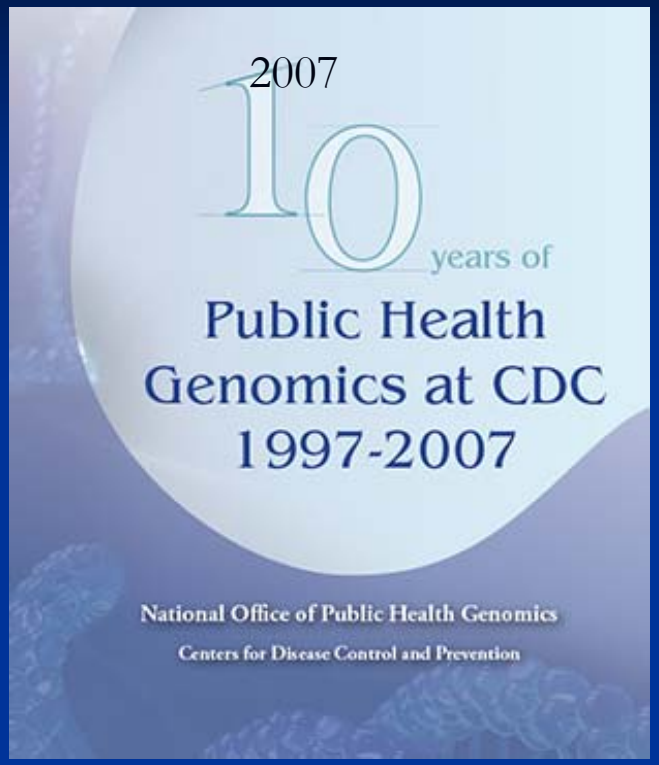
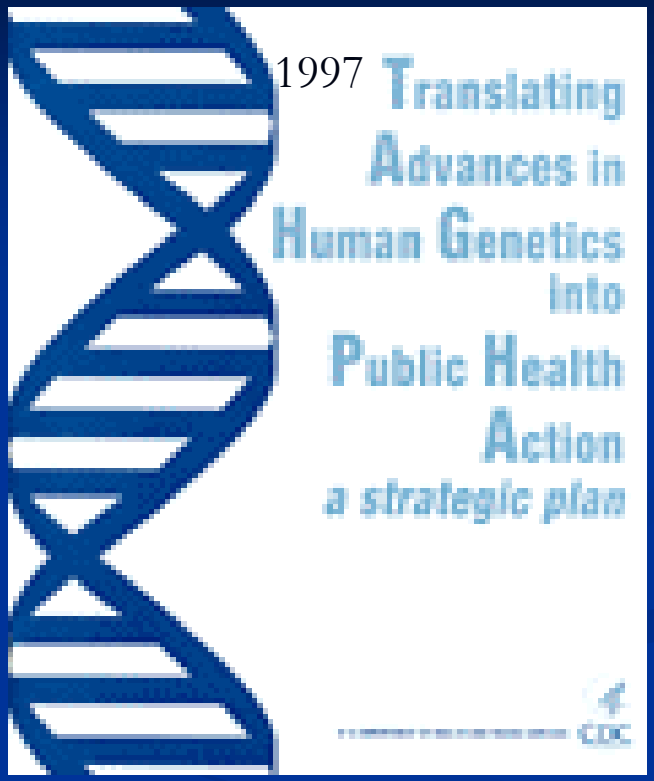
Public Health Genomics:
Translating Genome Discoveries into Population Health





Muin J. Khoury MD, PhD

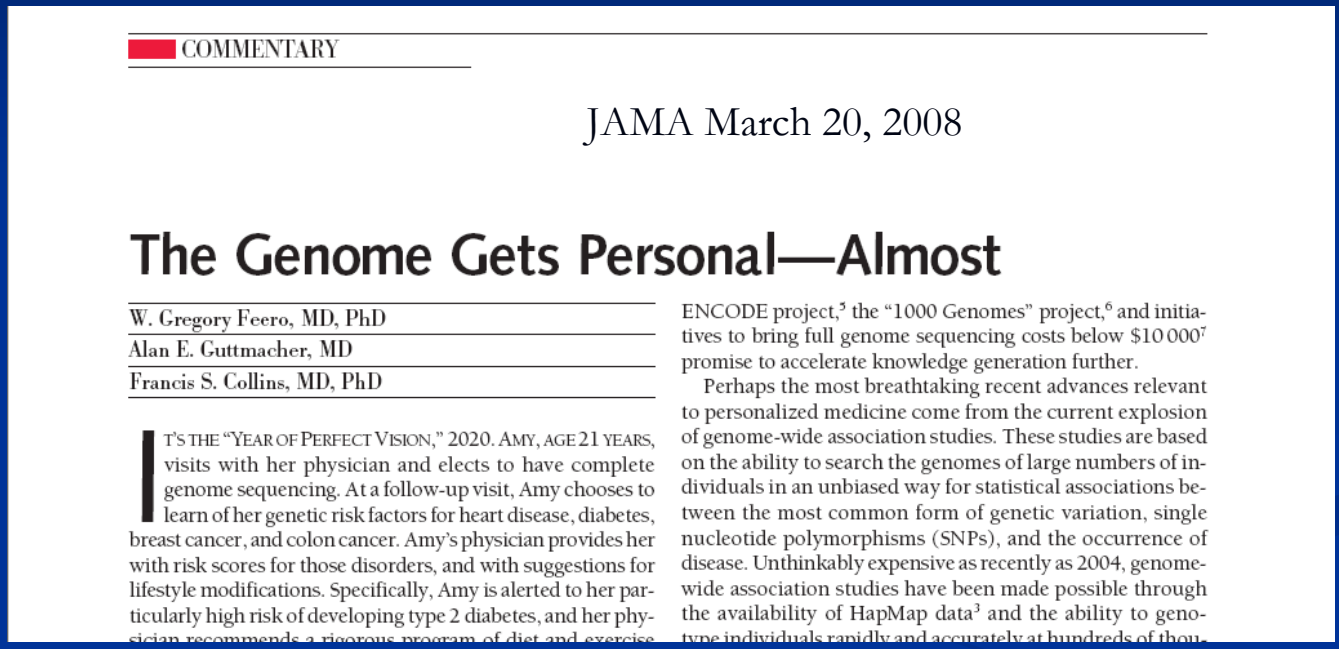
Director, CDC National Office of Public Health Genomics
Senior Consultant in Public Health Genomics, NCI Division of Cancer Control and Population Sciences

SAFER • HEALTHIER • PEOPLE™

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 Do You Do With Genes When You Find Them?



COMMENTARY

JAMA March 20, 2008

The Genome Gets Personal—Almost

W. Gregory Feero, MD, PhD
Alan E. Guttmacher, MD
Francis S. Collins, MD, PhD

IT'S THE "YEAR OF PERFECT VISION," 2020. AMY, AGE 21 YEARS, visits with her physician and elects to have complete genome sequencing. At a follow-up visit, Amy chooses to learn of her genetic risk factors for heart disease, diabetes, breast cancer, and colon cancer. Amy's physician provides her with risk scores for those disorders, and with suggestions for lifestyle modifications. Specifically, Amy is alerted to her particularly high risk of developing type 2 diabetes, and her physician recommends a rigorous program of diet and exercise

ENCODE project,[5] the "1000 Genomes" project,[6] and initiatives to bring full genome sequencing costs below $10 000[7] promise to accelerate knowledge generation further.

Perhaps the most breathtaking recent advances relevant to personalized medicine come from the current explosion of genome-wide association studies. These studies are based on the ability to search the genomes of large numbers of individuals in an unbiased way for statistical associations between the most common form of genetic variation, single nucleotide polymorphisms (SNPs), and the occurrence of disease. Unthinkably expensive as recently as 2004, genome-wide association studies have been made possible through the availability of HapMap data[3] and the ability to genotype individuals rapidly and accurately at hundreds of thou-

"I predict that comprehensive, genomics-based health care will become the norm with individualized preventive medicine and early detection of illnesses" (Zerhouni, 2006)

Predictive, Preventive and Personalized Medicine

Two Challenges in Genomics Translation

Challenge 1: Premature Translation

January 22, 2008

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- All Prostate Cancer Topics

PROSTATE CANCER GUIDE

Prostate Cancer Health Center

Prostate Cancer Gene Test Coming Soon

FONT SIZE A A A

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

By Miranda Hitti
WebMD Medical News

Reviewed by Louise Chang, MD

Jan. 16, 2008 -- Scientists at W
gene test for prostate cancer ris

The test screens men's blood o
prostate cancer. Once those blo
the test takes about a week.

