevention. The continuum includes four
Outline

- The phases of genomics translation
- Public health genomics: crucial role of clinical and population sciences in genomics translation
- Vision for the next decade: needs and opportunities
What is “Public Health Genomics?”

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

Focus:
- Populations
- Gene-environment Interaction
- Prevention
- Evidence-based applications
- ELSI integration
- Health disparities
Gene-Based Medicine
Critical Role of Clinical and Population Sciences

- **Multidisciplinary Approach**
  - Epidemiology - basic science of clinical observation and population health
  - Behavioral/social sciences
  - Intervention trials
  - Outcomes research
  - Economic analysis
  - Surveillance
  - Communication research
  - Legal and policy analysis
Public Health Genomics: Closing the Gap Between Gene Discovery and Population Health
Public Health Genomics: Closing the Gap Between Gene Discovery and Population Health

Population Studies
US Genome Profile
Public Health Studies

Gene Discovery       Closing the Gap       Population Health

The Role of Human Genomics in Acute Public Health Investigations: Current Practice and Future Strategies

Influenza Public Health Genomics
Workshop
January 11-12, 2007
Centers for Disease Control and Prevention
Atlanta, Georgia
Public Health Genomics: Closing the Gap Between Gene Discovery and Population Health

Population Studies
- US Genome Profile
- Public Health Studies

HuGENet
- Human
- Genome
- Epidemiology
- Network

Gene Discovery

Closing the Gap

Population Health
Human Genome Epidemiology Network (HuGENet)

- Global collaboration of individuals and organizations to assess population impact of genomics and how it can be used to improve health and prevent disease
  - 4 coordinating centers (UK, Canada, Greece, USA)
  - Dozens of networks
  - Hundreds of collaborators
  - 10 collaborating journals

A road map for efficient and reliable human genome epidemiology

John P Ioannidis1,2, Marta J Grimes3, Julian Little4, Julian P T Higgins5,6, James L Bernstein7, Paolo Boffetta8, Melissa Bondy9, Molly S Brady9, Paul E Branchley11, Patricia A Buffler12, Juan Pablo Casas9, Anand Chokkalingam12, John Danesh4, George Davey Smith13, Siobhan Dolan14, Ross Duncan14, Nelleke A Gruis18, Patricia Hartge13, Mia Hashibe6, David Hunter20, Marjo-Riitta Jarvelin11,12, Beatrice Malner13, Teri Manolio4, Demetrious M Maraganore22, Julia A Newton-Bishop22, Thomas R O’Brien15, Gloria Petersen16, Eliz Robe16, Georgia Salami17,18, Daniela Seminara18, Lisa Smooth18, Emanuela Taïoli12, Nick Timpson19, Andre G Uitterlinden19, Paolo Vineis18, Nick Wareham9, Deborah M Wein12, Ron Zimmerman6, Muij J Khoury18 & the Human Genome Epidemiology Network and the Network of Investigator Networks

Networks of investigators have begun sharing best practices, tools and methods for analysis of associations between genetic variation and common diseases. A Network of Investigator Networks has been set up to drive the process.
A Critical Appraisal of the Scientific Basis of Commercial Genomic Profiles Used to Assess Health Risks and Personalize Health Interventions

A. Cecile J.W. Janssens,1,4 Marta Gwinn,2 Linda A. Bradley,2 Ben A. Oostra,3 Cornelia M. v and Muin J. Khoury2

Predictive genomic profiling used to produce personalized nutrition and other lifestyle health recommendations is cur directly to consumers. By examining previous meta-analyses and HuGE reviews, we assessed the scientific evidence supporting gene-disease associations for genes included in genomic profiles offered online. We identified seven companies that provide genomic profiling. We searched Pubmed for meta-analyses and HuGE reviews of studies of gene-disease associations per 2000 through June 2007 in which the genotypes of people with a disease were compared with those of a healthy or general control group. The seven companies tested at least 49 different polymorphisms in 56 genes. Of the 56 genes tested, 24 (4 reviewed in meta-analyses). For the remaining 32 genes, we found 260 meta-analyses that examined 160 unique polymorphisms associated with disease risk. None of the 31 tested associations reached a significant level of evidence that genetic factors contributed significantly to disease risk in the general population.

Editorial

Turning the Pump Handle: Evolving Methods for Integrating the Evidence on Gene-Disease Association


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14 National Heart and Lung Institute, Imperial College.
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- US Genome Profile
- Public Health Studies

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HuGENet
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- Epidemiology
- Network

Closing the Gap

EGAPP
- Evaluation of Genomic Applications in Practice & Prevention

Population Health
EGAPP

- Non-regulatory
- Independent, non-federal, multidisciplinary Working Group
- Integrate existing processes for evaluation and appraisal
- Minimize conflicts of interest
- Evidence-based, transparent, and publicly accountable
Evaluation of Genomic Applications in Practice and Prevention

Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors

This statement summarizes the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group recommendations regarding CYP450 genetic testing in adult patients beginning treatment with selective serotonin reuptake inhibitors (SSRIs), and the supporting scientific evidence. EGAPP is a project developed by the National Office of Public Health Genomics at the Centers for Disease Control and Prevention to support a rigorous, evidence-based process for evaluating genetic tests and other genomic applications that are in transition from research to clinical and public health practice in the United States. A key goal of the EGAPP Working Group is to develop conclusions and recommendations regarding clinical genomic applications and to establish clear linkage to the supporting scientific evidence. The Working Group members are nongovernmental experts in genetics, laboratory medicine, and clinical epidemiology convened to establish methods and processess; set priorities for review topics; participate in technical expert panels for commissioned evidence reviews; publish recommendations; and provide guidance and feedback on other project activities.

