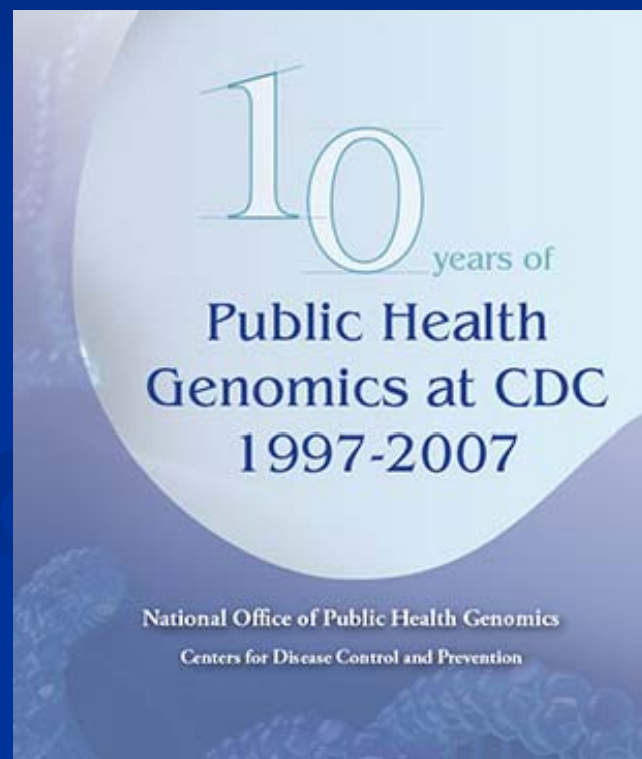# Genomics in Population Health and Healthcare: The Meaning and Phases of Translation

Muin J. Khoury MD, PhD

Director, CDC National Office of Public Health Genomics

Senior Consultant in Public Health Genomics, DCCPS, National Cancer Institute

10 years of
Public Health Genomics at CDC 1997-2007

National Office of Public Health Genomics
Centers for Disease Control and Prevention

SAFER • HEALTHIER • PEOPLE™

Outline

- 2008: science and expectations

- The phases of genomics translation

- The emergence of "public health genomics"

- A multidisciplinary framework for the assessment of genomics in population health and healthcare

2007-2008: GWAS!

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 know what in my DNA makes me me.

Inversion

Deletion

What makes the number a add variety to

GWAS articles

HuGENavigator
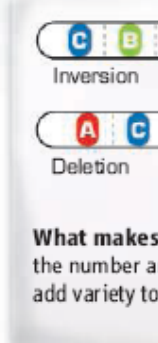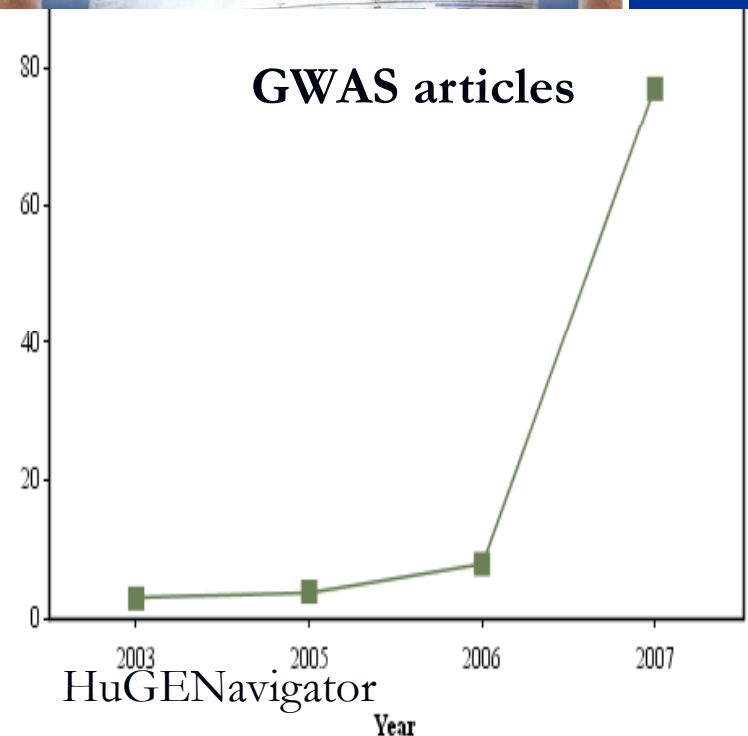
Pennisi E, *Science* 2007; 318:1842-43.

The Promise of "Omics" in Healthcare and Population Health: How do we Get There?

- **Healthcare**

- Personalized healthcare
  - BRCA, Lynch syndrome, HLA/abacavir

- Improvement in clinical management
  - Gene expression profiles in tumors

- New therapeutics
  - Gleevec, herception

- **Population Health**

- Population screening
  - Expanded newborn screening

- Identify environmental causes of human disease
  - Folate, MTHFR, birth defects

- Personal genome profiles?
  - Risk assessment and disease prevention?

Outline

- 2008: science and expectations

- The phases of genomics translation

- The emergence of "public health genomics"

- A multidisciplinary framework for the assessment of genomics in population health and healthcare

What Do You Do With Genes When You Find Them?
Two Challenges in Translation

- **Premature Translation**

- **Lost in Translation**

An Example of Premature Translation

January 22, 2008

WebMD
Better information. Better health.

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Prostate Cancer Glossary
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.,

Letting the Genome Out of the Bottle:
Will We Get Our Wish?

Hunter, Khoury and Drazen, NEJM Jan 10, 2008

From Discovery to Cancer Control: Lost in Translation

- **Basic science studies of the mechanisms leading to cancer and efforts to control cancer "often seem to inhabit separate worlds" H. Varmus)**

  - S Begley, Newsweek, 9/15/08

"Translation" Takes a Long Time!

MEDICINE

Science September 8, 2008

Life Cycle of Translational Research for Medical Interventions

From the initial discovery of a medical intervention to a highly cited article is a long road, and even this is not the end of the journey.

