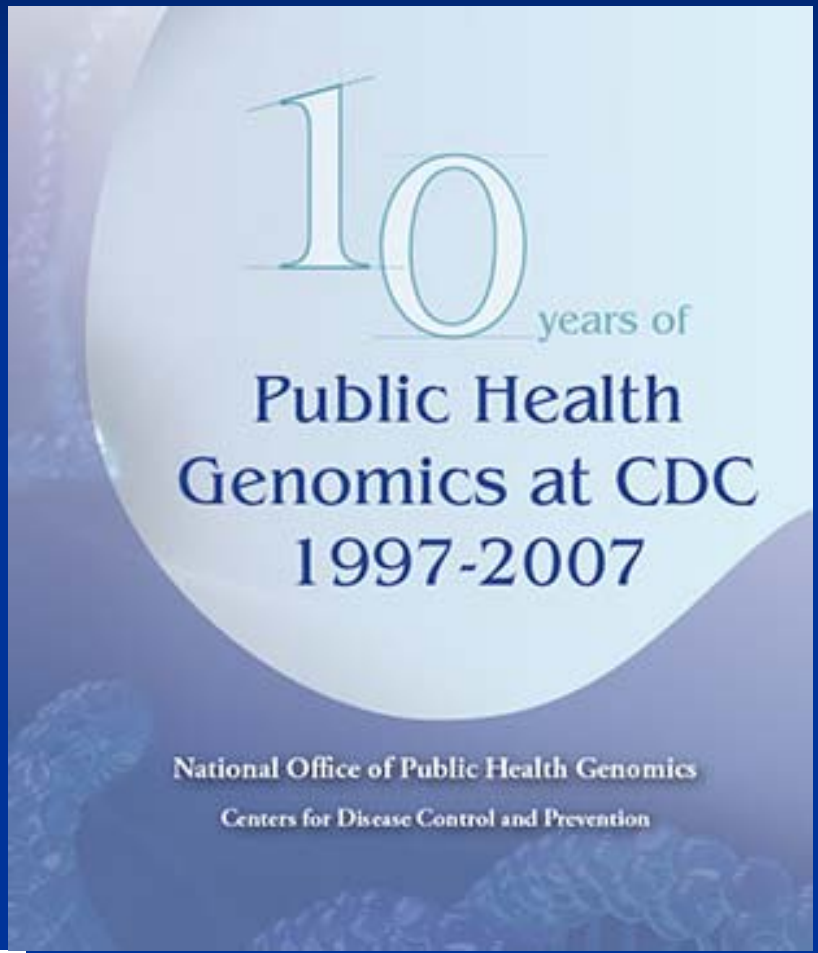
A Decade of Public Health Genomics at CDC
From Gene Discovery to Population Health Benefits



Muin J. Khoury MD, PhD

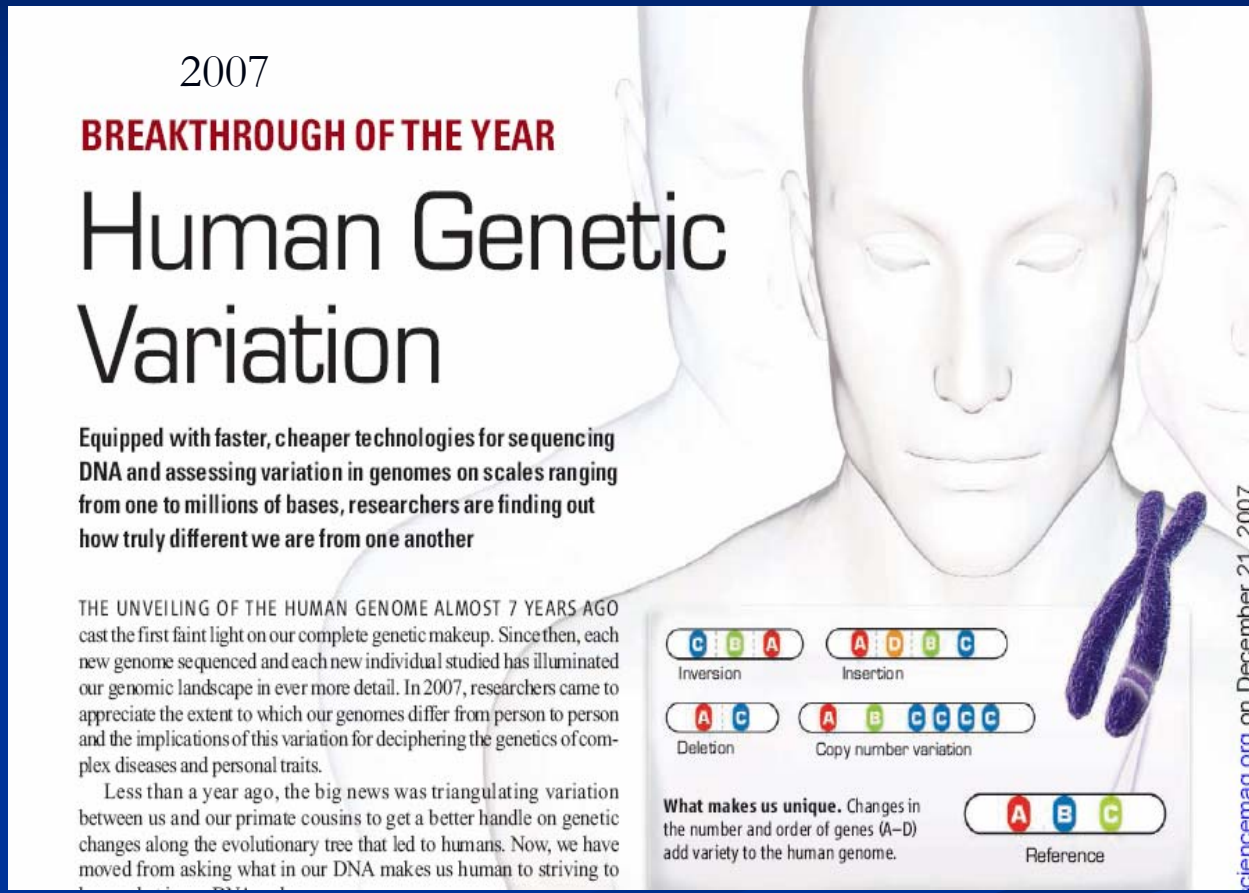
CDC National Office of
Public Health Genomics

Outline

- Genomics 2008: the gap between scientific excitement and health impact widens
- Public health genomics at CDC: closing the gap between genome discoveries and population health
- Vision for the next decade: focus on collaborations in translation research, policy and programs

Successes of Genome Wide Association Studies

- Celiac disease
- Atrial fibrillation
- Colorectal cancer
- Breast cancer
- Prostate cancer
- Diabetes
- Gallstones
- Asthma
- Multiple sclerosis
- Rheumatoid arthritis
- Crohn disease
- Age-related macular degeneration



2007

BREAKTHROUGH OF THE YEAR

Human Genetic Variation

Equipped with faster, cheaper technologies for sequencing DNA and assessing variation in genomes on scales ranging from one to millions of bases, researchers are finding out how truly different we are from one another

THE UNVEILING OF THE HUMAN GENOME ALMOST 7 YEARS AGO cast the first faint light on our complete genetic makeup. Since then, each new genome sequenced and each new individual studied has illuminated our genomic landscape in ever more detail. In 2007, researchers came to appreciate the extent to which our genomes differ from person to person and the implications of this variation for deciphering the genetics of complex diseases and personal traits.

Less than a year ago, the big news was triangulating variation between us and our primate cousins to get a better handle on genetic changes along the evolutionary tree that led to humans. Now, we have moved from asking what in our DNA makes us human to striving to

What Do You Do with Genes When You Find Them?

YANKEE DOODLING **Douglas Kamerow** BMJ Jan 5, 2008

Waiting for the genetic revolution

Will 2008 be the year that genomics delivers on its promises?

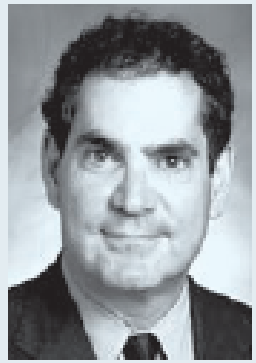
The sequencing of the human genome was completed in 2003. Since then we've been told that we're living in the "genomic era"—the biggest revolution in human health since antibiotics, some say, and the beginning of scientific, personalised medicine.

In the United States we've spent about $4bn (£2bn; €2.8bn) since 2000 to fund the National Human Genome Research Institute, so it seems fair to ask what we've got for our money.

Certainly there have been dramatic improvements in the efficiency of DNA sequencing and other related technologies. Polymerase chain reaction and other amplification techniques have made what was exotic and painstaking work commonplace and quick. And I guess that some indirect applications of genomics can be found in the doctor's

What about the common, everyday diagnoses—heart disease, diabetes, and other multigene disorders? I hope that there is some new information out about them. Generally when I hear experts addressing GPs on genomics they offer the same stock examples: the woman with breast and cervical cancer in her family history who is referred with her daughters for testing; the man with colorectal cancer at a young age who turns out to have a hereditary syndrome. But we knew about these kinds of things a long time ago—we just didn't have the exact gene. It comes down to taking a good family history.