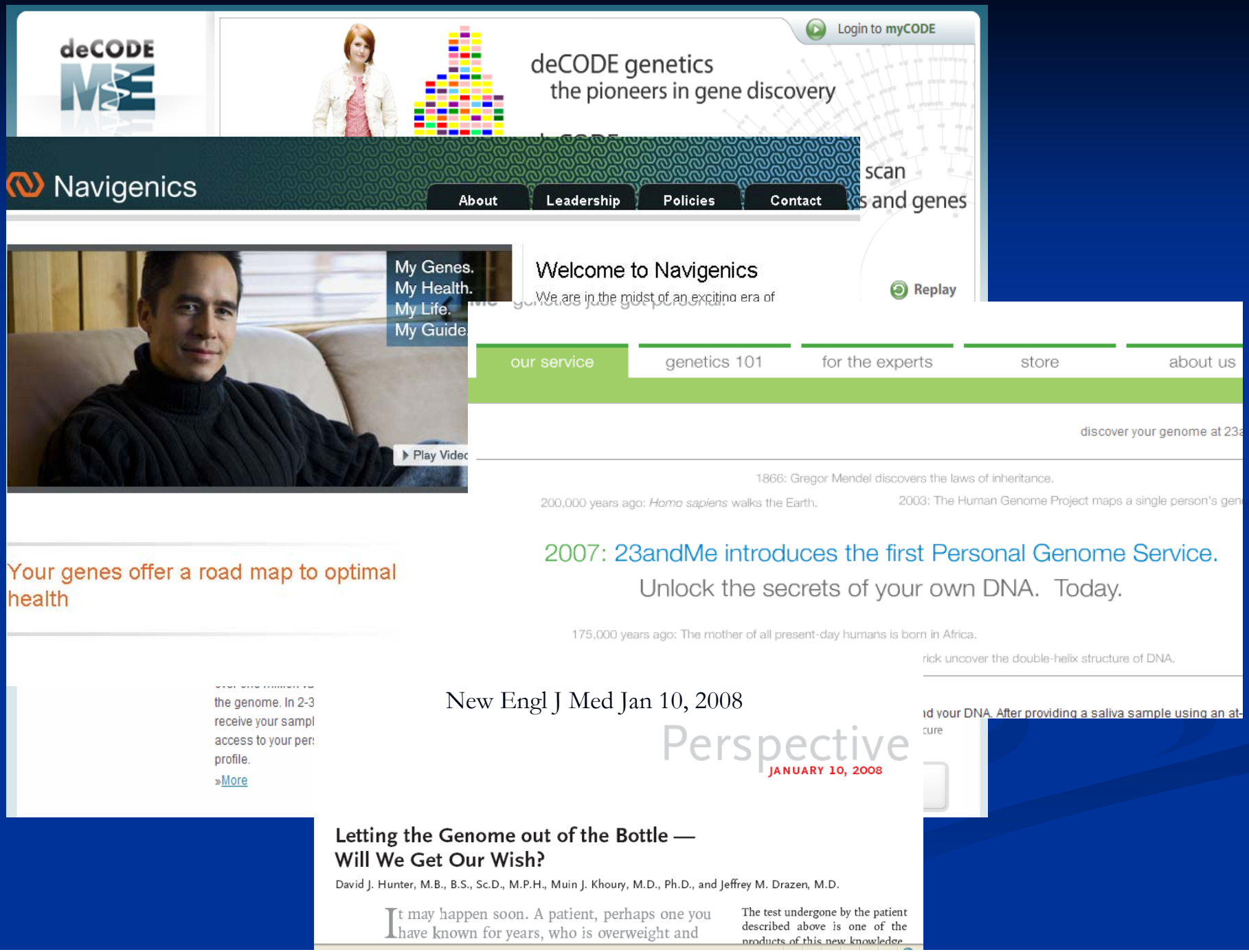
The NEW ENGLAND JOURNAL of MEDICINE

Jan 17, 2008

ORIGINAL ARTICLE

Cumulative Association of Five Genetic Variants with Prostate Cancer

S. Lilly Zheng, M.D., Jielin Sun, Ph.D., Fredrik Wiklund, Ph.D., Shelly Smith, M.S., Pär Stattin, M.D., Ph.D., Ge Li, M.D., Hans-Olov Adami, M.D., Ph.D.,


deCODE
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Navigenics
About
Leadership
Policies
Contact
scan
s and genes
My Genes.
My Health.
My Life.
My Guide
Play Video
Welcome to Navigenics
We are in the midst of an exciting era of
Replay
our service
genetics 101
for the experts
store
about us
discover your genome at 23
1866: Gregor Mendel discovers the laws of inheritance.
200,000 years ago: Homo sapiens walks the Earth.
2003: The Human Genome Project maps a single person's gen
2007: 23andMe introduces the first Personal Genome Service.
Unlock the secrets of your own DNA. Today.
175,000 years ago: The mother of all present-day humans is born in Africa.
rick uncover the double-helix structure of DNA.
Your genes offer a road map to optimal health
the genome. In 2-3
receive your sampl
access to your per
profile.
»More
id your DNA. After providing a saliva sample using an at-
cure
New Engl J Med Jan 10, 2008
Perspective
JANUARY 10, 2008
Letting the Genome out of the Bottle —
Will We Get Our Wish?
David J. Hunter, M.B., B.S., Sc.D., M.P.H., Muin 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
The test undergone by the patient described above is one of the products of this new knowledge

"My Genome, Myself: Seeking Clues in DNA"
A. Harmon, New York Times, Nov 17, 2007

TRACKING SNPS

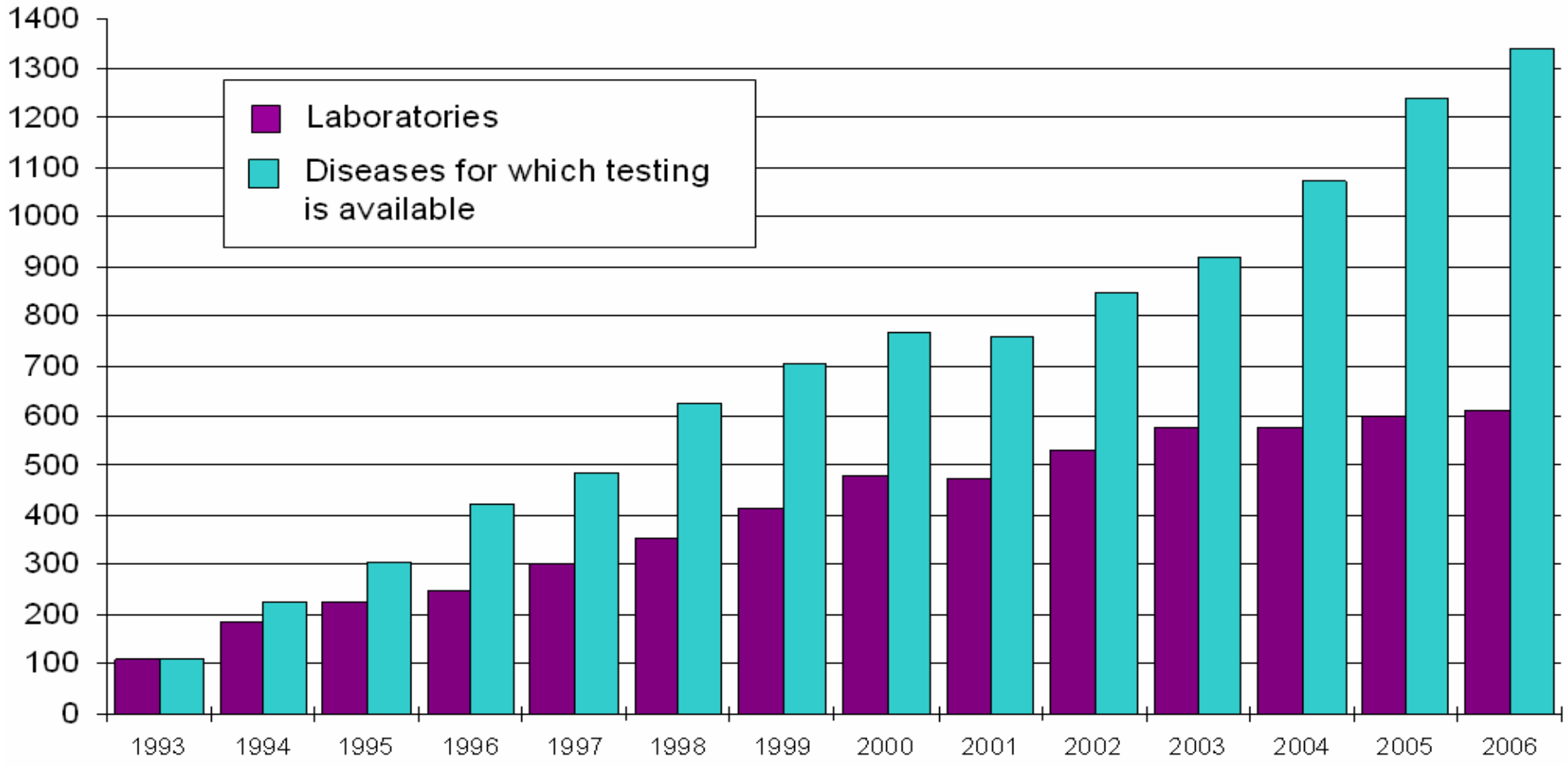
Using the Web site of 23andMe, a company that queried 550,000 SNPs in a sample of her DNA, the reporter determined that her genotype for adult lactose intolerance is **GG** (she is lactose intolerant). Some of her other genotypes are below:

SNP	Location	Genotype	Genotype associated with
rs662799	APOA5	AA	Tendency to gain weight when eating fatty foods
rs174575	FADS2	CC	Higher I.Q. if breast fed for nine months as infant
rs6920220	6q23	GG	Low risk of rheumatoid arthritis
rs17070145	KIBRA	CC	Relatively poor verbal memory
rs1801260	CLOCK	AA	Early rising
rs1953558	OR11H7P	CC	Sensitivity to smell of sweat
rs17822931	ABCC11	CC	Wet earwax

"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



Data source: GeneTests database (2006) / www.genetests.org

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"

HA Neil BMJ (2000)

Two Challenges in Genomics Translation

Challenge 2:"Lost in Translation"

C. Lenfant NEJM 2003;349:868

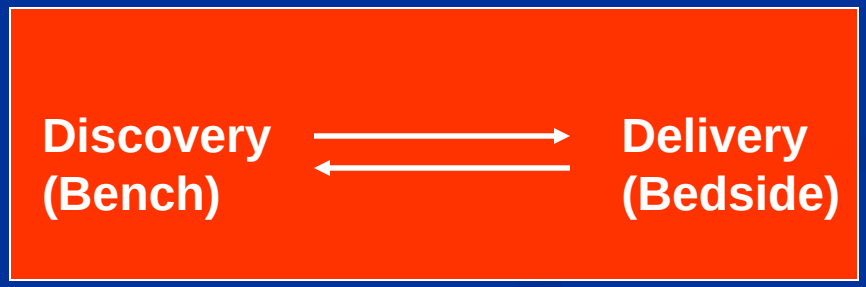
"Let's be realistic: If we didn't do it with aspirin, how can we expect to do it with DNA?"