Despina G. Contopoulos-Ioannidis,[1] George A. Alexiou,[2] Theodore C. Gouvias,[2] John P. A. Ioannidis[2,3,4]*

Despite a major interest in translational research (1–3), development of new, effective medical interventions is difficult. Of 101 very promising claims of new discoveries with clear clinical potential that were made in major basic science journals between 1979 and 1983, only five resulted in interventions with licensed clinical use by 2003 and only one had extensive clinical use (4). Drug discovery faces major challenges (5–8). Moreover, for several interventions supported by high-profile clinical studies, subsequent evidence from larger and/or better studies contradicts their effectiveness or shows smaller benefits (9). The problem seems to be even greater

ineffective, as well as those assessing management strategies rather than specific interventions, and we selected only the earliest article whenever two or more highly cited studies with >1000 citations had been published on the same intervention and indication. Thirty-two interventions for specific indications were thus evaluated, and we could place the milestone of when their first highly cited clinical study was published showing effectiveness (tables S1 and S2). We considered this an important time point in the translational process and estimated how long a time ("translation lag") it had taken from the initial discovery of each intervention to reach that point. Highly cited status does not

showed even longer translation lag, with median of 27 (interquartile range, 21 to 50) years and similar prolongations of the translation lag for refuted interventions.

Among the 18 nonrefuted interventions that had a highly cited randomized trial to support them, the median translation lag was 16.5 years (range 4 to 50 years) in the main analysis [22 years (range 6 to 50 years) considering the wider class]. The fastest successful translation occurred for indinavir (as part of triple antiretroviral therapy) and abciximab, both of which took only 4 years from their patenting to the publication of a highly cited randomized trial. Both of these fast successes involved

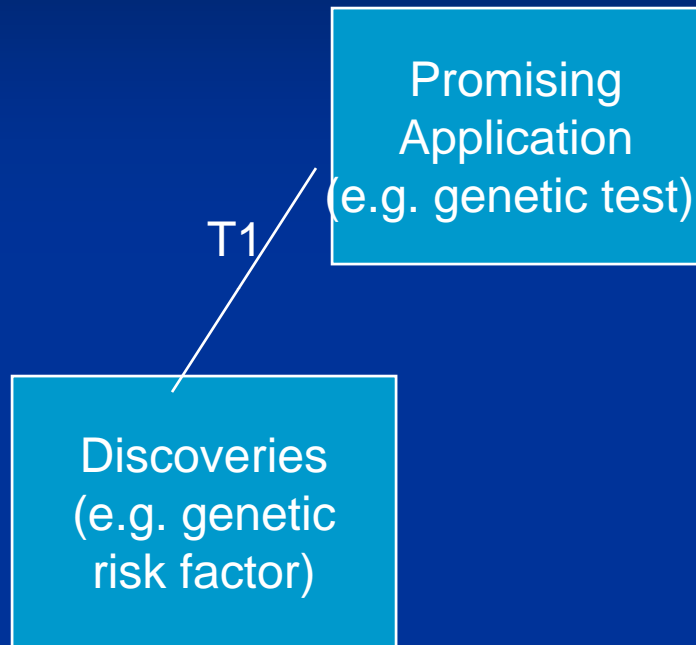# *"Lost in Translation"*
C. Lenfant NEJM 2003;349:868

< 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?"

The Phases of Genomics Translation: T1

Promising
Application
(e.g. genetic test)

T1

Discoveries
(e.g. genetic
risk factor)

Modified from Khoury et al
Genetics in Medicine 2007

The Phases of Genomics Translation: T1

Promising Application (e.g. genetic test)

T1

Discoveries (e.g. genetic risk factor)

"The scientists who have found applications for their discoveries often say they did so despite the system, not because of it."

NEWS FEATURE TRANSLATIONAL RESEARCH   NATURE Vol 453/12 June 2008

CROSSING THE VALLEY OF DEATH

A chasm has opened up between biomedical researchers and the patients who need their discoveries. **Declan Butler** asks how the ground shifted and whether the US National Institutes of Health can bridge the gap.

"NIH stands for the National Institutes of Health, not the National Institutes of Biomedical Research, or the National Institutes of Basic Biomedi-

the agency too there is a growing perception that the enormous resources being put into biomedical research, and the huge strides made in understanding disease mechanisms, are not resulting in

left behind is sometimes labelled the 'valley of death' — and neither basic researchers, busy with discoveries, nor physicians, busy with patients, are keen to venture there. "The clinical and basic scientists don't really communicate," says Barbara Alving, director of the