Maybe the future lies in the flashy new genetic testing websites that have sprung up, all planning to start collecting our money and DNA this year. Just pay your $995 to $2500, spit into a tube or scrape your cheek, and



> **Precious little is known about how people's knowledge of their genetic risks will affect their behaviour**

behaviours. And even less is known about how people's knowledge of their genetic risks will affect them. The US Centers for Disease Control and Prevention convened a panel of experts in 2004 to assess genetic tests and technologies for their appropriateness in practice. After three years of work setting up a systematic, evidence based process they have just issued their first recommendation. They evaluated pharmacogenomic testing for cytochrome P450 in depressed patients to predict how well selective serotonin reuptake inhibitors would work. Their conclusion: the evidence t recommend for or against such testing is insufficient (*Genetics in Medicine* 2007;7:819-25).

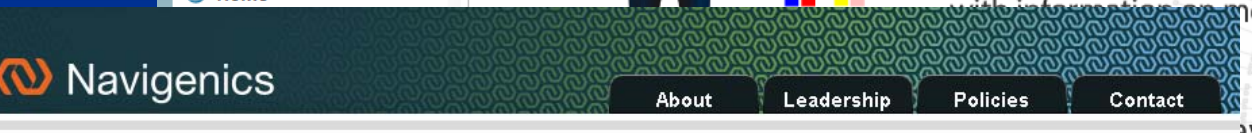
And what about all the legal and ethical challenges involved in genetic testing, especially the broad genetic

What Do You Do With Genes When You Find Them?

Two challenges for “translation” that need public health leadership

1. Premature Translation
2. “Lost in Translation”

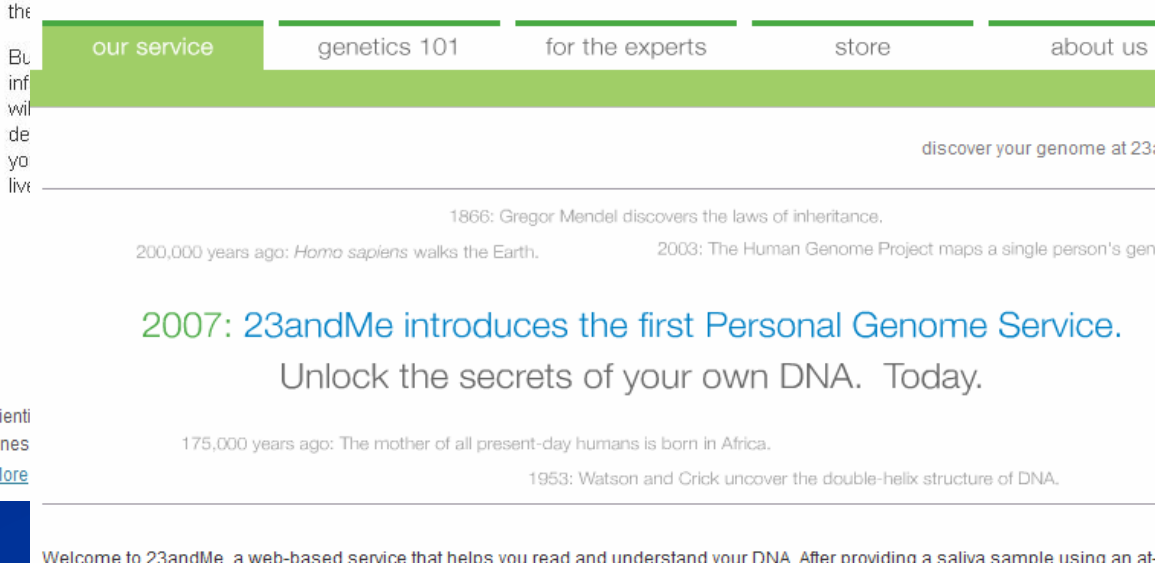
Challenge 1: Premature Translation



Welcome to Navigenics

We are in the midst of an exciting era of discoveries about the connections between our individual genetic composition and our personal health and wellness. These discoveries are providing a detailed map of thousands of genes

Your genes offer a road map to optimal health



profile.
»More

genes
»More

January 22, 2008

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PROSTATE CANCER GUIDE

1. Overview & Facts
2. Symptoms & Types
3. Diagnosis & Tests
4. Treatment & Care

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 Wake Forest University plan to start offering a new gene test for prostate cancer risk within months.

The test screens men's blood or saliva samples for five genetic variants linked to prostate cancer. Once those blood or saliva s
the test takes about a week.

"The genetic findings in our paper can be use
available in the next few months," says Jianfe
Center for Human Genomics, in a statement f

Xu's team describes the test in today's advan
Journal of Medicine.

The NEW ENGLAND JOURNAL of MEDICINE

Jan 17, 2008

ORIGINAL ARTICLE

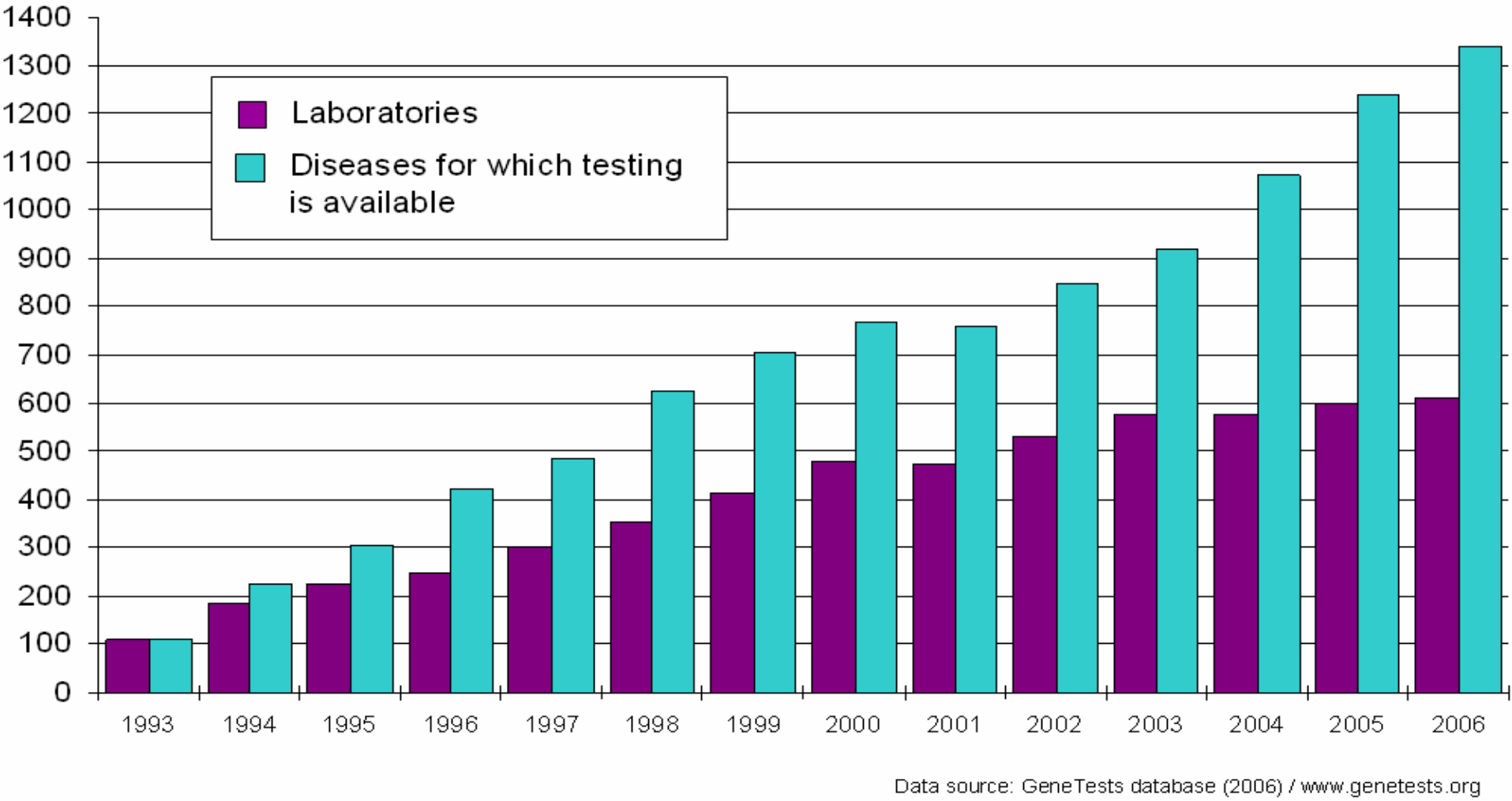
Cumulative Association of Five Genetic Variants with Prostate Cancer

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., Fang-Chi Hsu, Ph.D., Yi Zhu, B.S., Katarina Bälter, Ph.D., A. Karim Kader, M.D., Ph.D., Aubrey R. Turner, M.S., Wennuan Liu, Ph.D., Eugene R. Bleecker, M.D., Deborah A. Meyers, Ph.D., David Duggan, Ph.D., John D. Carpten, Ph.D., Bao-Li Chang, Ph.D., William B. Isaacs, Ph.D., Jianfeng Xu, M.D., D.P.H., and Henrik Grönberg, M.D., Ph.D.

Population level Questions are Important for Using Genetic Information in Practice

- How many people have this genetic variant?
- Is prevalence different in subgroups of the population?
- What is the magnitude of risk (with or without the variant)
- How much of the population burden of disease does it explain?
- Does the variant interact with other genes and modifiable risk factors?