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

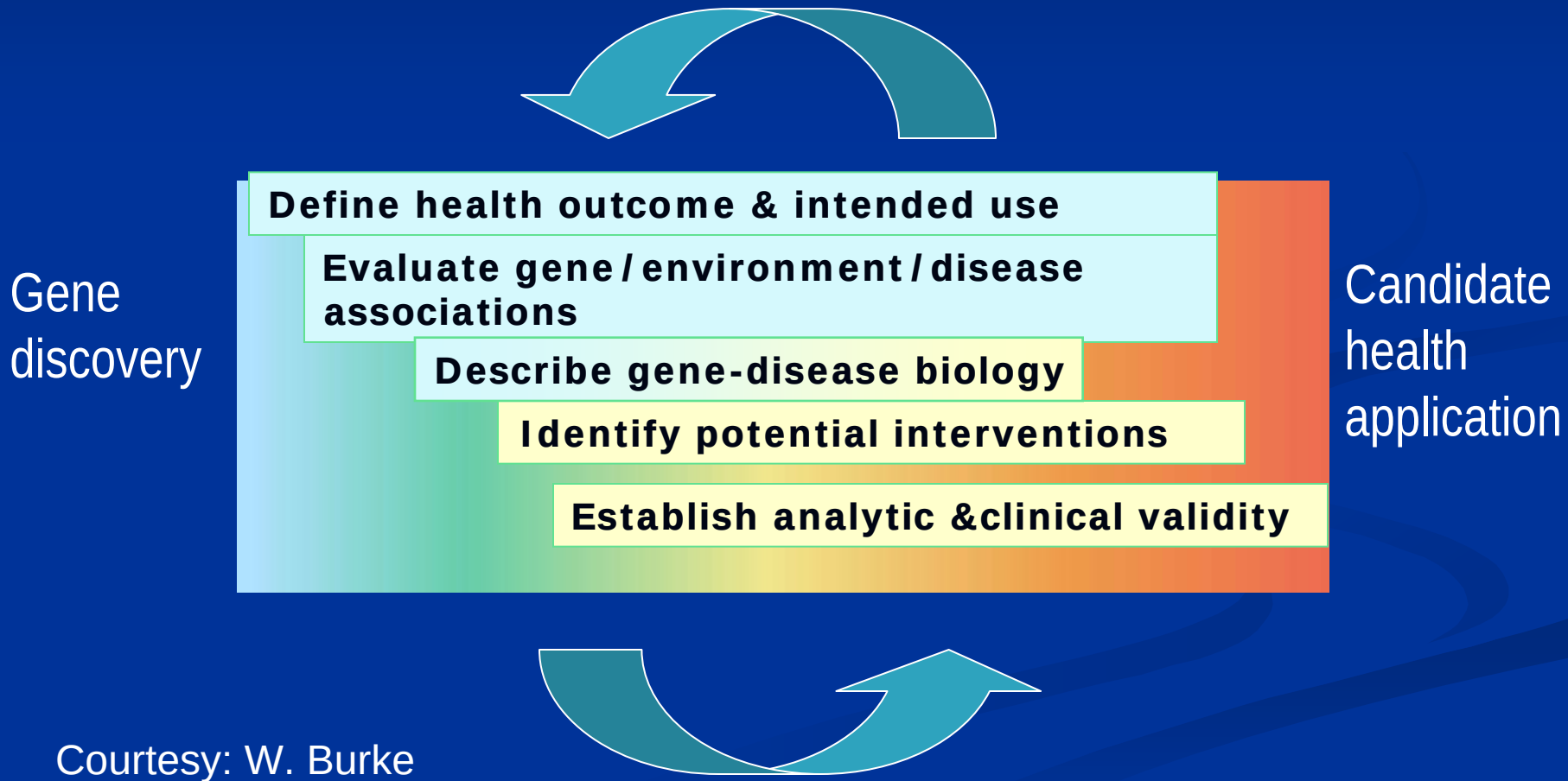
HA Neil BMJ (2000)

"Translational and Clinical Science—Time for a New Vision"

E. Zerhouni NEJM 2005;353:15



T1
Discovery to 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

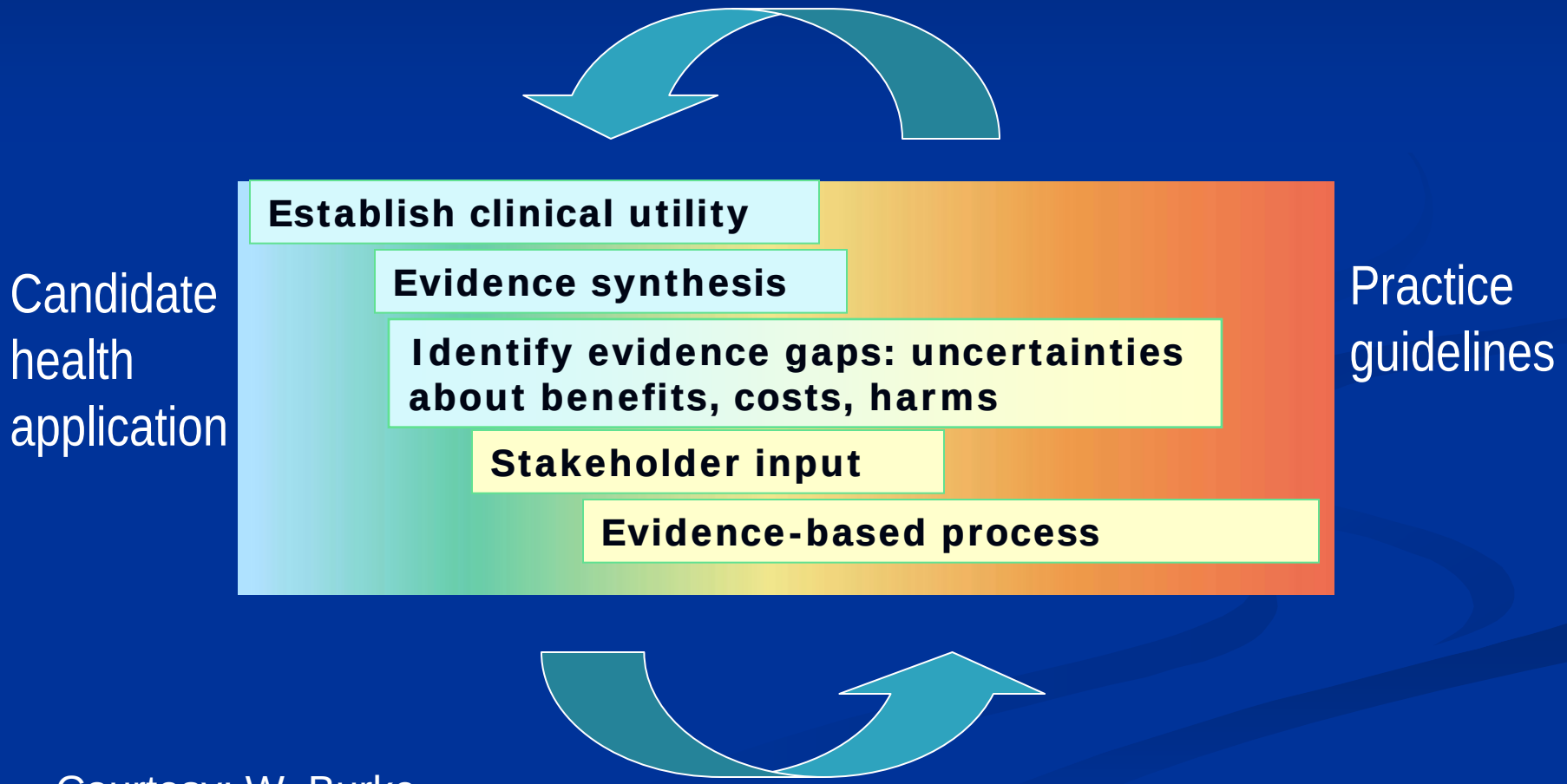
T2: Second block:

Translation from human studies into practice

Courtesy:
G Ginsberg

IOM Clinical Research Roundtable, Sung et al JAMA, 2003

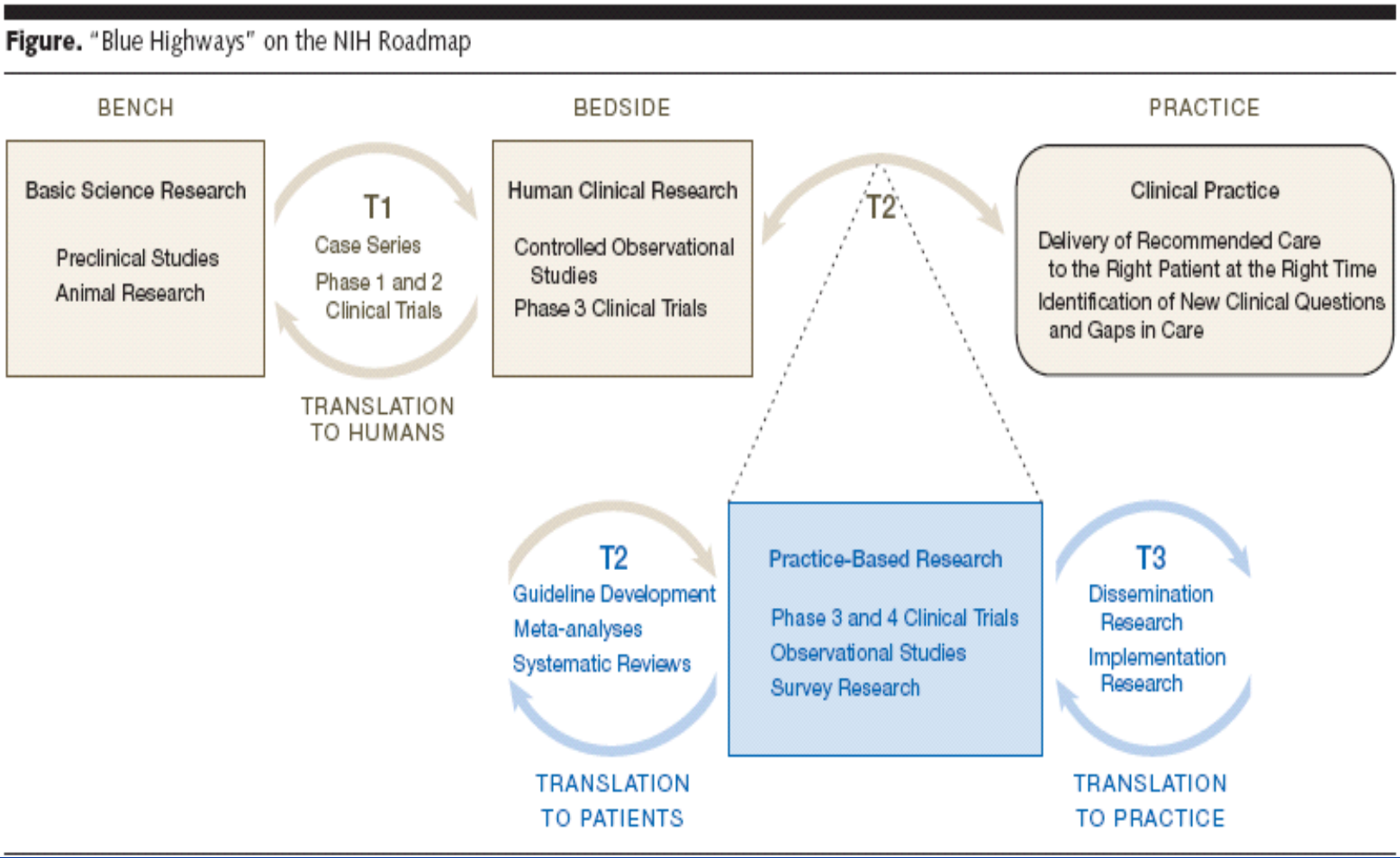
T2
Candidate Health Application to Evidence-based Practice Guidelines



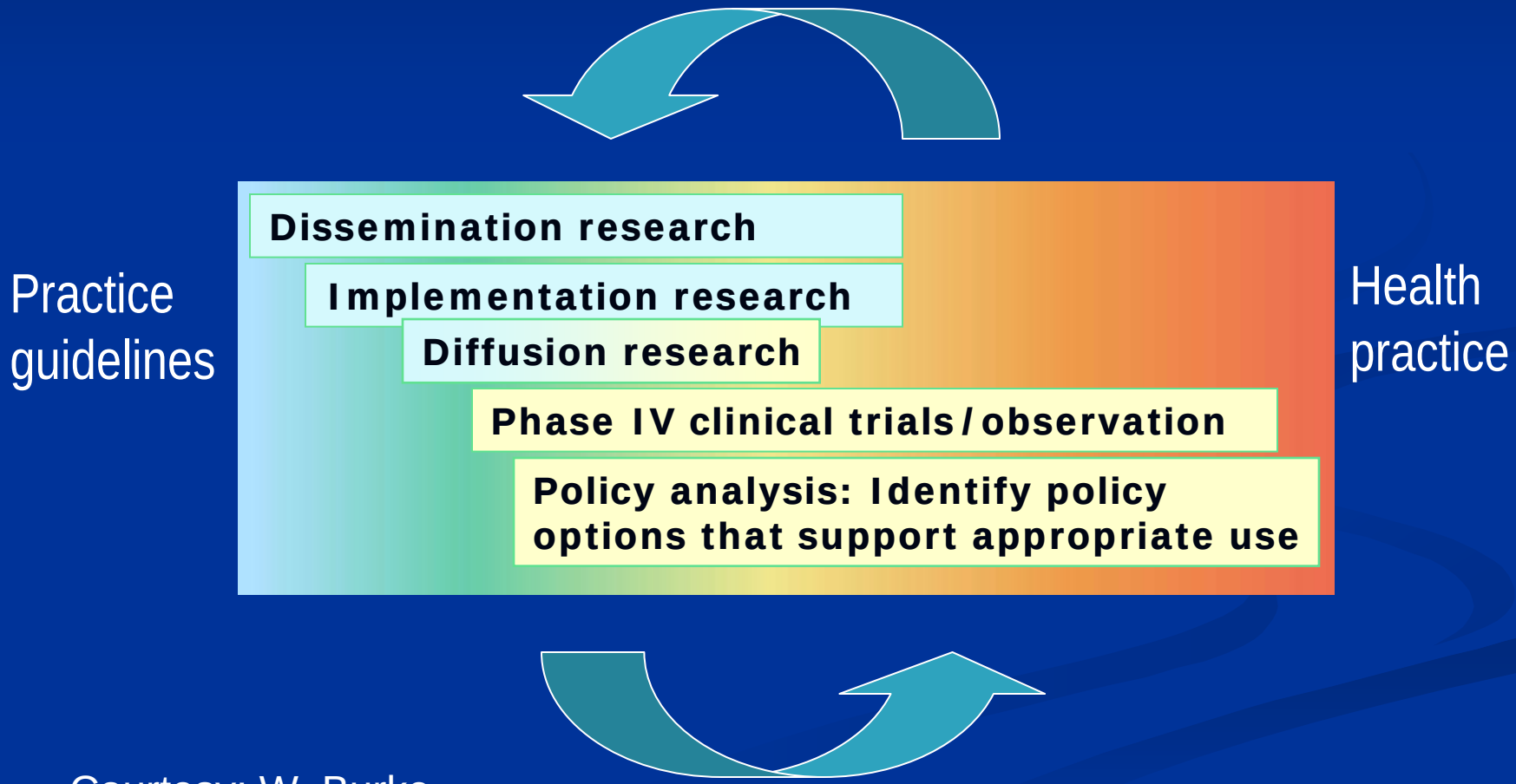
Courtesy: W. Burke
Based on Khoury et al. Genet Med 2007

The "Third" Phase in Translation

JM Westfall et al JAMA 2007;297:403.