Modified from Khoury et al Genetics in Medicine 2007

T1
Discovery to Candidate Health Application

Gene discovery

Candidate health application

Define health outcome & intended use

Evaluate gene/environment/disease associations

Describe disease biology

Identify potential interventions

Establish analytic &clinical validity
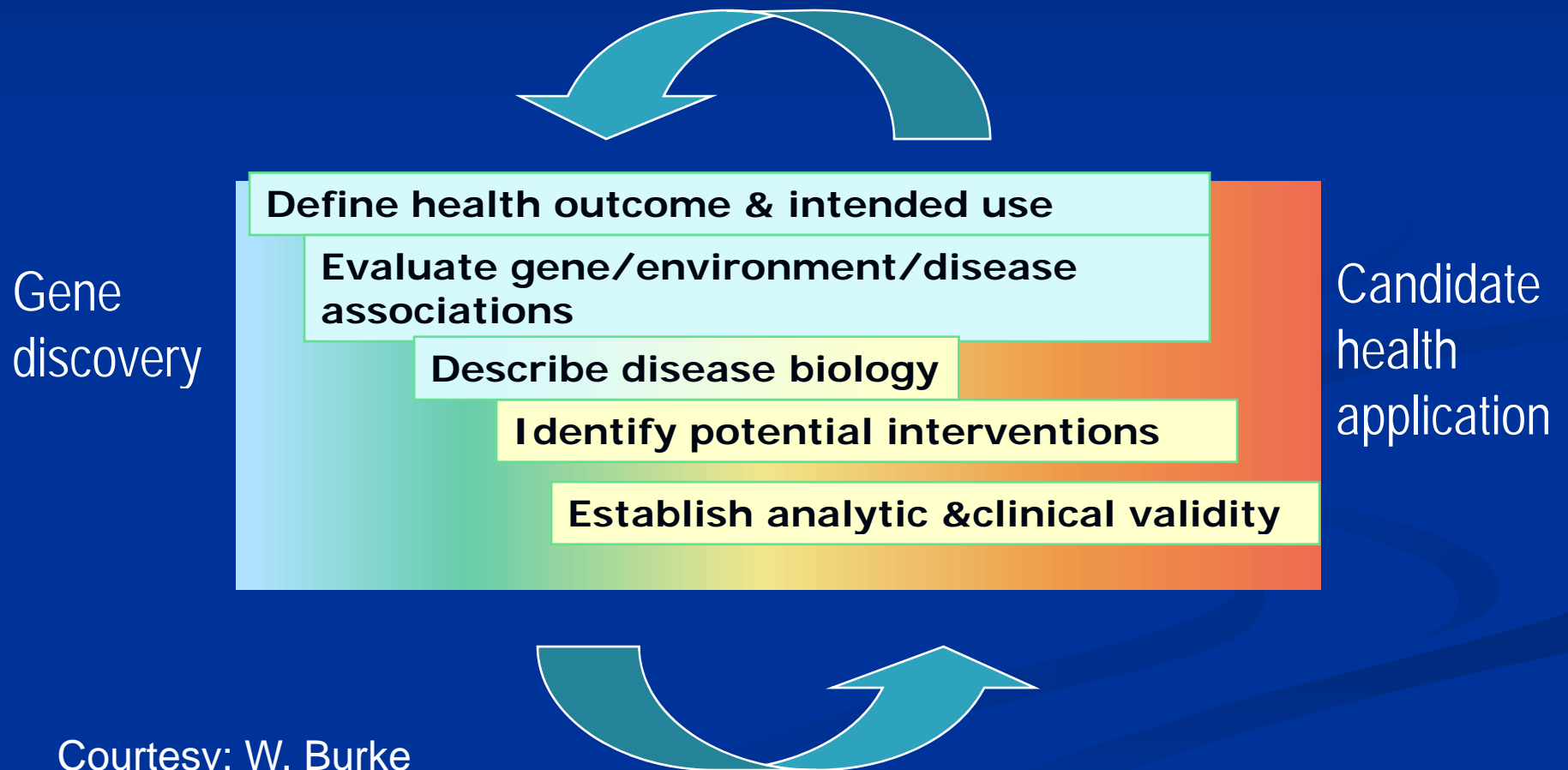
Courtesy: W. Burke
Based on Khoury et al. Genet Med 2007

The Phases of Genomics Translation: Post T1
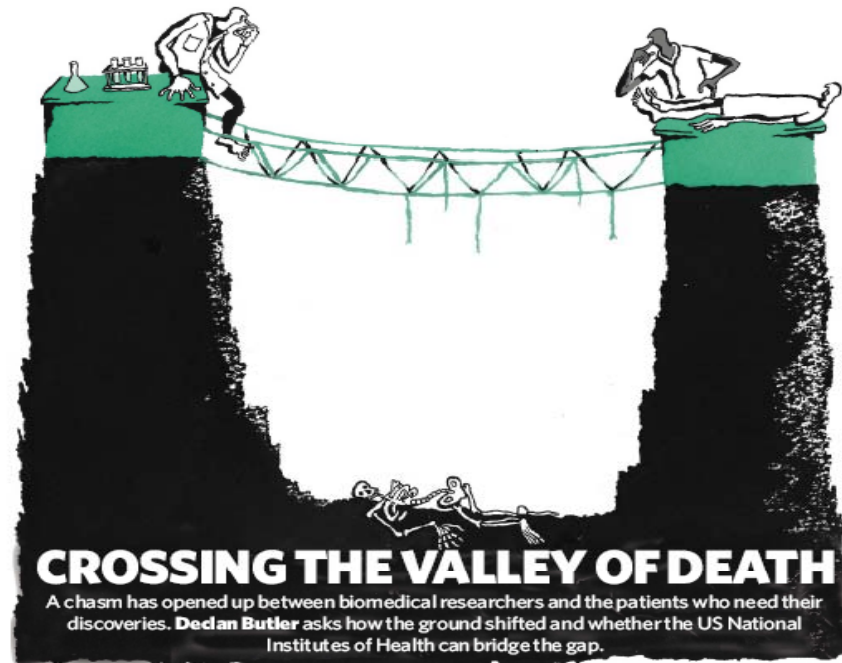
Promising Application (e.g. genetic test)

T1

Discoveries (e.g. genetic risk factor)

JAMA Jan 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 r
cording to McGlynn et al,[4] US patients receive
recommended services. The second area of trar
search seeks to close that gap and improve qu

Modified from Khoury et al
Genetics in Medicine 2007

The Roadmap less traveled (L Green)

The Second Translation Phase

Promising Application (e.g. genetic test)