Genetic Testing as a Public Health Issue
Evidence based Information Needed!



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

Challenge 2:
"Lost in Translation"

C. Lenfant NEJM 2003;349:868

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

”Lost in Translation”

C. Lenfant NEJM 2003;349:868

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

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

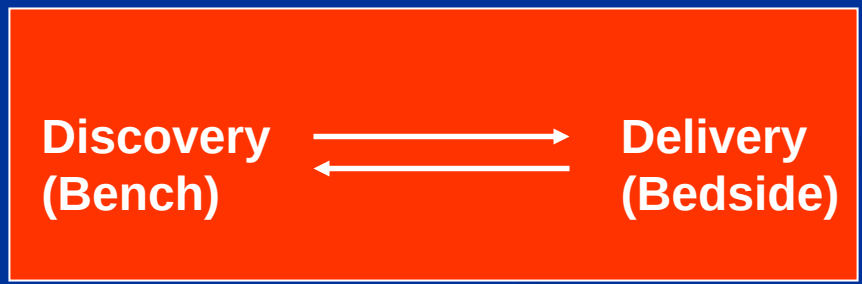
”Lost in Translation”

C. Lenfant NEJM 2003;349:868

- **It takes an estimated average of 17 years for 14% of new scientific discoveries to reach day to day clinical practice**
- **JM Westfall JAMA 2007;297:403**

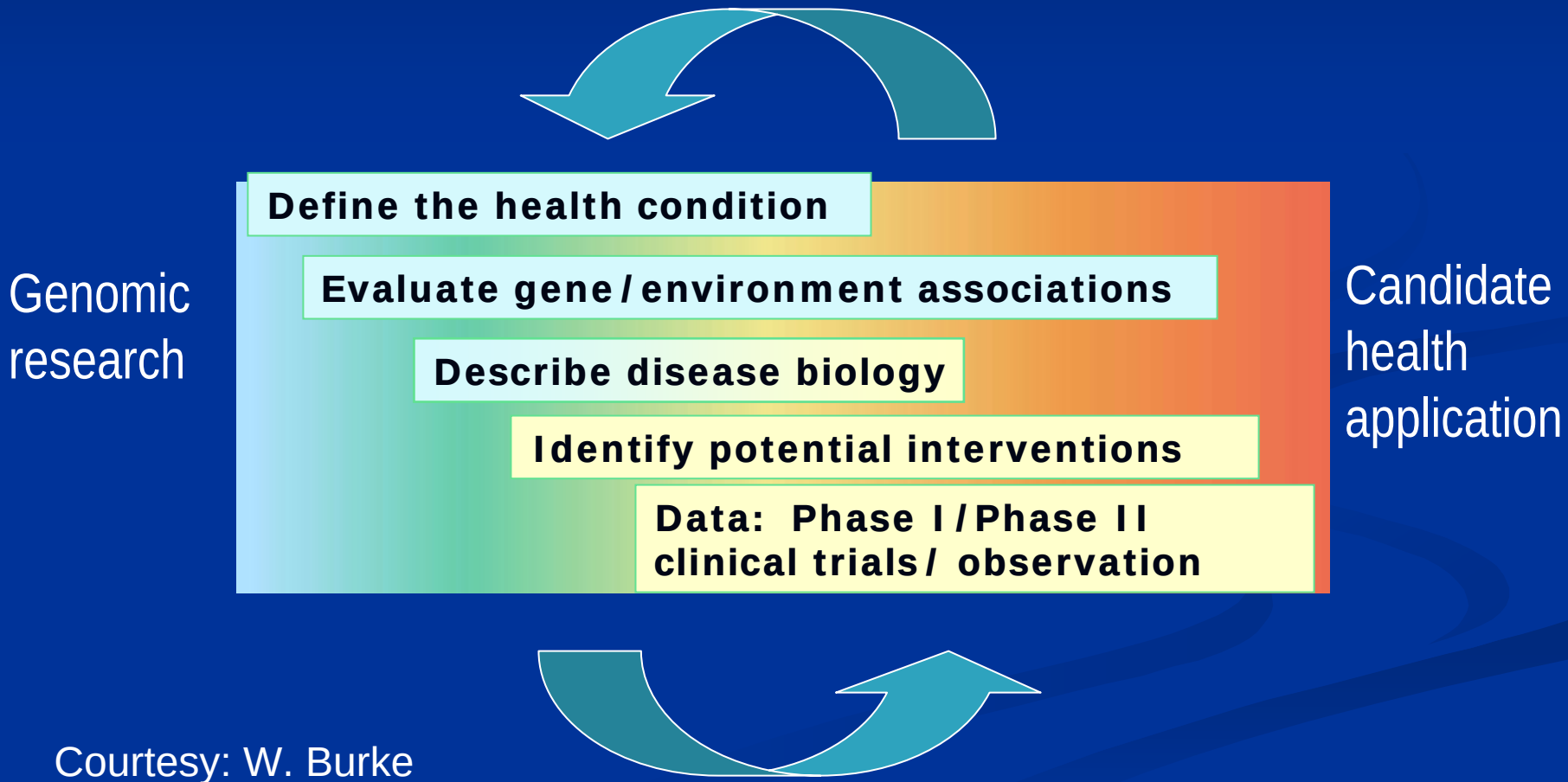
“Let's be realistic: If we didn't do it with aspirin, how can we expect to do it with DNA?”

"Translational and Clinical Science—Time for a New Vision"
E. Zerhouni NEJM 2005;353:15



The NIH Roadmap!!

T1
Discovery to Candidate Health Application



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

"Translational and Clinical Science—Time for a New Vision"
E. Zerhouni NEJM 2005;353:15

Discovery (Bench) ⟷ **Delivery (Bedside)**

JAMA Jan 9, 2008

The Meaning of Translational Research and Why It Matters

Steven H. Woolf, MD, MPH

TRANSLATIONAL RESEARCH MEANS DIFFERENT THINGS

only the starting point for this second area of research. According to McGlynn et al,[4] US patients receive only half of recommended services. The second area of translational research seeks to close that gap and improve quality by im-

The "Second" Translational Block

"The Roadmap Less Traveled" L. Green

T1: First block:

Translation from concept into first human studies

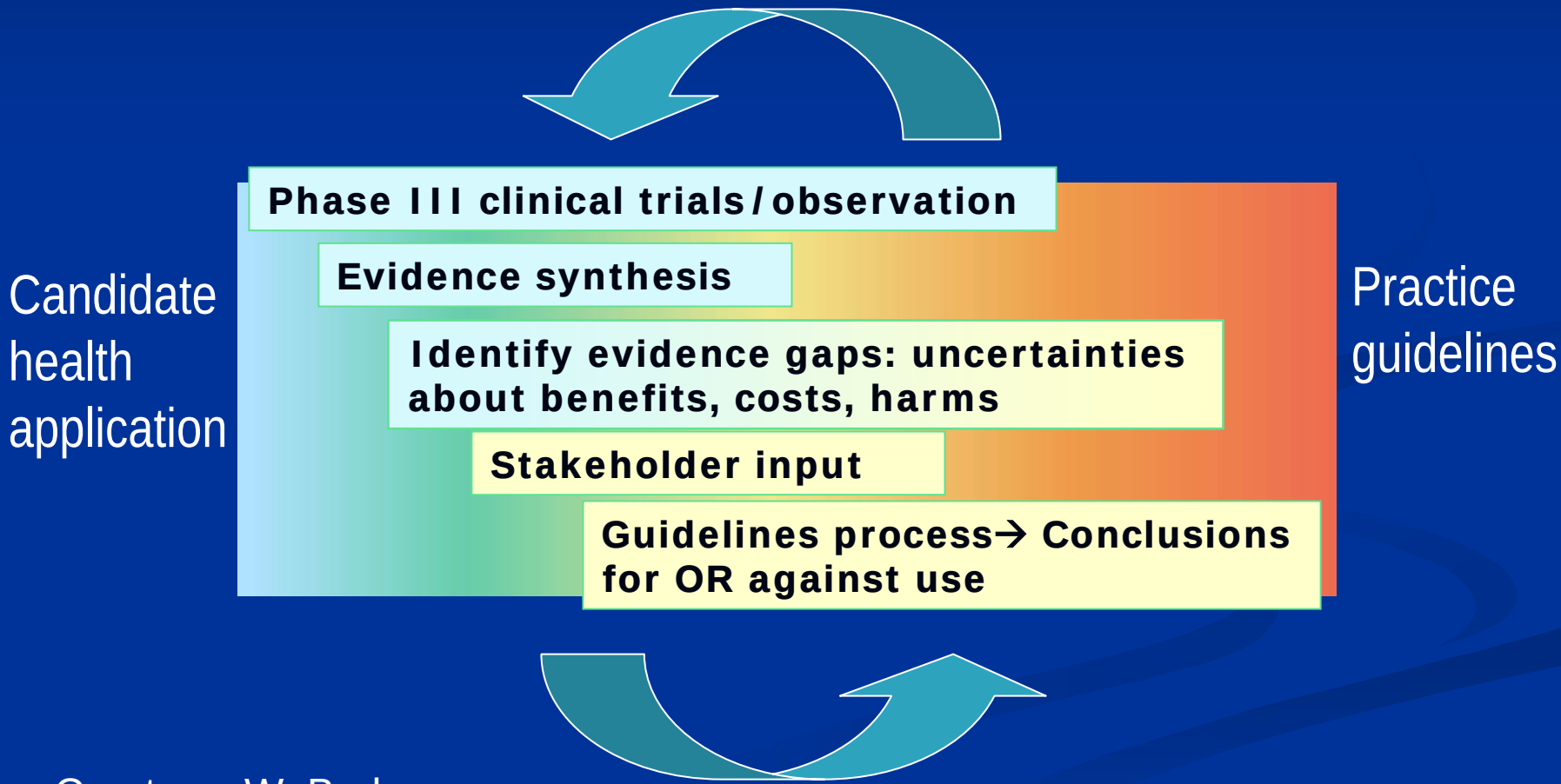
T2: Second block:

Translation from human studies into practice

Courtesy:
G Ginsberg

IOM Clinical Research Roundtable, Sung et al JAMA, 2003

T2
Health Application to Evidence-based Practice Guidelines

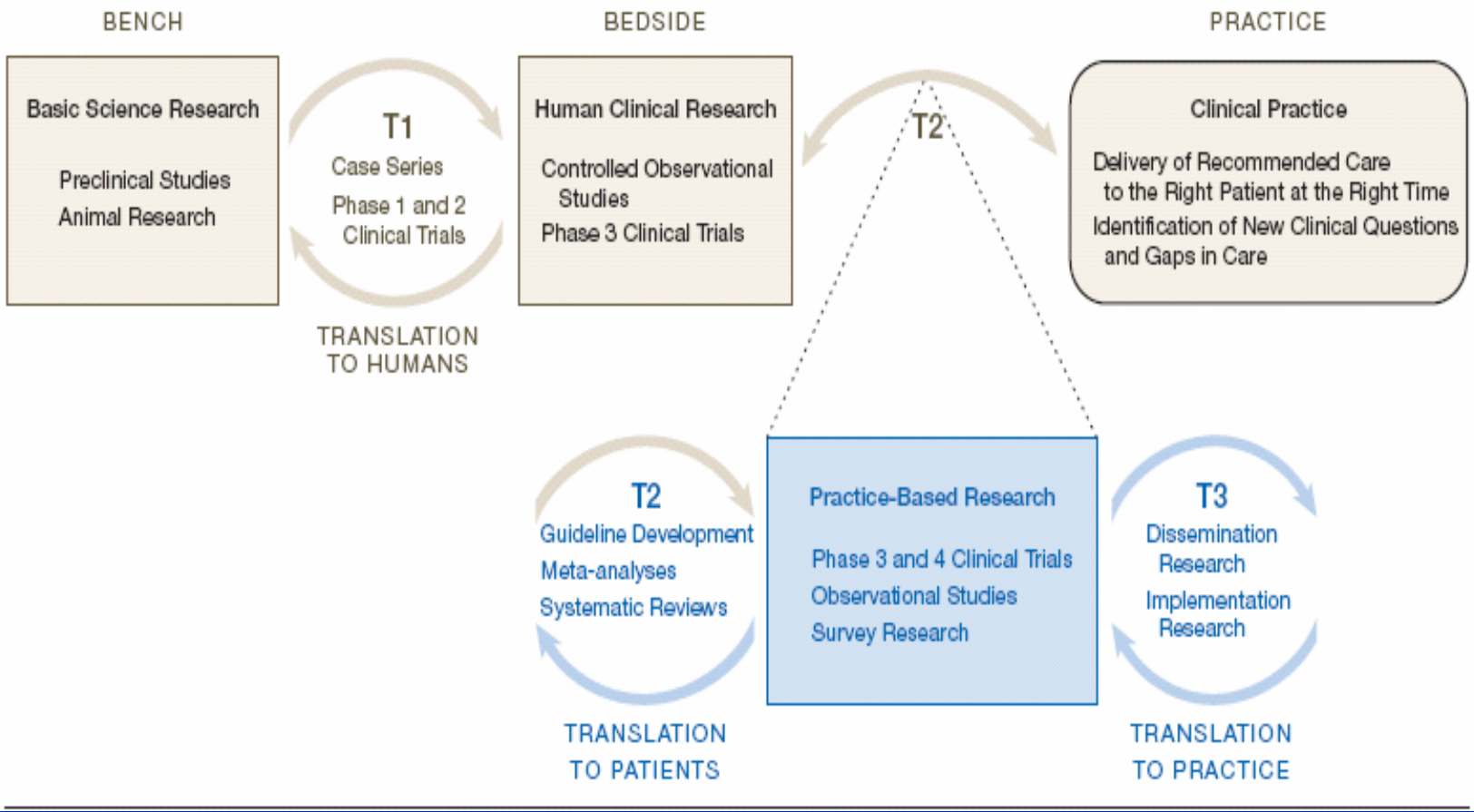


Courtesy: W. Burke
Based on Khoury et al. Genet Med 2007

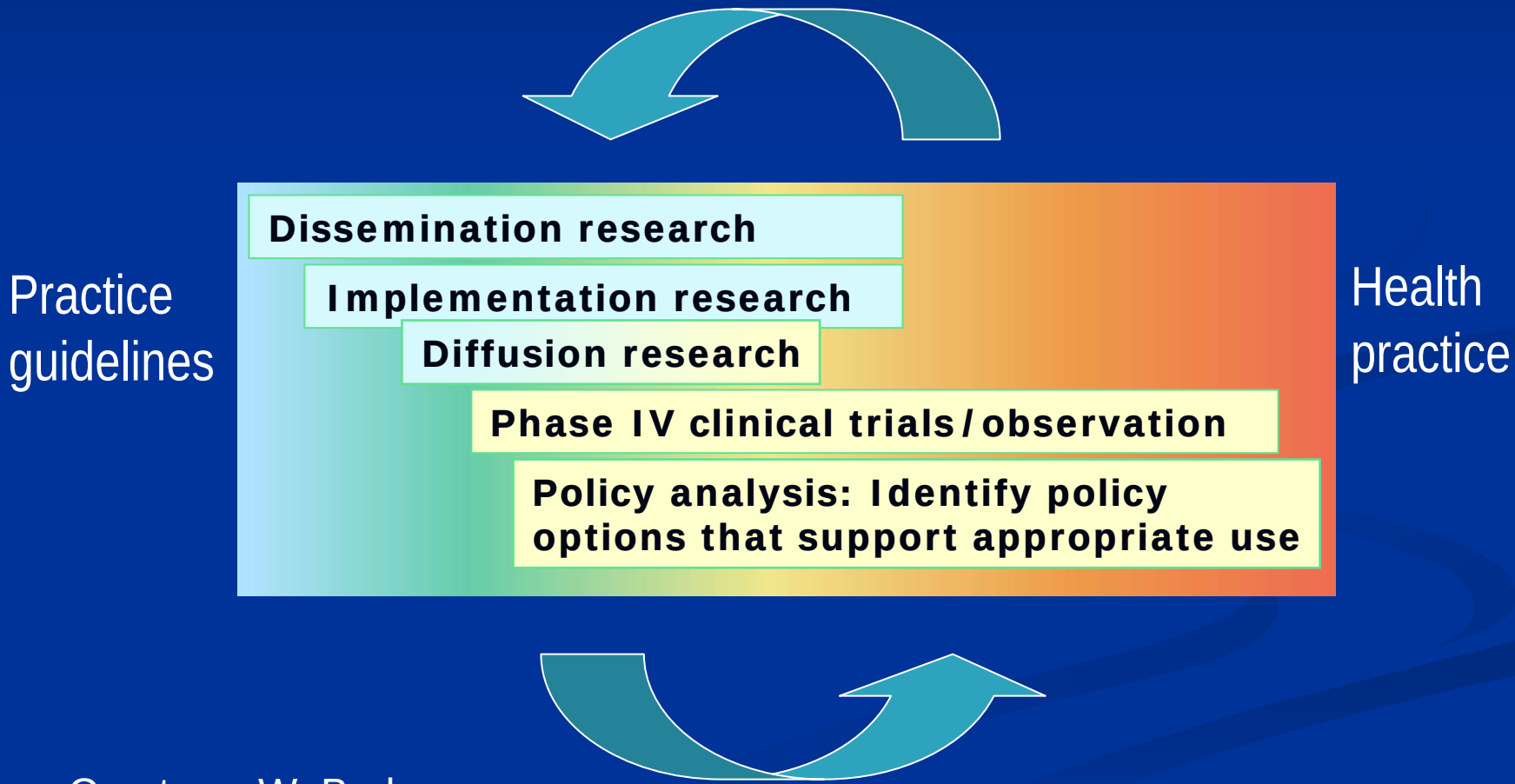
Practice-Based Research-Blue Highways on the NIH Road Map

JM Westfall et al JAMA 2007;2007;297:403.