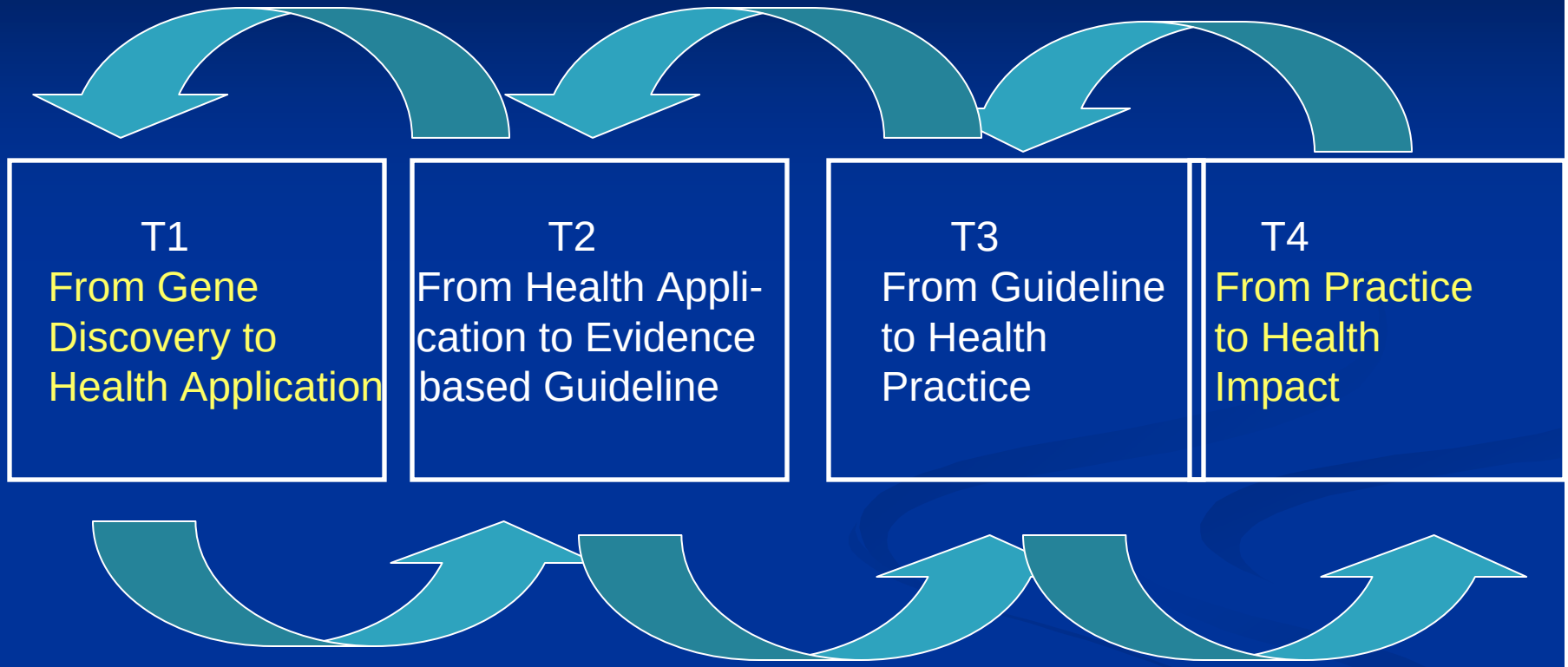


T3
Practice Guidelines to Health Practice



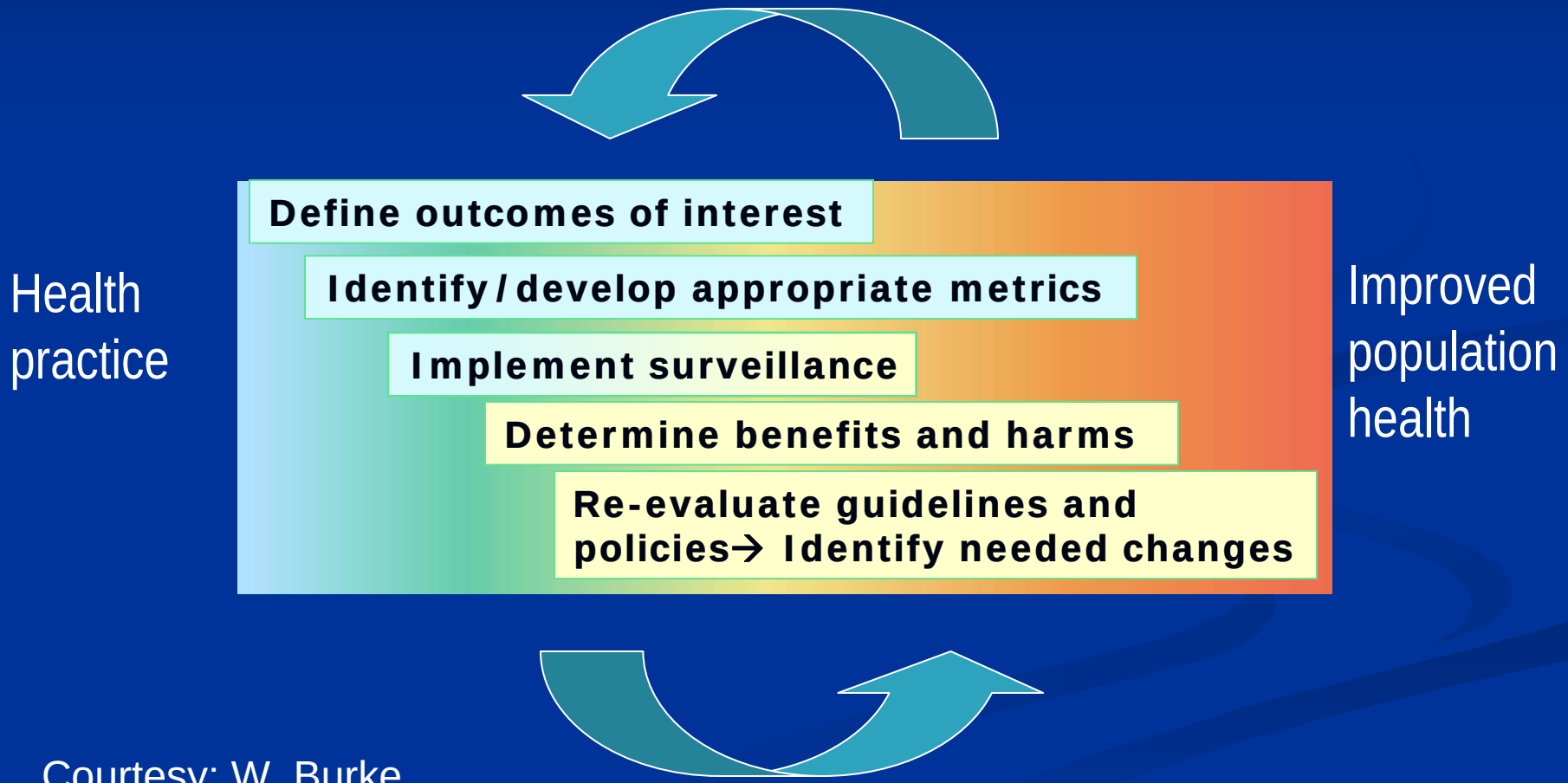
Courtesy: W. Burke
Based on Khoury et al/ Genet Med 2007

The "Fourth" Phase of Genomics Translation: Population Health Impact!



Khoury MJ et al. Genet Med 2007

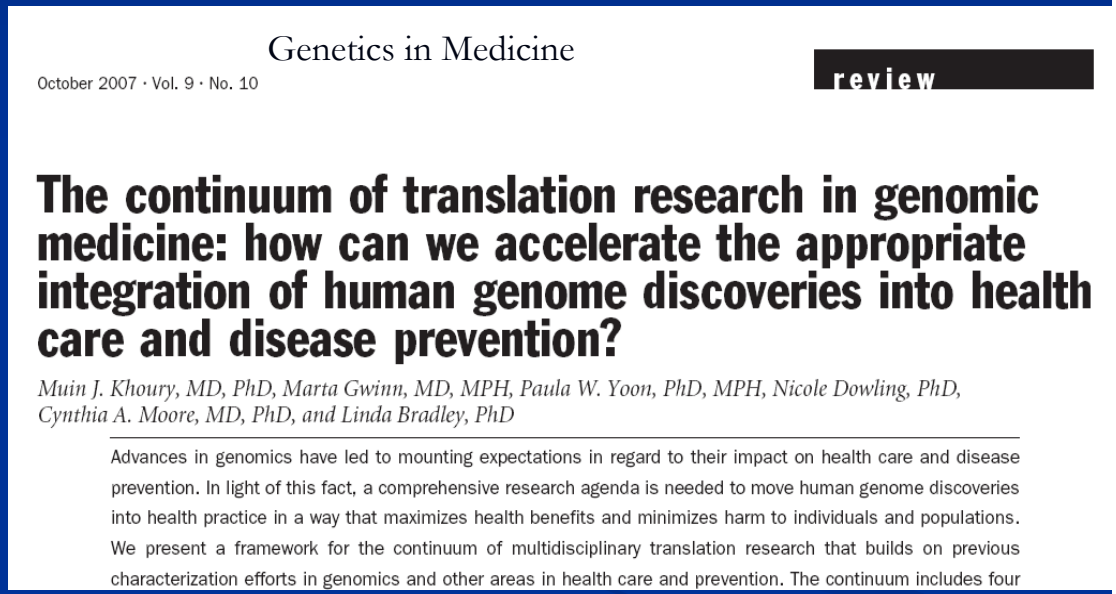
T4
Health Practice to Population Health Impact



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)



Genetics in Medicine
October 2007 · Vol. 9 · No. 10

review

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?