T2

Evidence based Guideline/ Policy

T1

Discoveries (e.g. genetic risk factor)
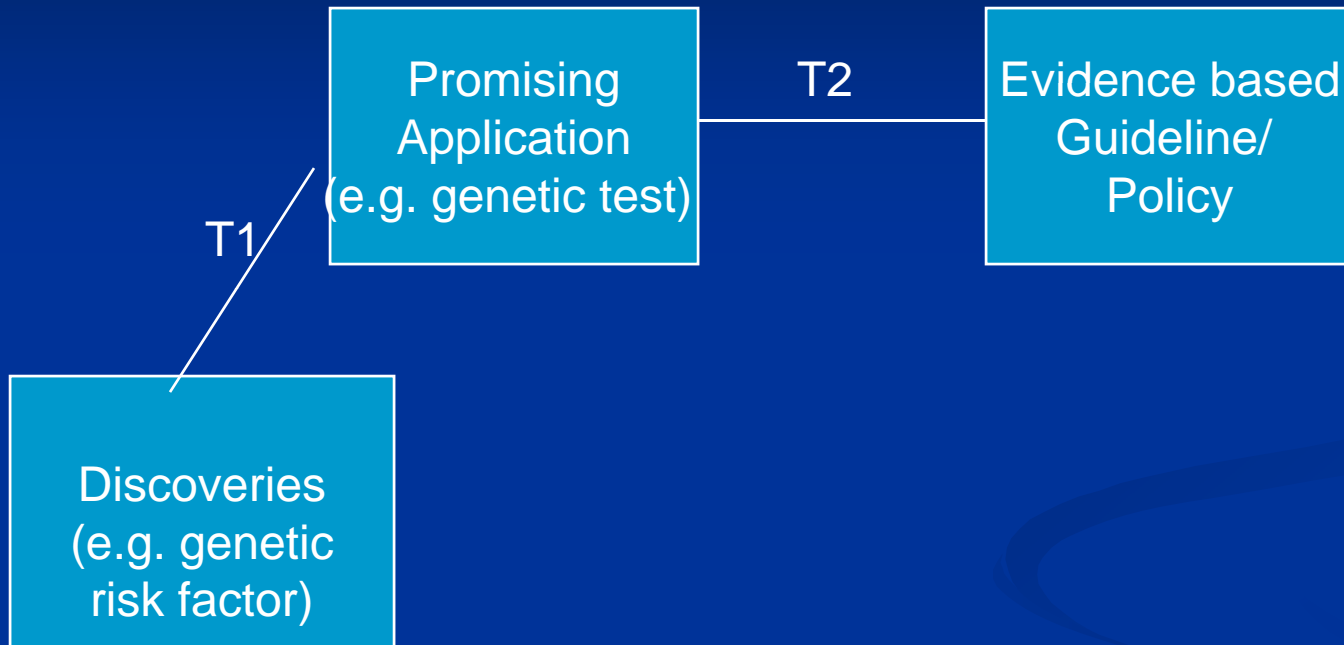
Modified from IOM Clinical Research Roundtable, Sung et al JAMA, 2003

Modified from Khoury et al
Genetics in Medicine 2007

T2
Health Application to Evidence-based Practice Guidelines

Candidate health application

Establish clinical utility

Evidence synthesis

Identify evidence gaps: uncertainties about benefits, costs, harms

Stakeholder input
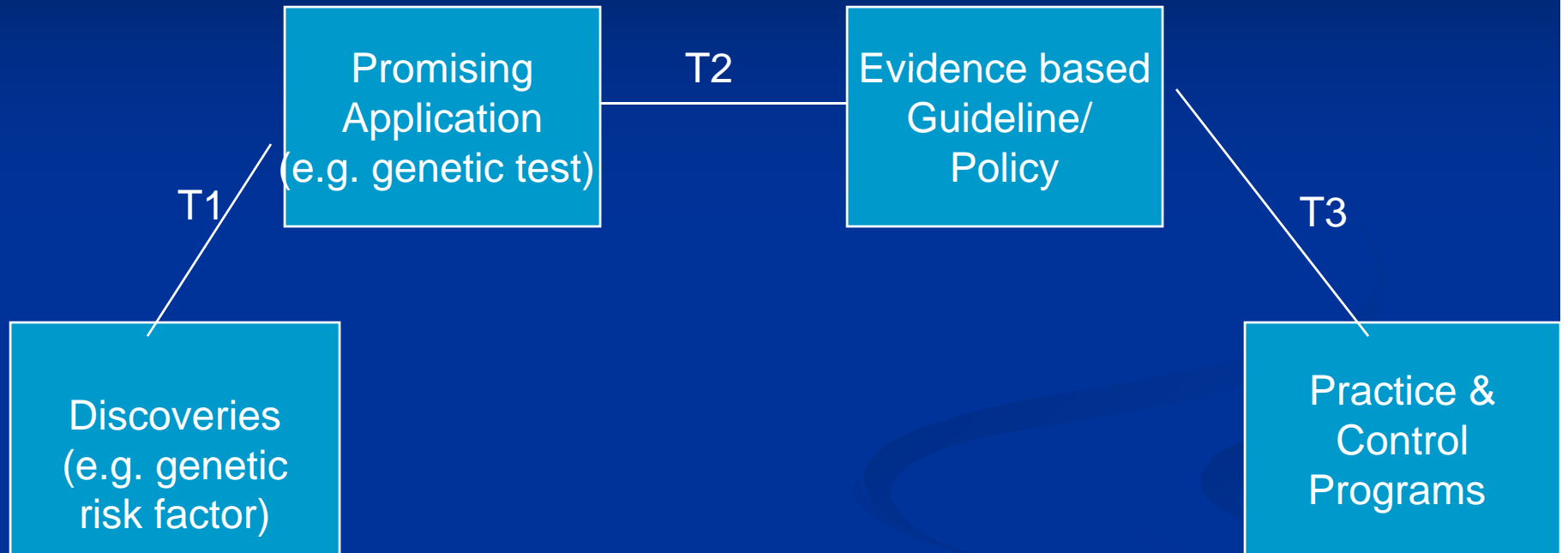
Evidence-based process