Figure. "Blue Highways" on the NIH Roadmap

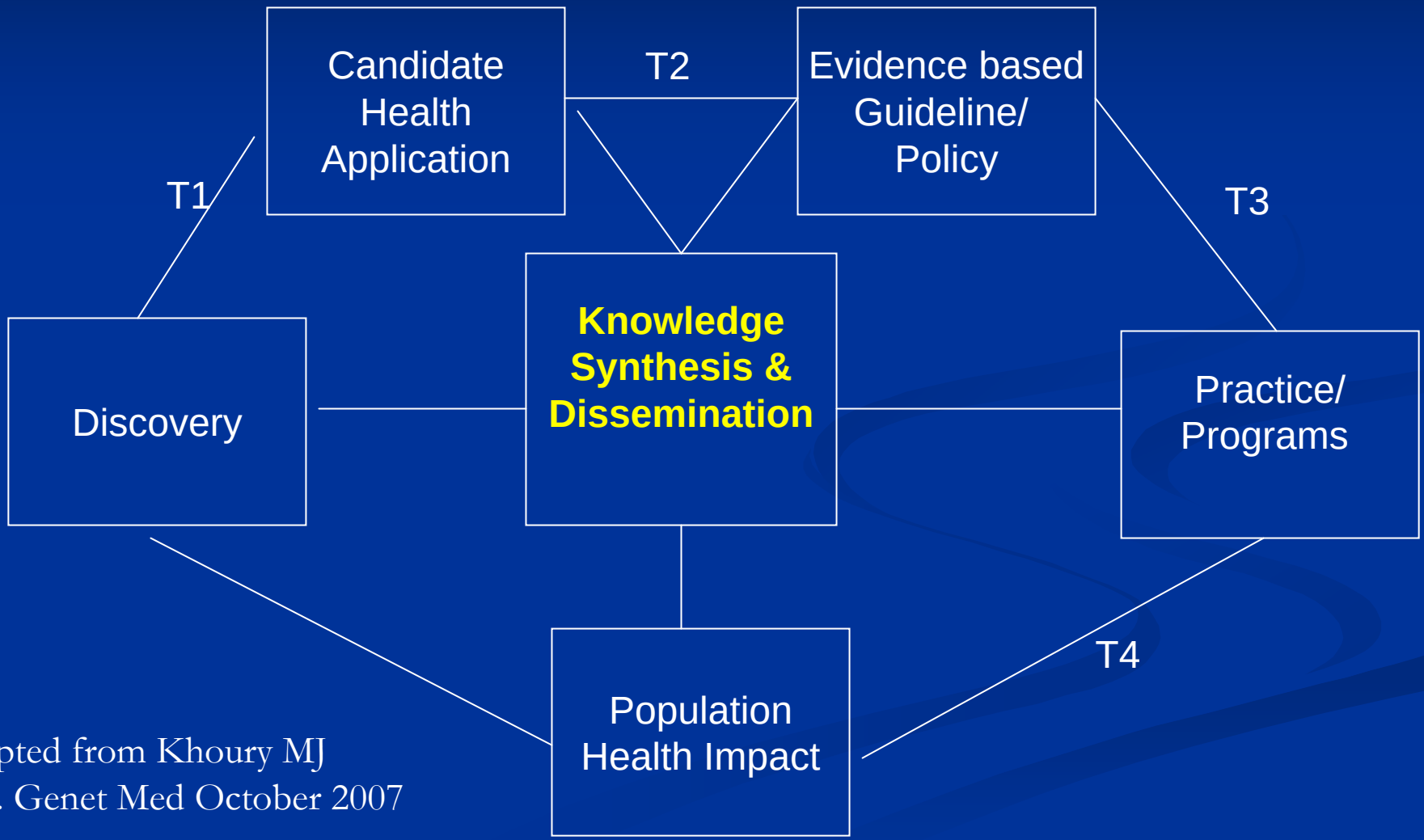


T3
Practice Guidelines to Health Practice



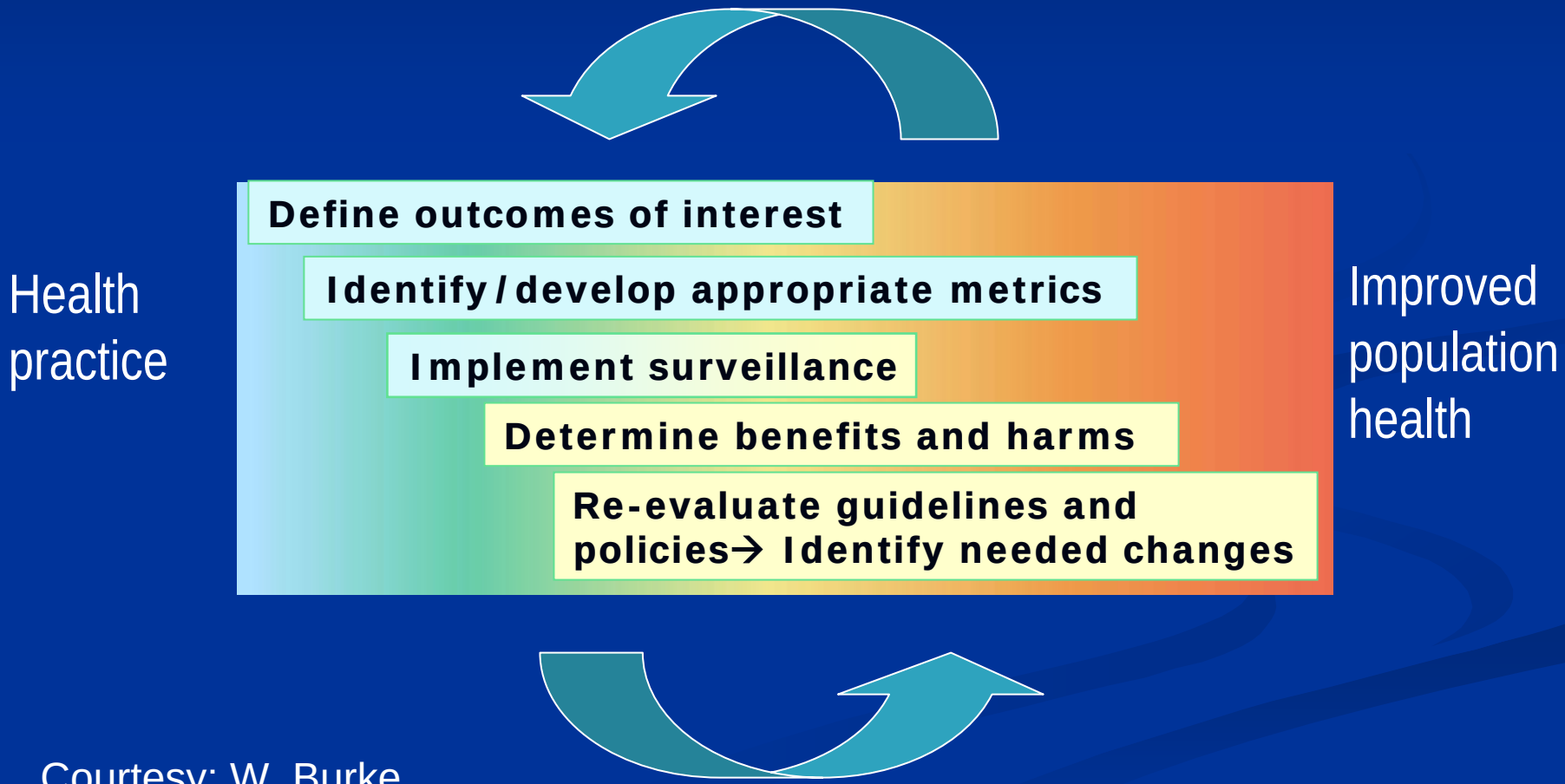
Courtesy: W. Burke
Based on Khoury et al/ Genet Med 2007

The Phases of Translation from "Discovery" to "Population Health Impact"



Adapted from Khoury MJ et al. Genet Med October 2007

T4
Health Practice to 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
  - < 3% deal with Translation Research T2 and Beyond
  - Only 2 USPSTF Evidence-based recommendations
    - *BRCA1*
    - *HFE*

Outline

- Genomics 2008: the gap between scientific excitement and health impact widens
- Public health genomics at CDC: closing the gap between genome discoveries and population health
- Vision for the next decade: Focus on collaborations

CDC's National Office of Public Health Genomics

Vision

- To use genomic knowledge to improve the lives and health of all people

Mission

- To integrate genomics into public health research, policy, and programs

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

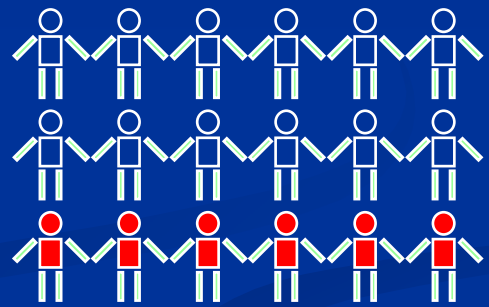
US Genome Profile

Public Health Studies

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

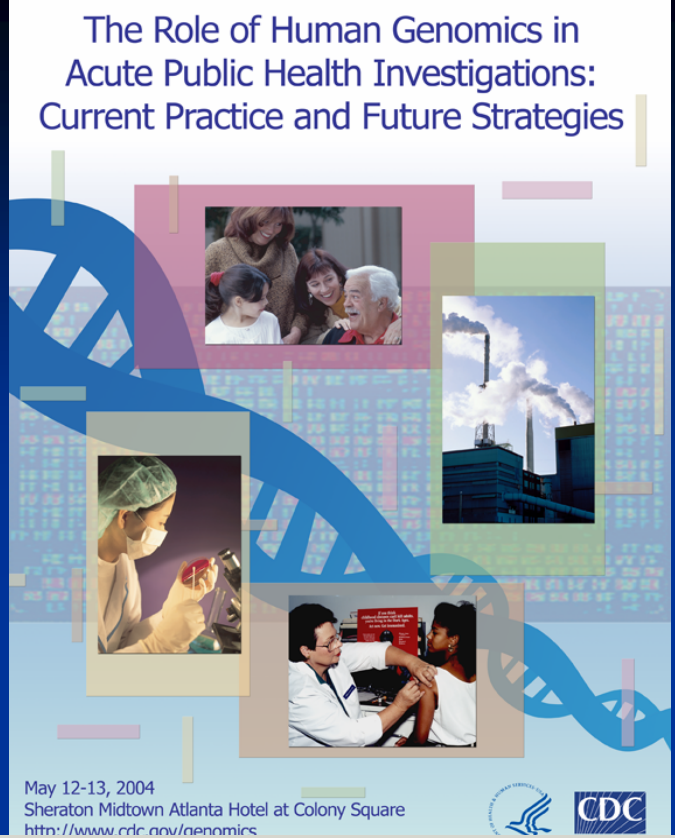
National Profile of Genome Variation Beyond Gene Discovery Initiative