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

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

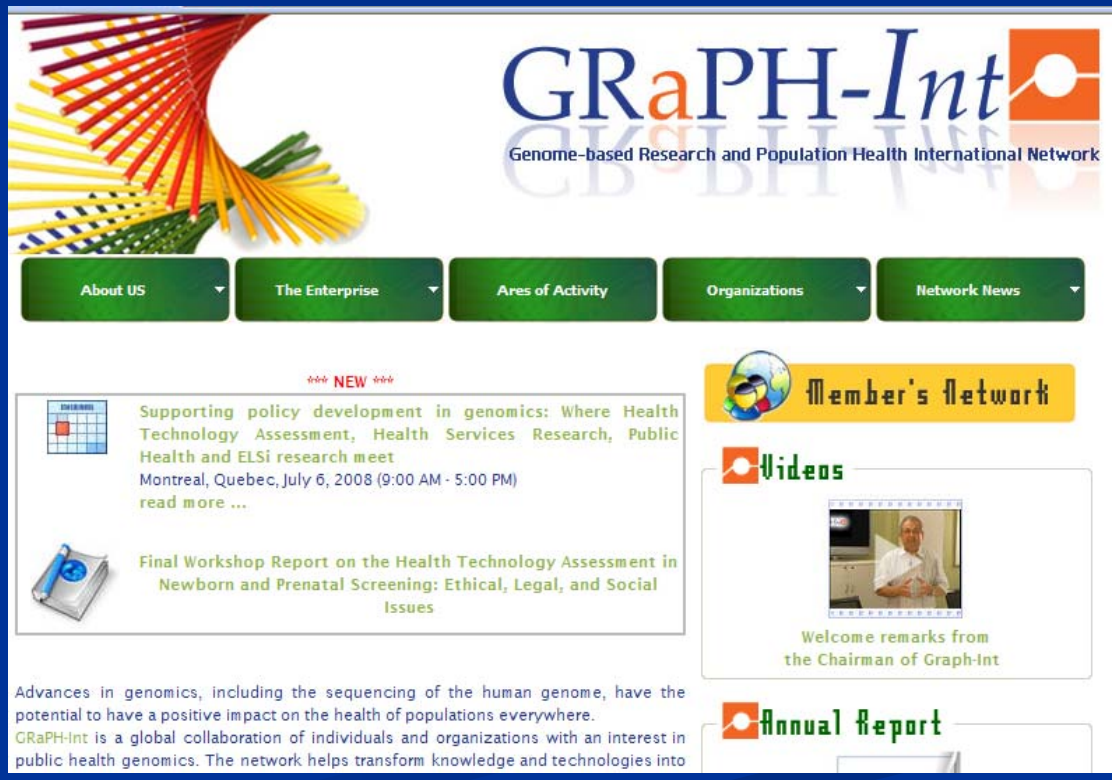
Outline

- 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



International Collaboration

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

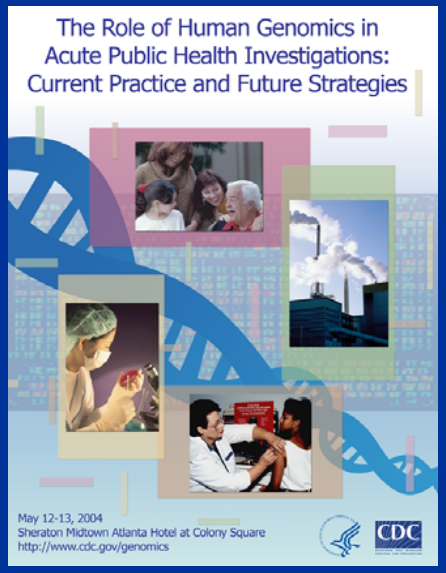
Public Health Genomics: Closing the Gap Between Gene Discovery and Population Health

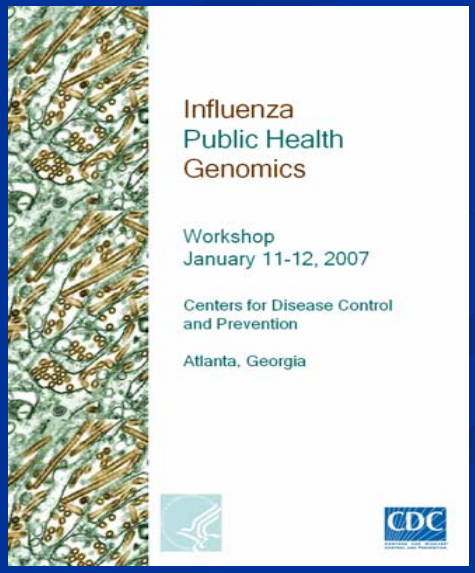
Population Studies

US Genome Profile

Public Health Studies

Gene Discovery ⇢ **Closing the Gap** ⇢ **Population Health**





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**

Nat Genet 2006

COMMENTARY

A road map for efficient and reliable human genome epidemiology

John P A Ioannidis[1,2], Marta L Gwinn[3], Julian Little[4], Julian P T Higgins[5,6], Jonine L Bernstein[7], Paolo Boffetta[8], Melissa Bondy[9], Molly S Bray[10], Paul E Brenchley[11], Patricia A Buffler[12], Juan Pablo Casas[13], Anand Chokkalingam[12], John Danesh[14], George Davey Smith[15], Siobhan Dolan[16], Ross Duncan[17], Nelleke A Gruis[18], Patricia Hartge[19], Mia Hashibe[8], David Hunter[20], Marjo-Riitta Jarvelin[21,22], Beatrice Malmer[23], Teri Manolio[24], Demetrius M Maraganore[25], Julia A Newton-Bishop[26], Thomas R O'Brien[19], Gloria Petersen[27], Elio Riboli[8], Georgia Salanti[1,5], Daniela Seminara[28], Liam Smeeth[13], Emanuela Taioli[29], Nic Timpson[15], Andre G Uitterlinden[30], Paolo Vineis[20,31], Nick Wareham[32], Deborah M Winn[28], Ron Zimmern[6], Muin J Khoury[3] & the Human Genome Epidemiology Network and the Network of Investigator Networks

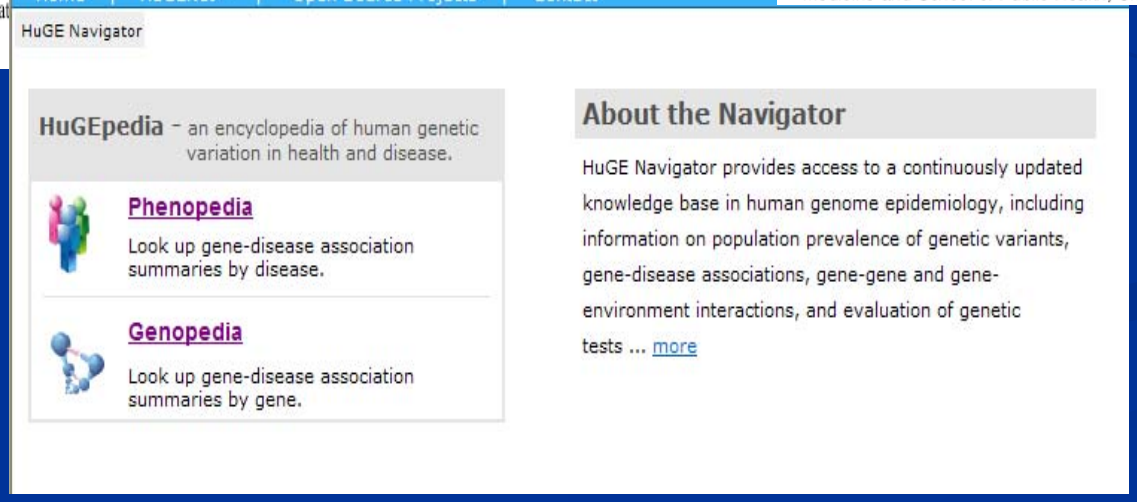
Networks of investigators have begun sharing best practices, tools and methods for analysis of associations between genetic variation and common diseases. A Network of Investigator Networks has been set up to drive the process,

AJHG March 2008 **ARTICLE**

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,*] Marta Gwinn,[2] Linda A. Bradley,[2] Ben A. Oostra,[3] Cornelia M. va and Muin J. Khoury[2]

Predictive genomic profiling used to produce personalized nutrition and other lifestyle health recommendations is curr directly to consumers. By examining previous meta-analyses and HuGE reviews, we assessed the scientific evidence suppo ported gene-disease associations for genes included in genomic profiles offered online. We identified seven companies that tive genomic profiling. We searched PubMed for meta-analyses and HuGE reviews of studies of gene-disease associations pu 2000 through June 2007 in which the genotypes of people with a disease were compared with those of a healthy or gener control group. The seven companies tested at least 69 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 polymor associat differen tective noncar signific that ge mendat



American Journal of Epidemiology

DOI: 10.1093/aje/kwm248

Editorial

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

Julian P. T. Higgins[1], Julian Little[2], John P. A. Ioannidis[3,4], Molly S. Bray[5], Teri A. Manolio[6], Liam Smeeth[7], Jonathan A. Sterne[8], Betsy Anagnostelis[9], Adam S. Butterworth[10], John Danesh[10], Carol Dezateux[11], John E. Gallacher[12], Marta Gwinn[13], Sarah J. Lewis[8], Cosetta Minelli[14], Paul D. Pharoah[15], Georgia Salanti[3], Simon Sanderson[10], Lesley A. Smith[16], Emanuela Taioli[17], John R. Thompson[18], Simon G. Thompson[1], Neil Walker[19], Ron L. Zimmern[20], and Muin J. Khoury[13]

[1] MRC Biostatistics Unit, Cambridge, United Kingdom.
[2] Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa, Ontario, Canada.
[3] Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina, Greece.
[4] Center for Human Genetics, Institute of Molecular Medicine and School of Public Health, University of Texas,
[11] Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, London, United Kingdom.
[12] Department of Epidemiology, Cardiff University, Cardiff, Wales, United Kingdom.
[13] National Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, GA.
[14] National Heart and Lung Institute, Imperial College,