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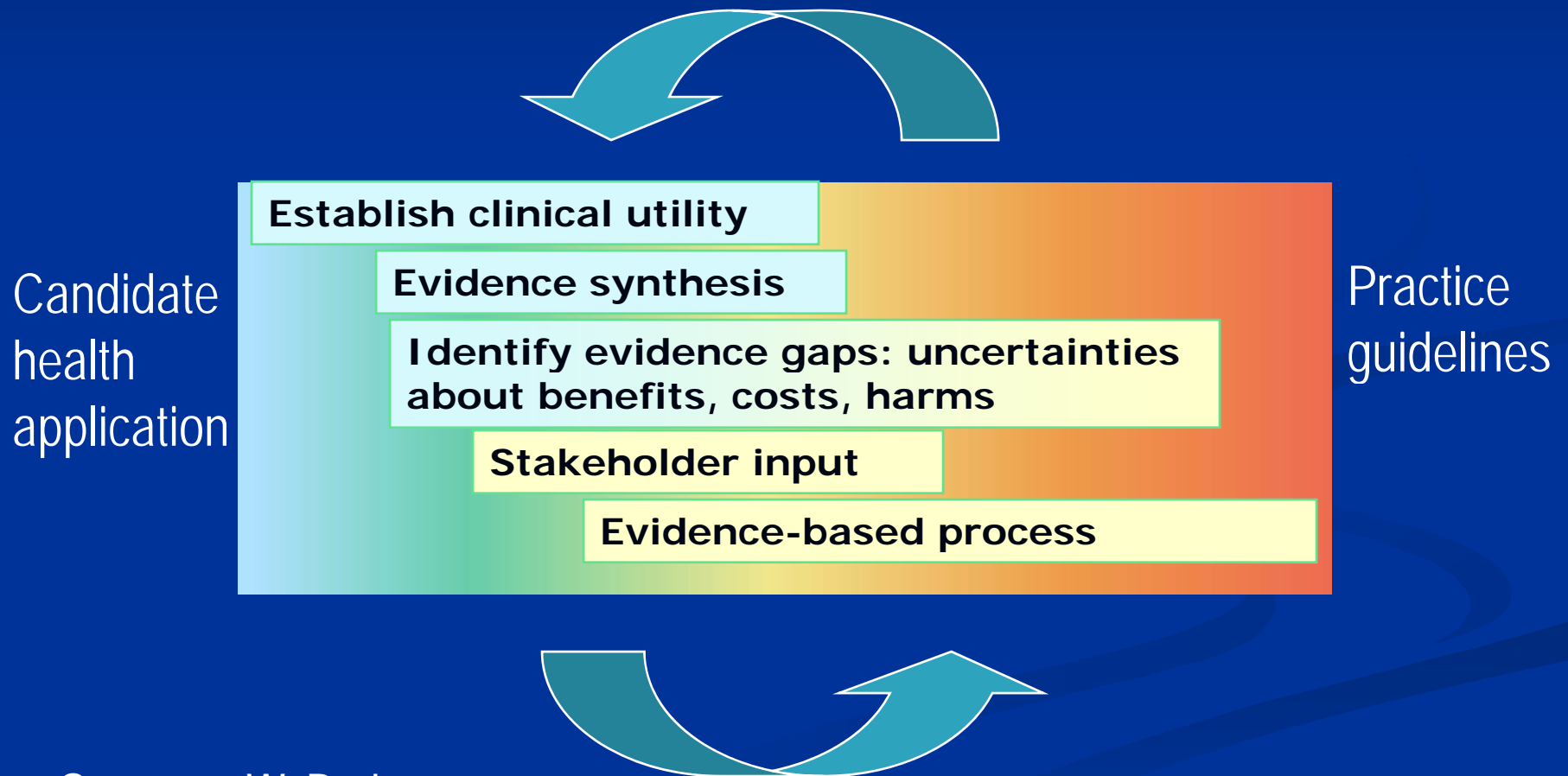
Courtesy: W. Burke
Based on Khoury et al. Genet Med 2007

The Third Phase in Translation
JM Westfall et al JAMA 2007;297:403.

Promising Application (e.g. genetic test)

T2

Evidence based Guideline/ Policy

T1

T3

Discoveries (e.g. genetic risk factor)