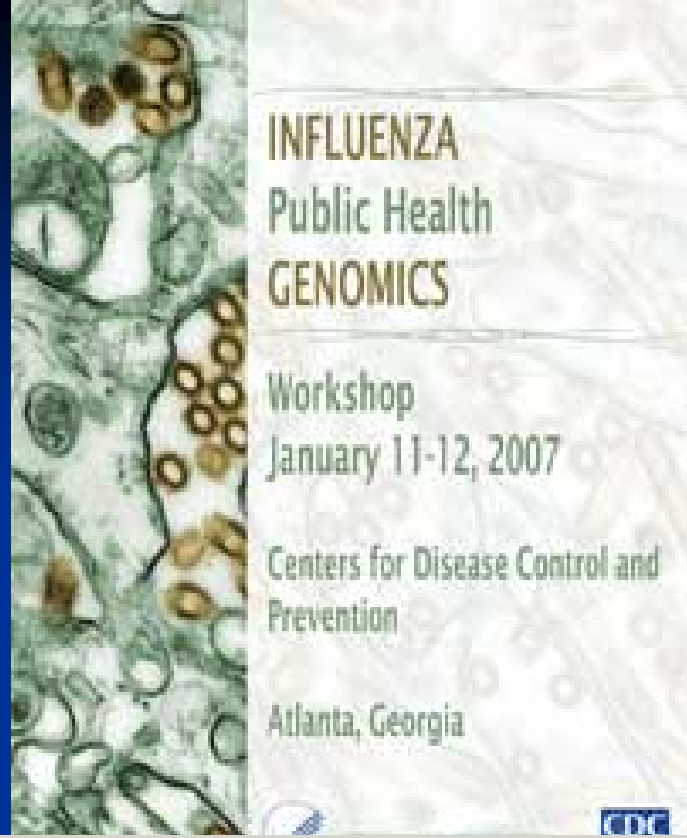
- NHANES: representative cross sectional surveys of U.S. population
- Extensive phenotypic data, risk factors, biological markers



- Prevalence: health impact
- Genotype-phenotype correlations
- Gene-environment interactions

- From 100 genetic variants to >1,000,000 variants





2006, 2008 Seed funded Projects

From: CDC Announcements

To: CDC SSDL Public Health Events

Cc:

Subject: Understanding the Basis of Vaccine Safety Meeting

Understanding the Genetic Basis of Vaccine Safety Meeting

Wednesday, January 30 and Thursday, January 31
8:00 a.m. to 4:00 p.m. (both days)

CDC Roybal Campus
1600 Clifton Road, N.E.
Building 19, Auditorium A

The purpose of the "Understanding the Genetic Basis of Vaccine Safety" meeting is to examine the role of genetics in adverse respons
presentations about genetic studies being done in vaccine safety, followed by discussions that will carry over into breakout sessions.

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

Population Studies

US Genome Profile

Public Health Studies

HuGENet

Human

Genome

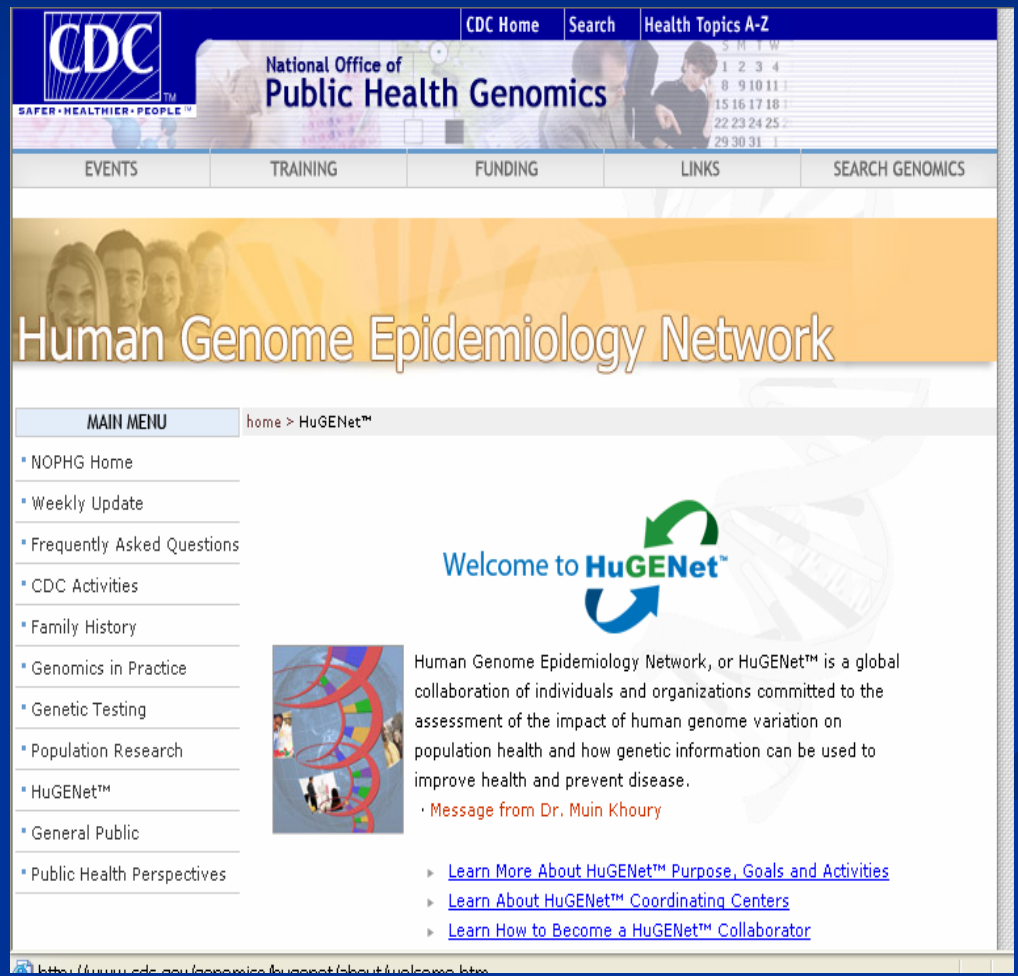
Epidemiology

Network

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

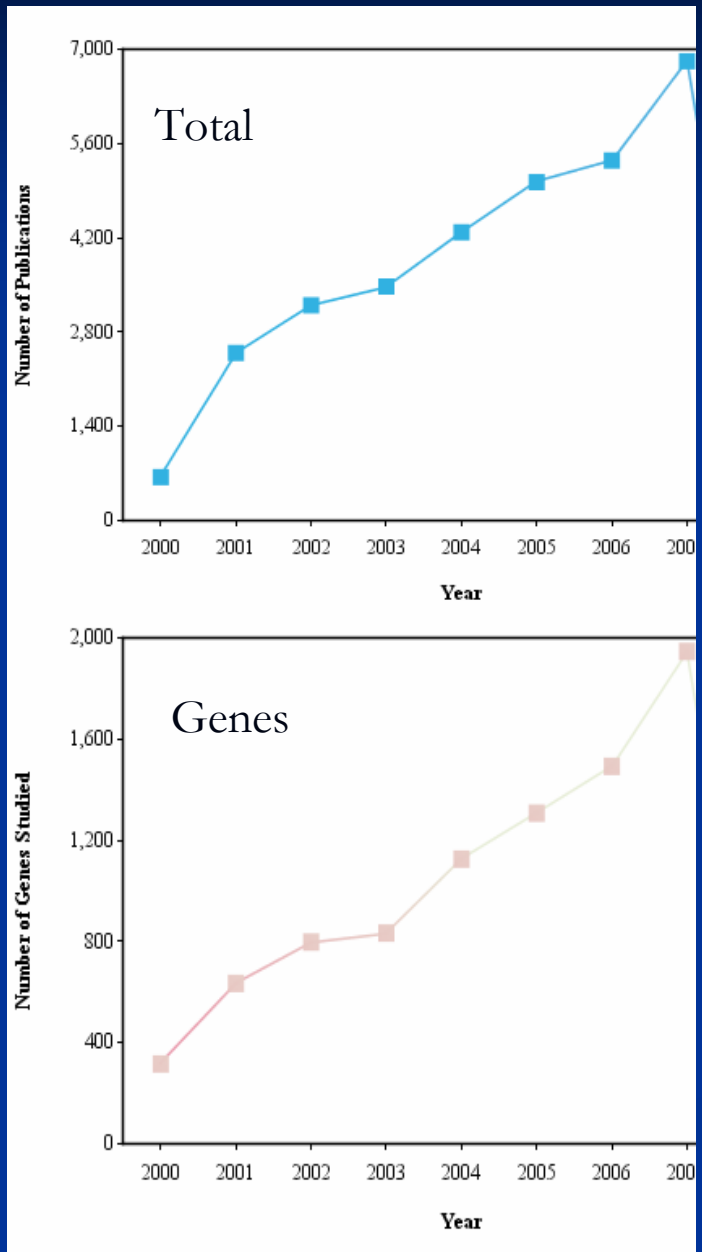
Human Genome Epidemiology Network (HuGENet)