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EGAPP

Evaluation of

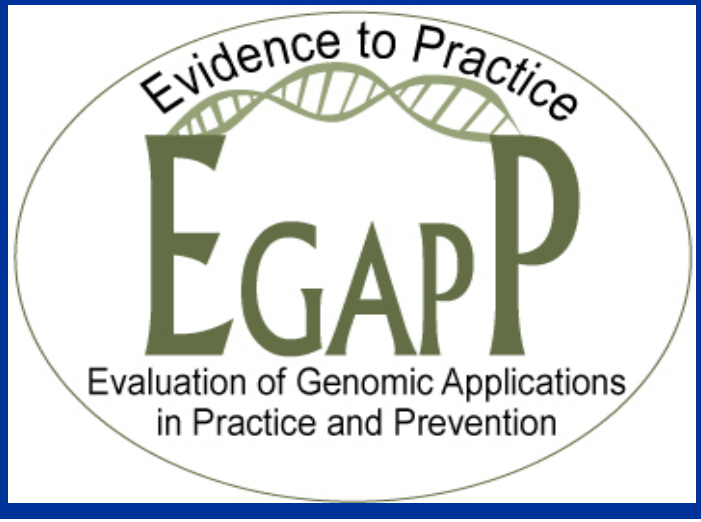
Genomic

Applications in

Practice &
Prevention

EGAPP

Evaluation of
Genomic
Applications in
Practice and
Prevention



- 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

Evidence to Practice

EGAPP

Evaluation of Genomic Applications in Practice and Prevention

- Home
- About EGAPP
- Working Group
- Topics
- Methods
- Evidence Reports
- Recommendations
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- Resources
- Contact Us

Evaluation of Genomic Applications in Practice and Prevent
systematic process for evaluating genetic tests and other geno
public health practice in the United States.

The EGAPP Working Group was established in 2005 to support
evidence regarding the validity and utility of rapidly emerging genetic tests for cli
and selects tests, reviews CDC-commissioned evidence reports and other contextu
on appropriate use of genetic tests in specific clinical scenarios.

What's New

EGAPP Working Group Releases First Recommendation Stater
recommendation statement.*

December 2007 · Vol. 9 · No. 12

EGAPP recommendation statement

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

*Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group**

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 nonfederal experts in genetics, laboratory medicine, and clinical epidemiology convened to establish methods and processes; 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 Recommendation

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 contextual 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 drugs

December 2007 · Vol. 9 · No. 12

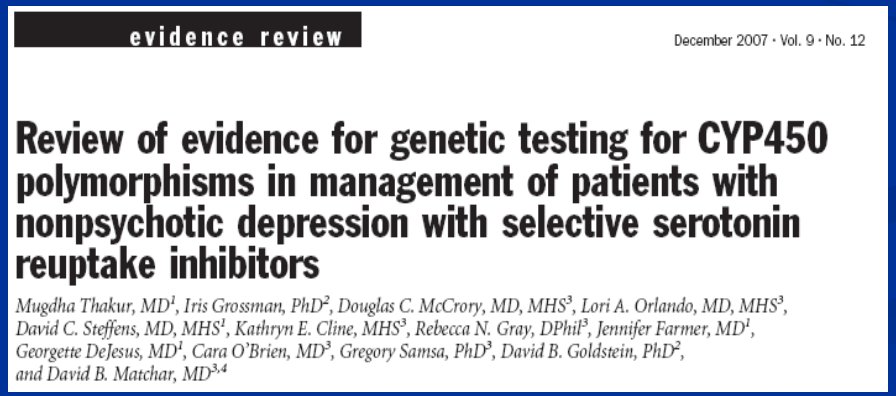
commentary

Evidence based medicine meets genomic medicine

Jim Evans, MD, PhD[1], and Muin J. Khoury, MD, PhD[2]

EGAPP Recommendation (Dec-2007)

- *"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."*



evidence review

December 2007 · Vol. 9 · No. 12

Review of evidence for genetic testing for CYP450 polymorphisms in management of patients with nonpsychotic depression with selective serotonin reuptake inhibitors

Mugdha Thakur, MD[1], Iris Grossman, PhD[2], Douglas C. McCrory, MD, MHS[3], Lori A. Orlando, MD, MHS[3], David C. Steffens, MD, MHS[1], Kathryn E. Cline, MHS[3], Rebecca N. Gray, DPhil[3], Jennifer Farmer, MD[1], Georgette DeJesus, MD[1], Cara O'Brien, MD[3], Gregory Samsa, PhD[3], David B. Goldstein, PhD[2], and David B. Matchar, MD[3,4]

EGAPP Topics Under Review 2008

Disorder/Effect	Test	Target Population	Intended Use	
Breast Cancer	*CYP2D6*	Individuals prior to treatment for BrCa	Treatment with Tamoxifen	Sel
Diabetes, Type II	*TCF7L2*	General population	Risk assessment	Plan
Cardiovascular Disease	Multigene panels	General population	Risk prediction; drug or nutritional/lifestyle management	In prog
Thrombophilia	*F5, F2*	Individuals with family history or clinical suspicion of thrombophilia	Prevention and management	In prog
Breast Cancer	Gene expression profiles	Women diagnosed with breast cancer	Treatment and recurrence risk	ER ☑
Colorectal Cancer (CRC)	*UGT1A1*	Individuals diagnosed with CRC	Treatment with Irinotecan	ER ☑
Hereditary Nonpolyposis Colorectal Cancer (HNPCC)	Mismatch repair gene mutations	Individuals diagnosed with CRC and their family members	Management of individuals and early detection/prevention for family members	ER ☑
Depression	*CYP450*	Individuals diagnosed with depression	Treatment with SSRI drugs	☑
Ovarian Cancer	Genomic Tests	1) General population of women and; 2) women at increased risk for ovarian cancer	Detection and management	ER ☑

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EGAPP

Evaluation of

Genomic

Applications in

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Prevention

Practice

Family history

Surveillance

G&PH Centers

PH Capacity

Competencies

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- Public health genomics: crucial role of clinical and population sciences in genomics translation
- Vision for the next decade: needs and opportunities

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

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Disease Control and Prevention (CDC)

Genomic Applications in Practice and Prevention (GAPP): Translation Programs in Education, Surveillance, and Policy

Announcement Type: New – Type 1

Funding Opportunity Announcement (FOA) Number: CDC-RFA-GD08-801

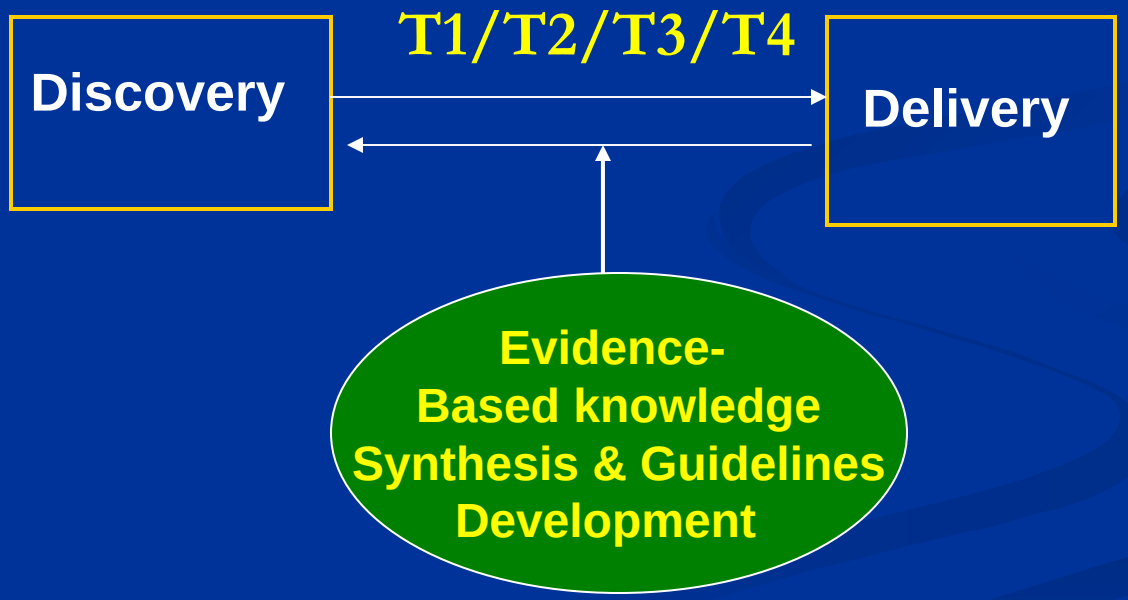
Catalog of Federal Domestic Assistance Number: 93.283 Centers for Disease Control and Prevention Investigations and Technical Assistance

Key Dates:

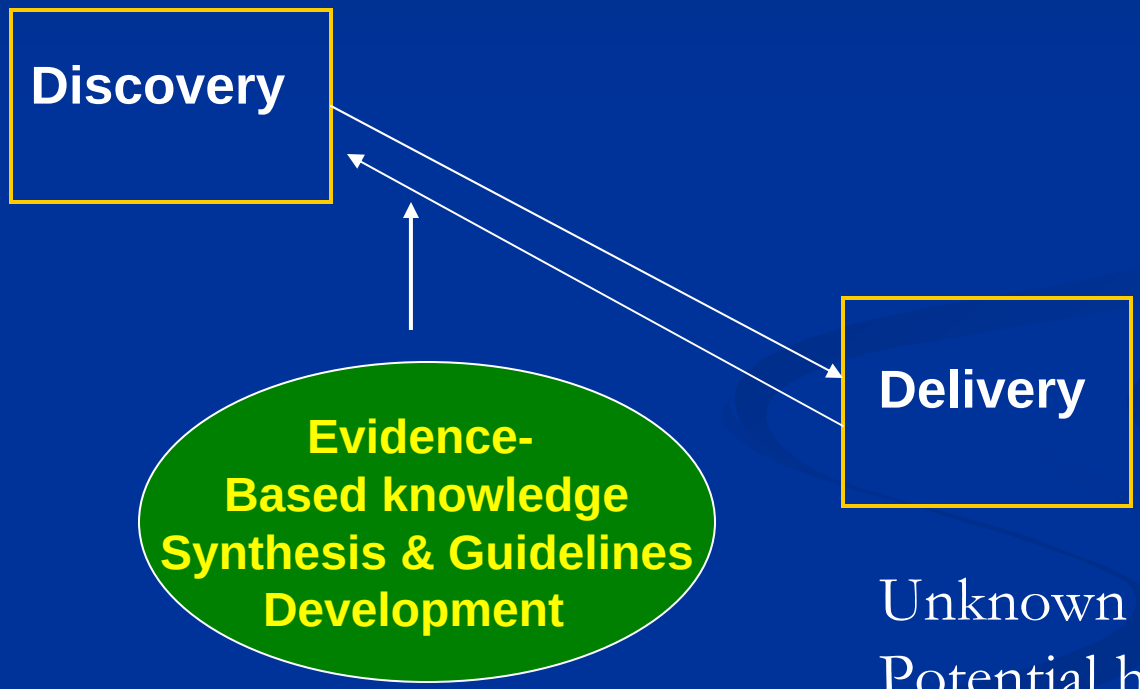
Letter of Intent Deadline: May 7, 2008

Application Deadline: June 6, 2008

Genomic Medicine Meets Evidence-Based Medicine: Where is the Right Threshold Between Research and Practice?

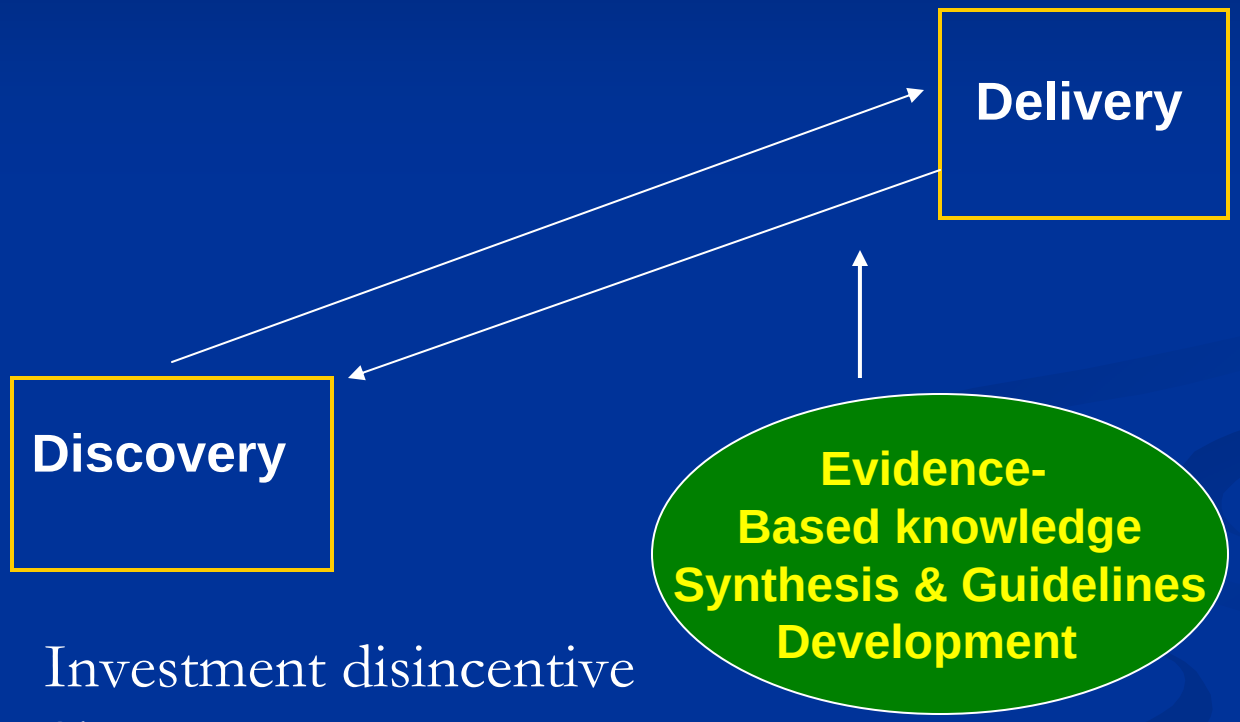


Genomic Medicine Meets Evidence-Based Medicine: Problems with Low Threshold



Unknown benefits
Potential harms
Expensive technologies
Lack of coverage
Disparities

Genomic Medicine Meets Evidence-Based Medicine: Problems with High Threshold

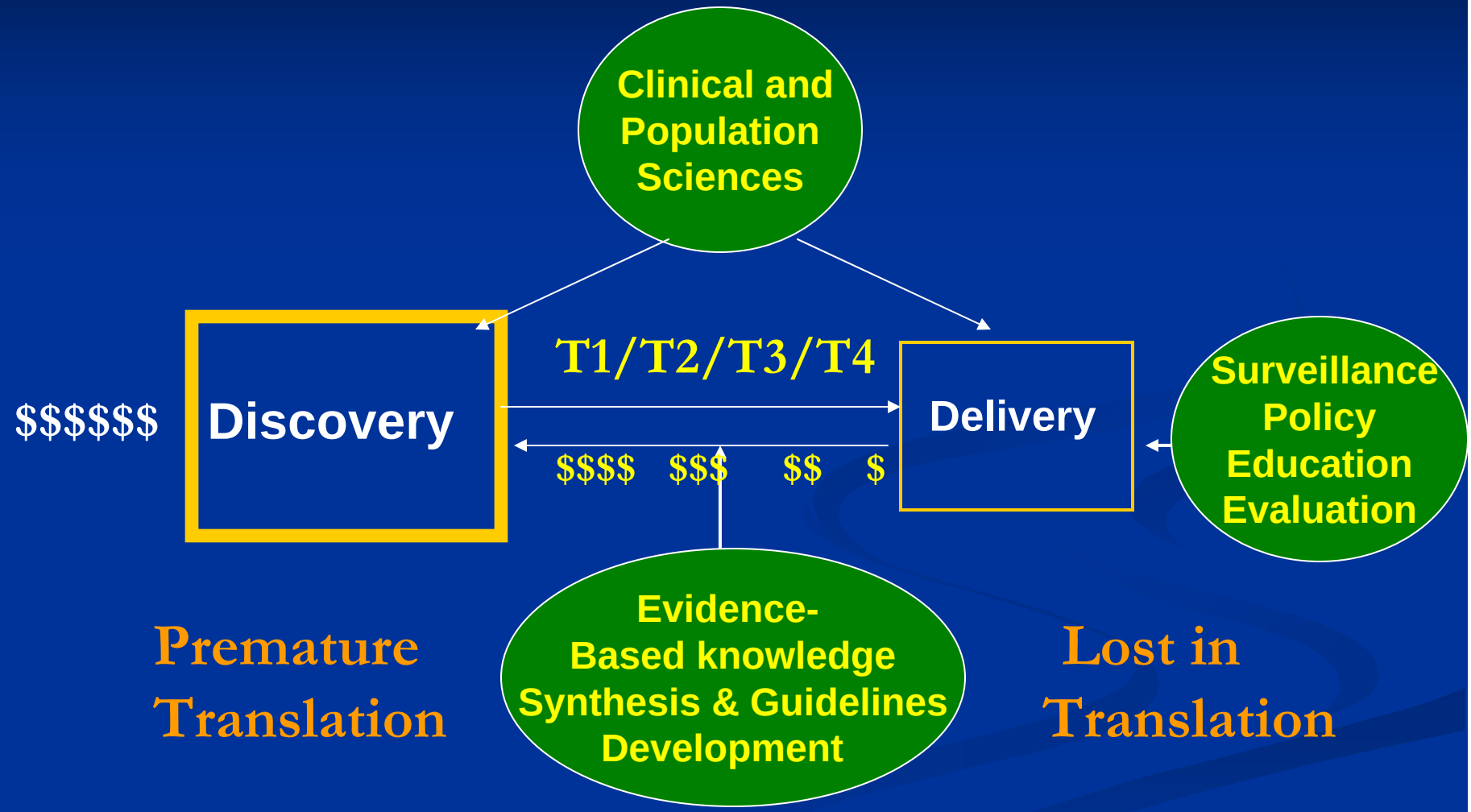


Investment disincentive
Slow integration
Delayed access
Lack of coverage
Disparities

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?



Khoury MJ et al. Am J Prev Med 2007