Practice & Control Programs

Modified from Khoury et al
Genetics in Medicine 2007

T3
Practice Guidelines to Health Practice

Practice guidelines

Dissemination research

Implementation research

Diffusion research

Phase IV clinical trials/observation
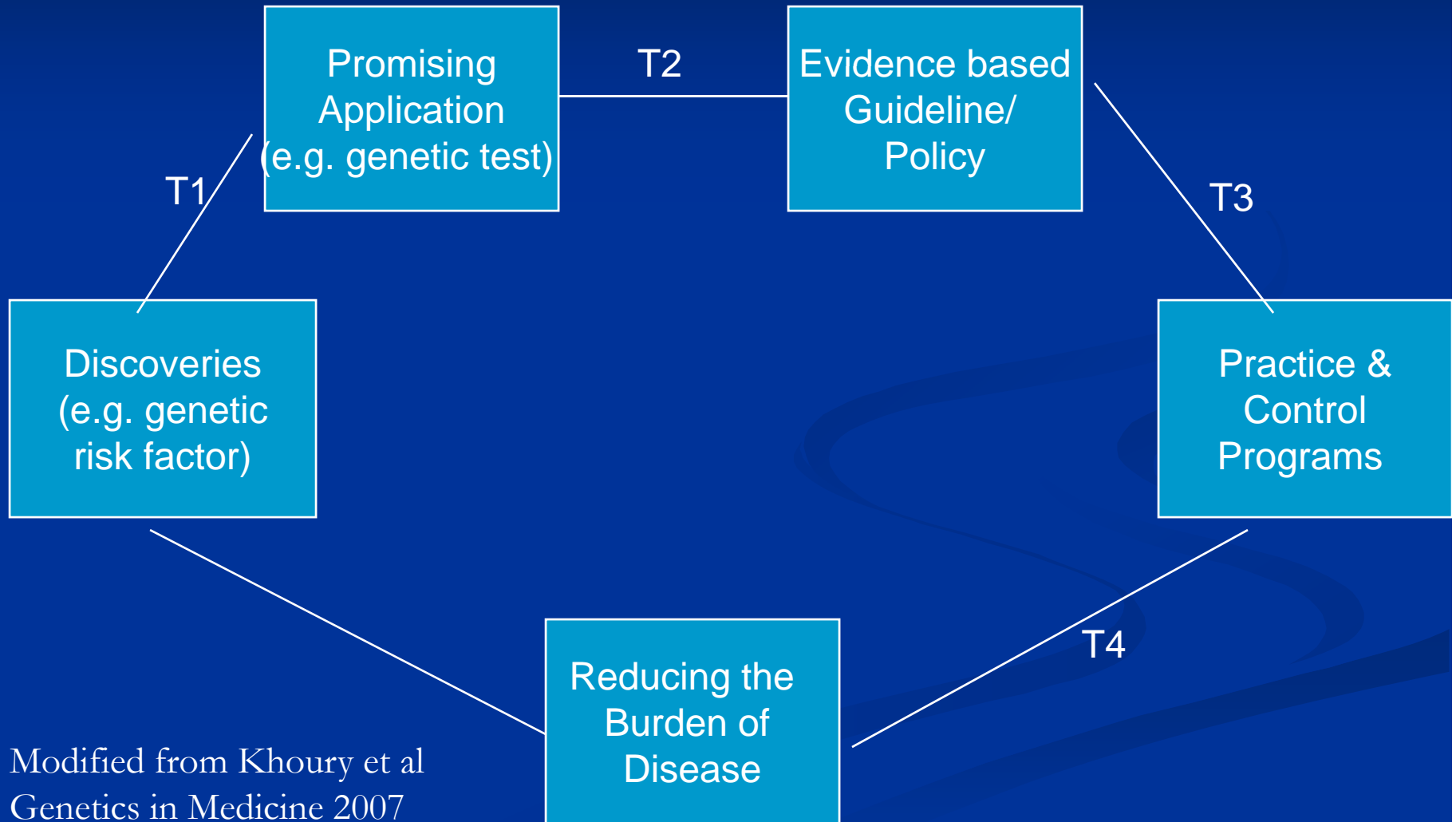
Policy analysis: Identify policy options that support appropriate use
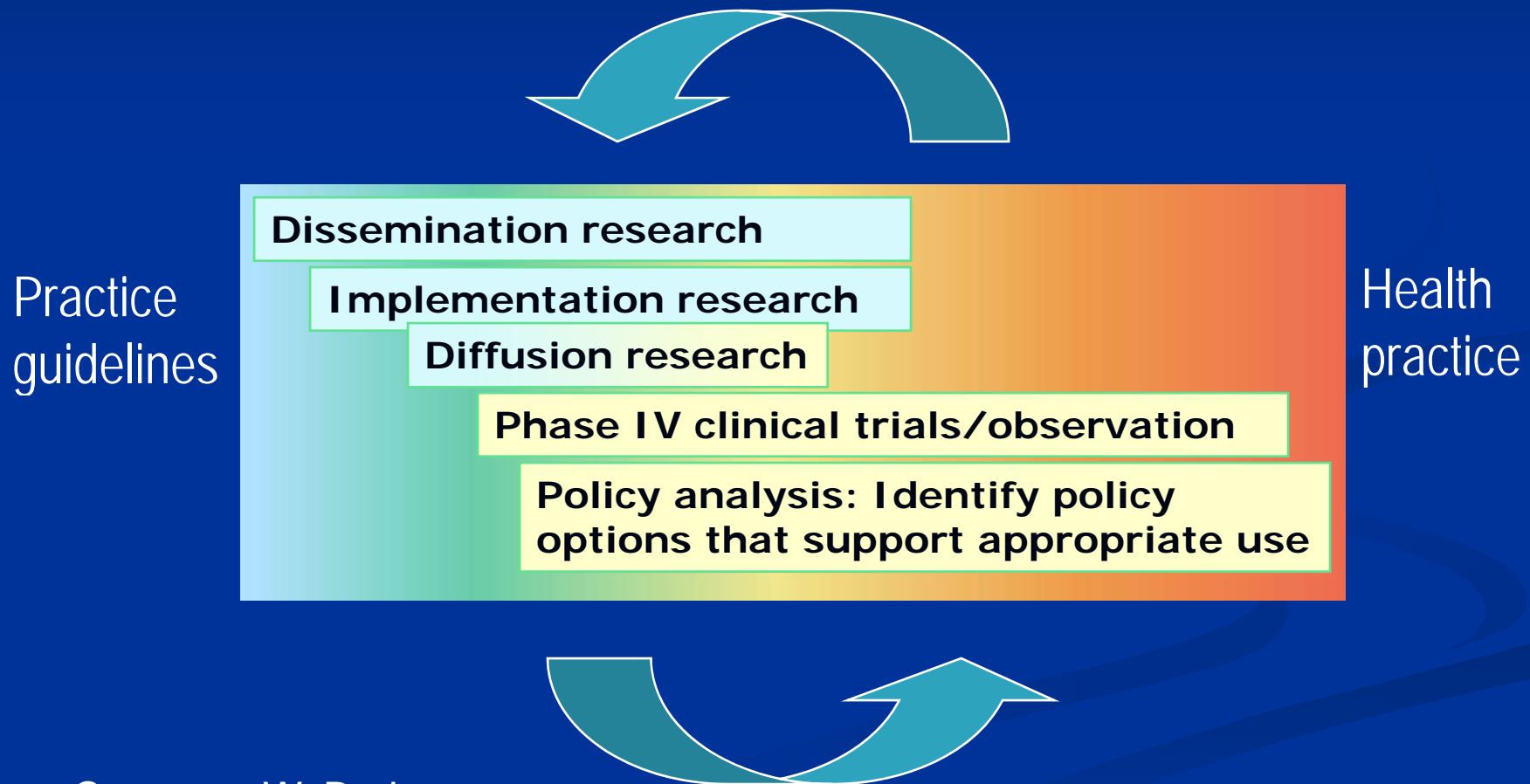
Health practice

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

The Fourth Phase of Translation: Assessing Population Health Benefits

Promising Application (e.g. genetic test)

T2

Evidence based Guideline/ Policy

T1

T3

Discoveries (e.g. genetic risk factor)