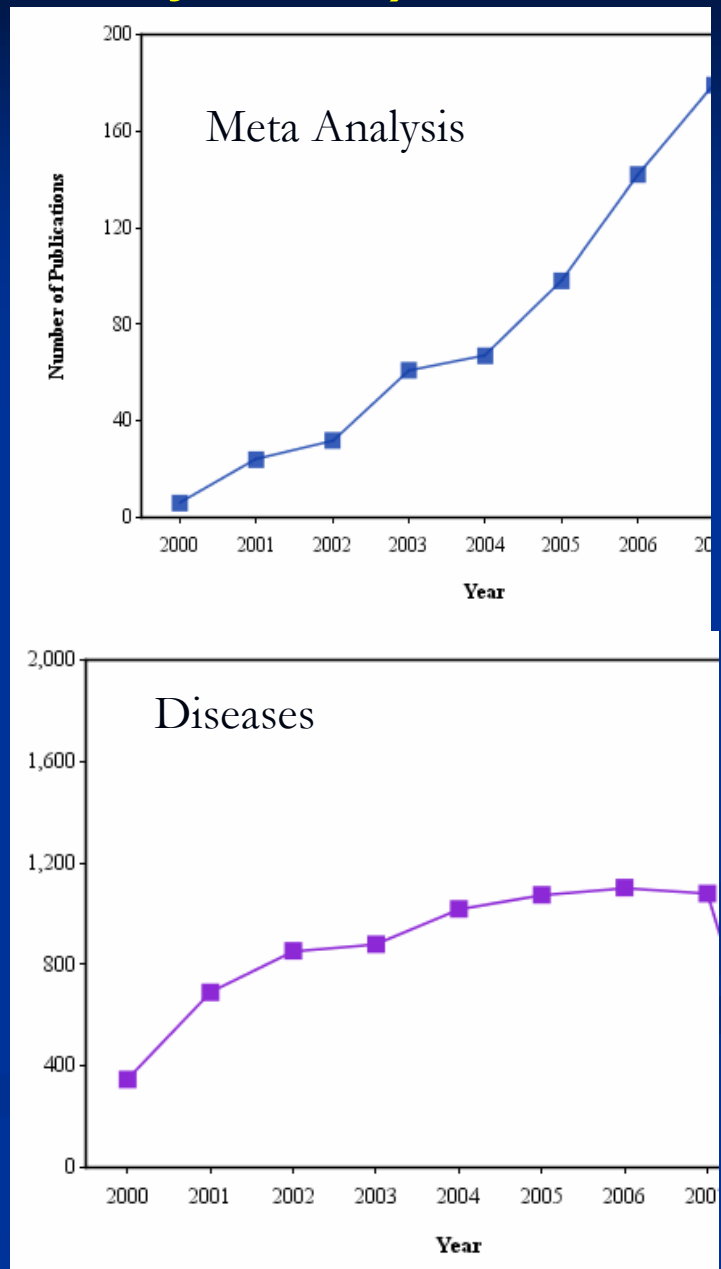
- **Global collaboration of individuals and organizations to assess population impact of genomics and how it can be used to improve health and prevent disease**
  - **4 coordinating centers**
  - **Dozens of networks**
  - **Hundreds of collaborators**
  - **10 collaborating journals**



HuGE Literature Trends

(HuGE Navigator as of January 3, 2008)





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EGAPP

Evaluation of

Genomic

Applications in

Practice &
Prevention

www.egappreviews.org

Evaluation of Genomic Application

EGAPP
Evaluation of Genomic Applications in Practice and Prevention

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

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

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

What's New

EGAPP Working Group Releases First Recommendation Sta
recommendation statement.*

December 2007 · Vol. 9 · No. 12

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

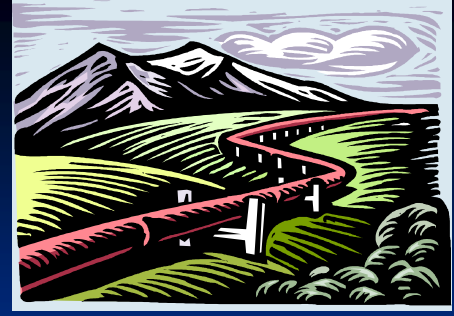
The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for nonpsychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 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 effective treatment with SSRI drugs, or inappropriate use of genotype information in the management of other drugs metabolized by CYP450 enzymes. *Genet Med* 2007:9(12):819–825.

Key Words: *P450, CYP450, pharmacogenomic, SSRI, depression*

Genetics in Medicine is making EGAPP recommendations open access – free to all!

EGAPP Pipeline



- Genomic Tests for Ovarian Cancer Detection and Management
- Hereditary Nonpolyposis Colorectal Cancer (HNPCC): Diagnostic Strategies and Their Implications
- UGT1A1 Mutation Analysis in Colorectal Cancer Patients Treated with Irinotecan
- Gene Expression Profiling Tests on Breast Cancer Outcomes
- Impact of Factor V Leiden Mutation Testing on Health Outcomes in Individuals with a History of or Increased Risk for Thromboembolic Events
- Use of Genomic Profiling to Assess Risk for Cardiovascular Disease and Identify Individualized Prevention Strategies