Summary of Recommendations

The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for nonpsychotic depression. In the absence of supporting evidence, and with consideration of other clinical issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.

Rationale: The EGAPP Working Group found no evidence linking testing for CYP450 to clinical outcomes in adults treated with SSRIs. While some studies of a single SSRI dose in healthy patients report an association between genotypic CYP450 drug metabolizer status and circulating SSRI levels, this association was not supported by studies of patients receiving ongoing SSRI treatment. Further, CYP450 genotypes are not consistently associated with the patient outcomes of interest, including clinical response to SSRI treatment or adverse events as a result of treatment. No evidence was available showing that the results of CYP450 testing influenced SSRI choice or dose and improved patient outcomes, or was useful in medical, personal, or public health decision-making. In the absence of evidence supporting clinical utility, it is not known if potential benefits from CYP450 testing will outweigh potential harms. Potential harms may include increased cost without impact on clinical decision making or improvement in patient outcomes, less frequent exposure to potentially harmful drugs, or decreased clinical efficacy.

Evidence based medicine meets genomic medicine

Jim Evans, MD, PhD, and Muin J. Khoury, MD, PhD
The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non-psychotic depression. ...EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.
<table>
<thead>
<tr>
<th>Disorder/Effect</th>
<th>Test</th>
<th>Target Population</th>
<th>Intended Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>CYP2D6</td>
<td>Individuals prior to treatment for BrCa</td>
<td>Treatment with Tamoxifen</td>
</tr>
<tr>
<td>Diabetes, Type II</td>
<td>TCF7L2</td>
<td>General population</td>
<td>Risk assessment</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>Multigene panels</td>
<td>General population</td>
<td>Risk prediction; drug or nutritional/lifestyle management</td>
</tr>
<tr>
<td>Thrombophilia</td>
<td>F5, F2</td>
<td>Individuals with family history or clinical suspicion of thrombophilia</td>
<td>Prevention and management</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>Gene expression profiles</td>
<td>Women diagnosed with breast cancer</td>
<td>Treatment and recurrence risk</td>
</tr>
<tr>
<td>Colorectal Cancer (CRC)</td>
<td>UGT1A1</td>
<td>Individuals diagnosed with CRC</td>
<td>Treatment with Irinotecan</td>
</tr>
<tr>
<td>Hereditary Nonpolyposis Colorectal Cancer (HNPCC)</td>
<td>Mismatch repair gene mutations</td>
<td>Individuals diagnosed with CRC and their family members</td>
<td>Management of individuals and early detection/prevention for family members</td>
</tr>
<tr>
<td>Depression</td>
<td>CYP450</td>
<td>Individuals diagnosed with depression</td>
<td>Treatment with SSRI drugs</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>Genomic Tests</td>
<td>1) General population of women and; 2) women at increased risk for ovarian cancer</td>
<td>Detection and management</td>
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Gene Discovery

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Genome
Epidemiology
Network

Closing the Gap

EGAPP
Evaluation of Genomic Applications in Practice & Prevention

Population Health Practice
Family history
Surveillance
G&PH Centers
PH Capacity
Competencies
Outline

- The phases of genomics translation
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Translating Genomics: Needs and Opportunities for the Next Decade

- Accelerate **translation research** to close the widening gap (with balanced investment in T1 through T4)

- Enhance **knowledge synthesis and evidence based guidelines and policies** for better decision making

- Engage/empower consumers and educate providers with decision support tools such as family history and genetic test information

- Expand **public-private partnerships** to enhance the pipeline for appropriate integration of genomics into health and health care
We Need More Genomics Translation Research

- 2008: 2 CDC initiatives to fund genomics translation research and programs
- Includes genetic/genomic tests and family history
- Close the gaps identified through EGAPP
- Partnership development process (federal, state, academia, private sector)
- Translation Network for Genomic Applications in Practice and Prevention (GAPPNet)

CDC’s National Office of Public Health Genomics Announces New Funding Opportunity!

CDC’s National Office of Public Health Genomics announces a new funding opportunity for those interested in genomic translation research. The funding opportunity announcement (FOA), entitled "Genomic Applications in Practice and Prevention: Translation Research," offers award amounts from $200,000 to $350,000.

This FOA seeks applications to conduct research that will accelerate the translation of genomics into public health practice, in cooperation with federal, state, and local agencies, private sectors, and academic institutions. The announcement is open for applications from May 7, 2008, to June 6, 2008.
Genomic Medicine Meets Evidence-Based Medicine: Where is the Right Threshold Between Research and Practice?
Genomic Medicine Meets Evidence-Based Medicine: Problems with Low Threshold

Discovery

Evidence-Based knowledge Synthesis & Guidelines Development

Delivery

Unknown benefits
Potential harms
Expensive technologies
Lack of coverage
Disparities
Genomic Medicine Meets Evidence-Based Medicine: Problems with High Threshold

- Investment disincentive
- Slow integration
- Delayed access
- Lack of coverage
- Disparities
Is there a Solution to the Current Evidence Dilemma in Genomic Medicine?

- Explore the concept of “Coverage with Evidence Development (CED)”
- Clinical and public health data collection for certain tests that meet minimal evidentiary standards
- Post market data collection and research as a prerequisite
- Registry and decision support tools for consumers and providers
- Different thresholds for different types of tests or applications
Can we Travel the Genomics Translation Roadmap?