Practice & Control Programs

Reducing the Burden of Disease

T4

Modified from Khoury et al Genetics in Medicine 2007

T4
Health Practice to Health Impact

Health practice

Improved population health

Define outcomes of interest

Identify/develop appropriate metrics

Implement surveillance

Determine benefits and harms

Re-evaluate guidelines and policies→ Identify needed changes
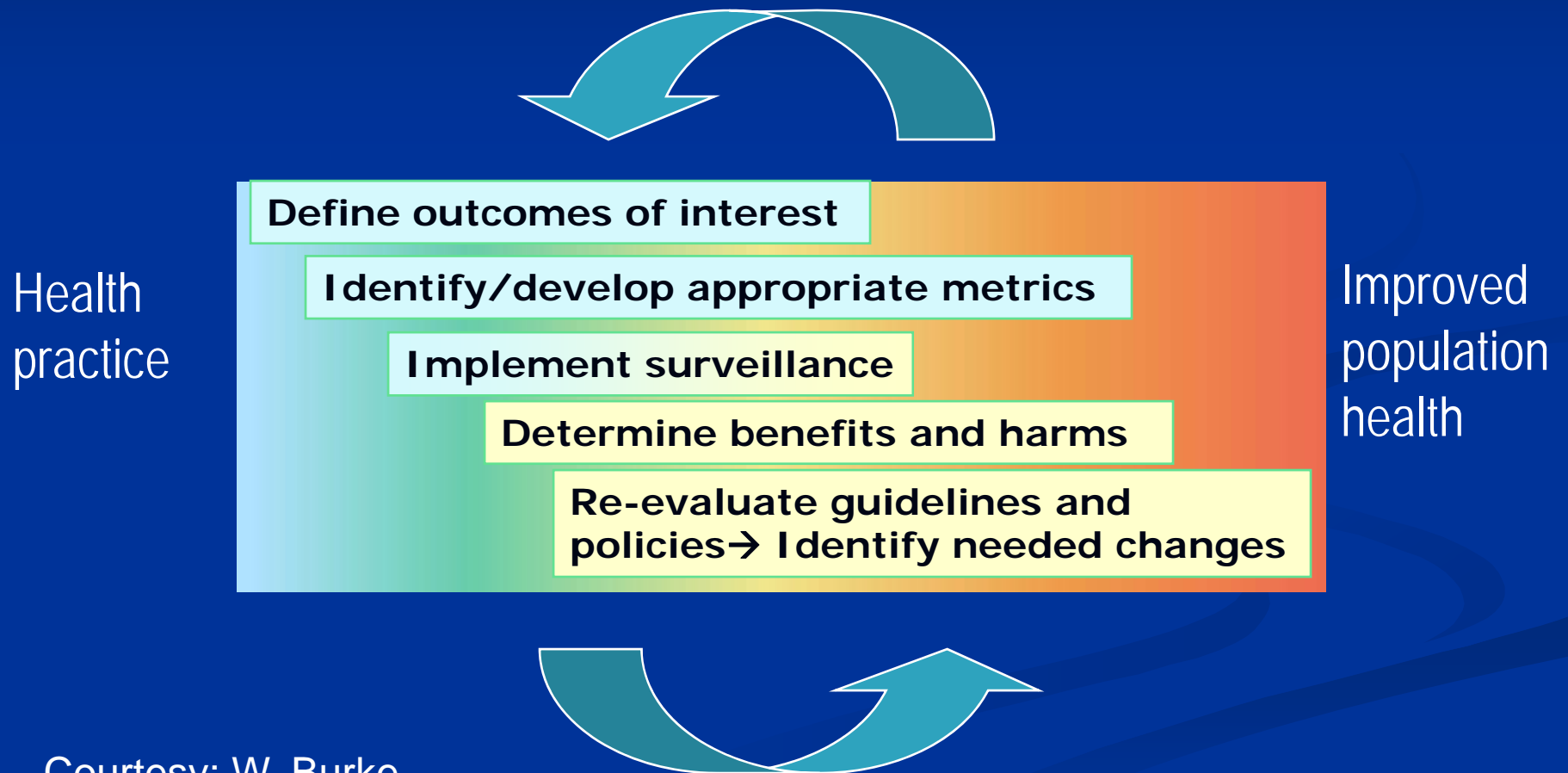
Courtesy: W. Burke
Based on Khoury et al. Genet Med 2007

The Genomics Translation Continuum: 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
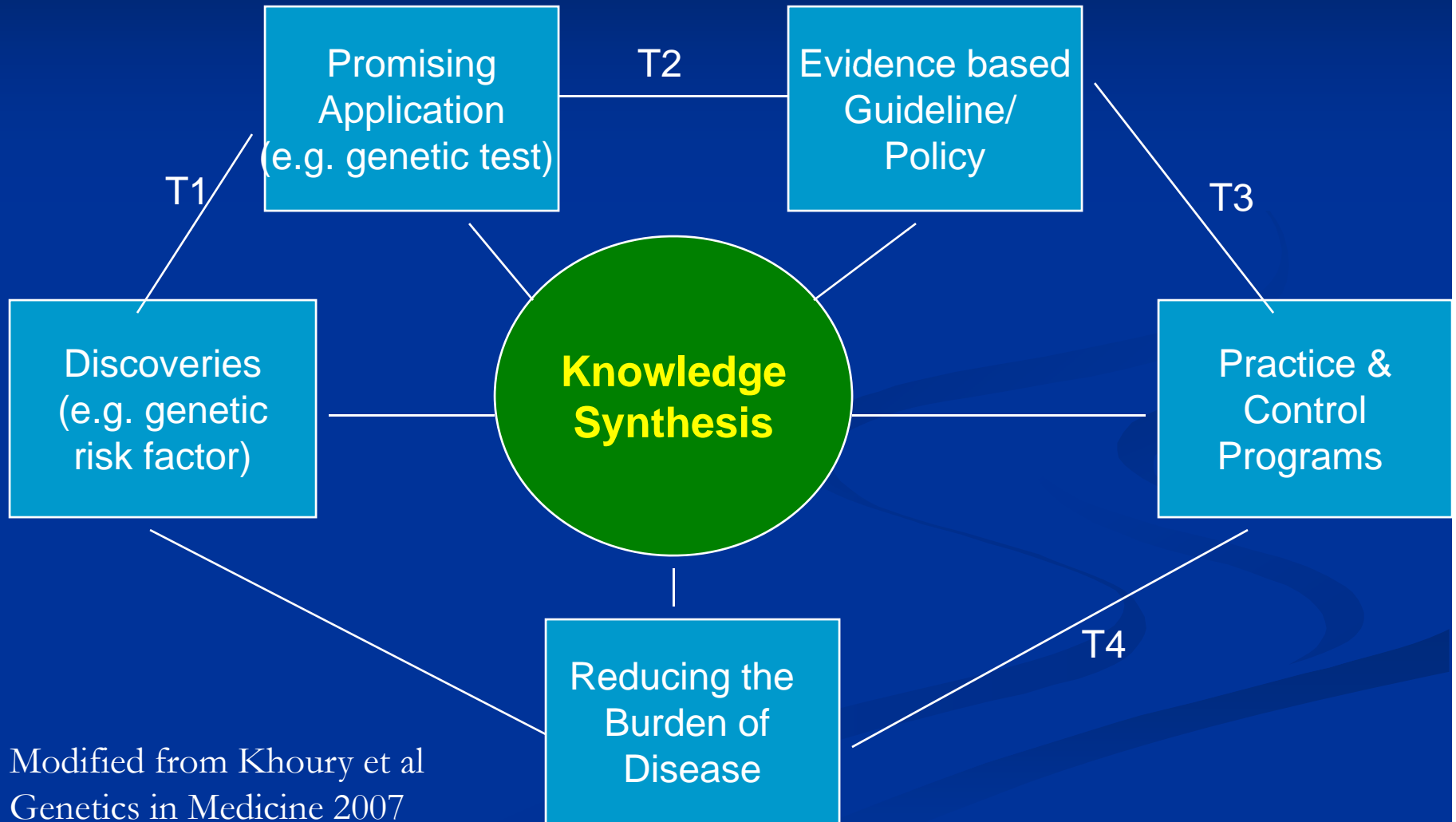
October 2007 · Vol. 9 · No. 10