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EGAPP

Evaluation of

Genomic

Applications in

Practice &

Prevention

Practice

Family history

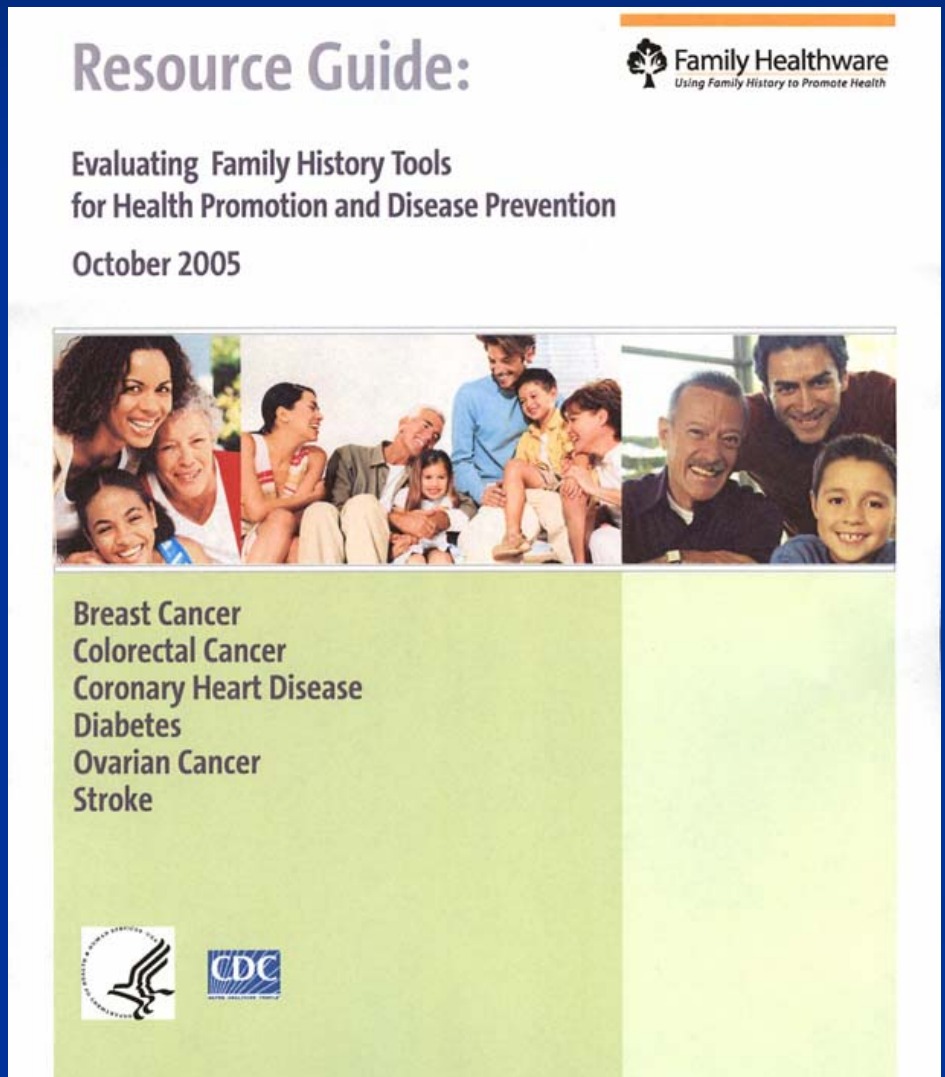
State Capacity

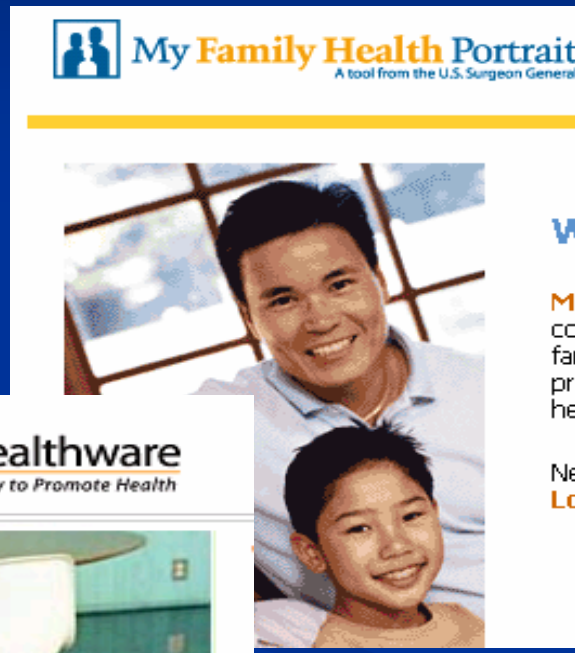
Genomics Centers

Website/Reports/

Competencies

The CDC Family History Public Health Initiative





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Public Health Genomics at CDC: The Next Decade

- Accelerate the process of translation to close the widening gap
- Continue knowledge synthesis for better decision making
- Engage/empower consumers and educate providers with decision support tools
- Expand partnerships to enhance the appropriate integration of genomics into health and health care

Genomics Translation Research RFA

- FY08 to fund genomics translation research and public health assessment
- Includes genetic/genomic tests and family history
- Close the gaps identified through EGAPP
- Partnership development process (federal, state, academia, private sector)
- Form a Research and Surveillance Network in the Evaluation of Genomic Applications in Practice and Prevention (GAPPNet)

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

Important Deadlines

Letter of Intent:
January 28, 2008

Final Application:
February 27, 2008

Do you have more questions about this opportunity? Please email us at

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 such areas as cancer, diabetes, educational and community-based programs, heart disease, stroke, and mental health. Such research will advance knowledge about the validity, utility, utilization, and population health impact of genomic and family health history applications for improving health and preventing disease.

Focusing on filling the gaps within current

Genomics for Early Disease Detection and Intervention Initiative (GEDDI)

- Develop a public health approach to use genetic information to make early diagnosis for improved outcomes (newborn screening is the current example)
- Focuses on diseases for which early detection and intervention can substantially improve health outcomes
- Focuses on genetic and genomic applications ready for T3 and T4
- Develop decision support tools to Integrate into clinical and public health programs

http://www.cdc.gov/ncbddd/hemochromatosis/training/index.htm

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CDC ...HEALTHIER...PEOPLE...

Hemochromatosis for Health

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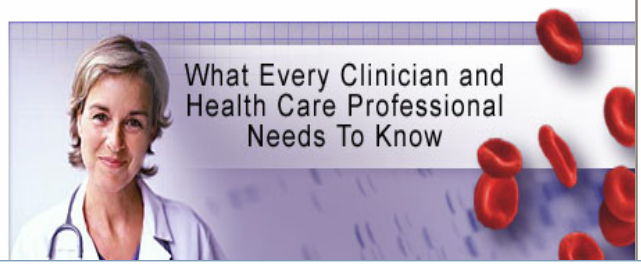

Address http://www.medped.org/

Inherited Cholesterol Disorders--Familial Hypercholesterolemia

MED PED FH — Make Early Diagnosis Prevent Early Deaths

Make Early Diagnosis to Prevent Early Death

For people with inherited high cholesterol

A Non-profit World Wide Preventive Medicine Project

School of Medicine

Search

Address http://www.info4pi.org/patienttopatient/index.cfm?section=patienttopatient&content=warningsigr

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10 Warning Signs of Primary Immunodeficiency

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Primary Immunodeficiency (PI) causes children and young adults to have infections that c
frequently or are unusually hard to cure. In America alone, up to 1/2 million people suffer fr
100 known Primary Immunodeficiency diseases. If you or someone you know are affected
more of the following warning signs, speak to a physician about the possible presence of
Primary Immunodeficiency.

	r more new ear ns within 1 year.	Recurrent, deep skin or organ abscesses.	6
2	Two or more serious sinus infections within 1 year.	Persistent thrush in mouth or elsewhere on skin, after age 1.	7
3	Two or more months on antibiotics with little effect.	Need for intravenous antibiotics to clear infections.	8
4	Two or more pneumonias within 1 year.	Two or more deep-seated infections.	9
5	Failure of an infant to gain weight or grow normally.	A family history of Primary Immunodeficiency.	10

Presented as a public service by:

CDC — Department of Health and Human Services — Centers for Disease Control and Prevention

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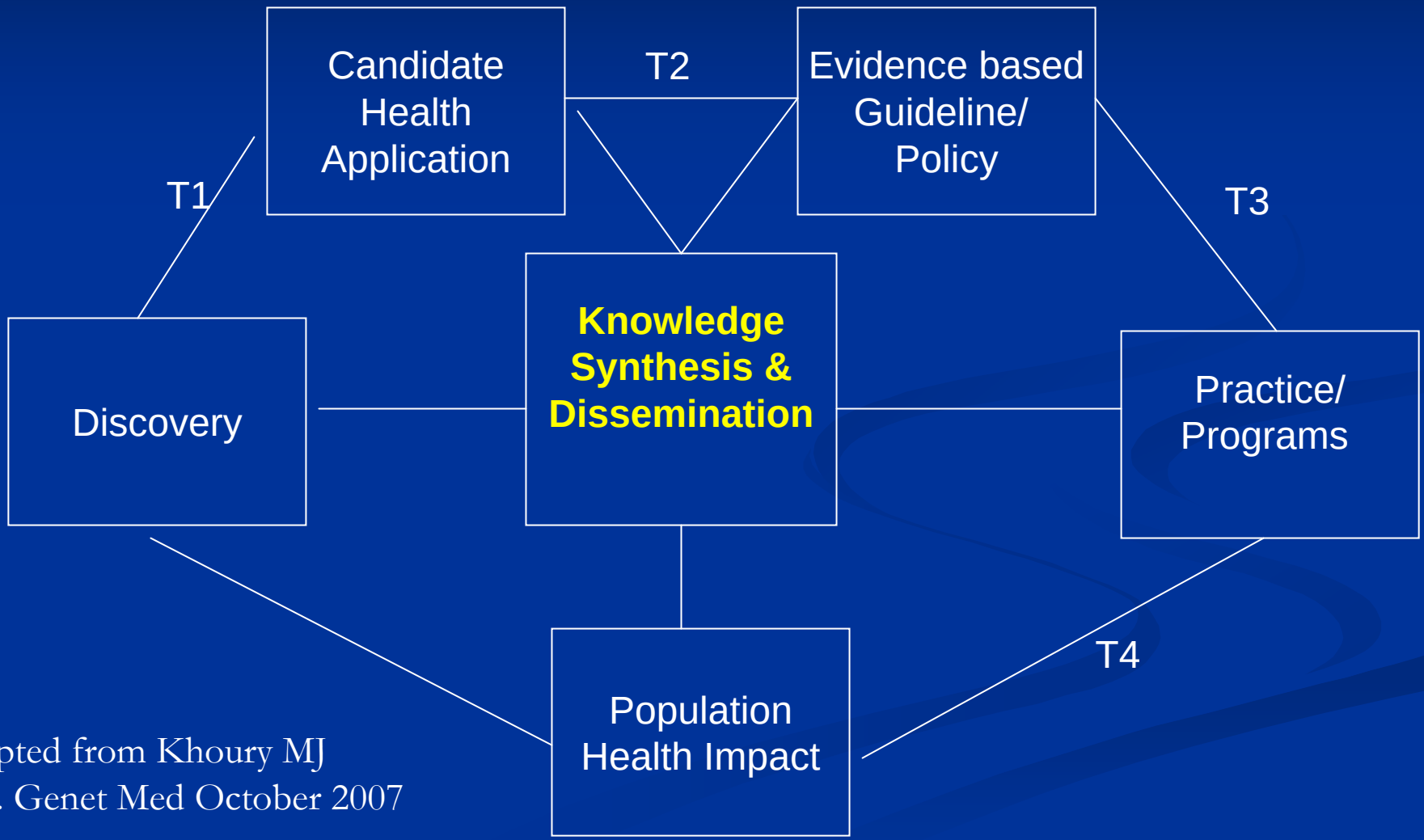
NEWBORN SCREENING

Quality Assurance and Proficiency Testing for Newborn Screening

For more than 26 years, CDC's Environment Health Laboratory has been the only comprehensive source in the world for qualit assurance and proficiency testing involving t testing of newborns for preventable disease these diseases are not accurately diagnosed and treated, they cause mental retardation, severe illness, and premature death in newborns.

Within 48 hours of a child's birth, a sample of blood is obtained fr

The Phases of Translation from "Discovery" to "Population Health Impact"



Adapted from Khoury MJ et al. Genet Med October 2007