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

The Role of Knowledge Synthesis

Promising Application (e.g. genetic test)

Evidence based Guideline/ Policy

T2

T1

Discoveries (e.g. genetic risk factor)

Knowledge Synthesis

Practice & Control Programs

T3

Reducing the Burden of Disease

T4

Modified from Khoury et al Genetics in Medicine 2007

Knowledge Synthesis is not a Simple Literature Search

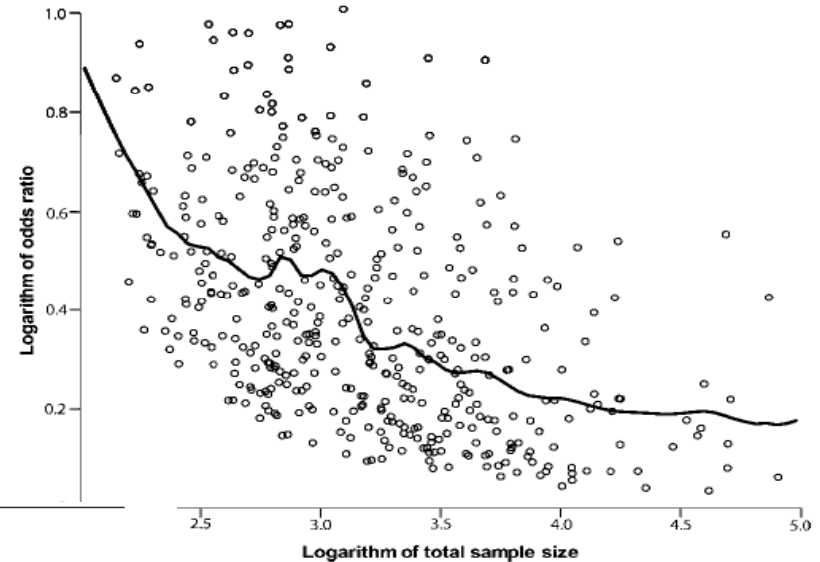Ioannidis JP et al.. Epidemiology 2008;19:640.

Ioannidis JP et al.. Int J Epi 2007

Relationship between total sample size and the odds ratio) for 256 Cochrane meta-analyses with istically significant results ($P < 0.05$ according to cts calculations) and at least 4 included studies. e In log10 scale. Also shown is a fit LOESS line. All ave been coined to be >1.00 for consistency. The ct size for the 40 meta-analyses with at least cts is 1.53. Not shown are 5 outliers with extreme or effect size.

Assessment of cumulative evidence on genetic associations: interim guidelines

John P A Ioannidis,[1-3]* Paolo Boffetta,[4] Julian Little,[5] Thomas R O'Brien,[6] Andre G Uitterlinden,[7] Paolo Vineis,[8] David J Balding,[8] Anand Chokkalingam,[9] Siobhan M Dolan,[10] W Dana Flanders,[11] Julian P T Higgins,[12] Mark I McCarthy,[13,14] David H McDermott,[15] Grier P Page,[16] Timothy R Rebbeck,[17] Daniela Seminara[18] and Muin J Khoury[19]

Established guidelines for causal inference in epidemiological studies may be inappropriate for genetic associations. A consensus process was used to develop guidance criteria for assessing cumulative epidemiologic evidence in genetic associations. A proposed semi-quantitative index assigns three levels for the amount of evidence, extent of replication, and protection from bias, and also generates a composite assessment of 'strong', 'moderate' or 'weak' epidemiological credibility. In addition, we discuss how additional input and guidance can be derived from biological data. Future empirical research and consensus

Outline

- 2008: science and expectations

- The phases of genomics translation

- The emergence of "public health genomics"

- A multidisciplinary framework for the assessment of genomics in population health and healthcare

The "Schism" between Medicine and Public Health (K White, 1991)

Medicine

- Health care
- Individuals
- Treatment
- Biomedical research
- Genes

Public Health

- Health
- Populations
- Prevention
- Behavioral/Social/Policy
- Environment

Khoury MJ et al. Am J Prev Med 2007

Dissecting Complex Disease: The Search for the Philosopher's Stone

A Buchanan et al. Int J Epidemiol 2006 ;35:562

- "If a minor fraction of the billions spent on technological research were spent instead on simpler things like, yes, early health education to improve diet and promote exercise, the benefits could grossly dwarf even the greatest plausible genetic successes"
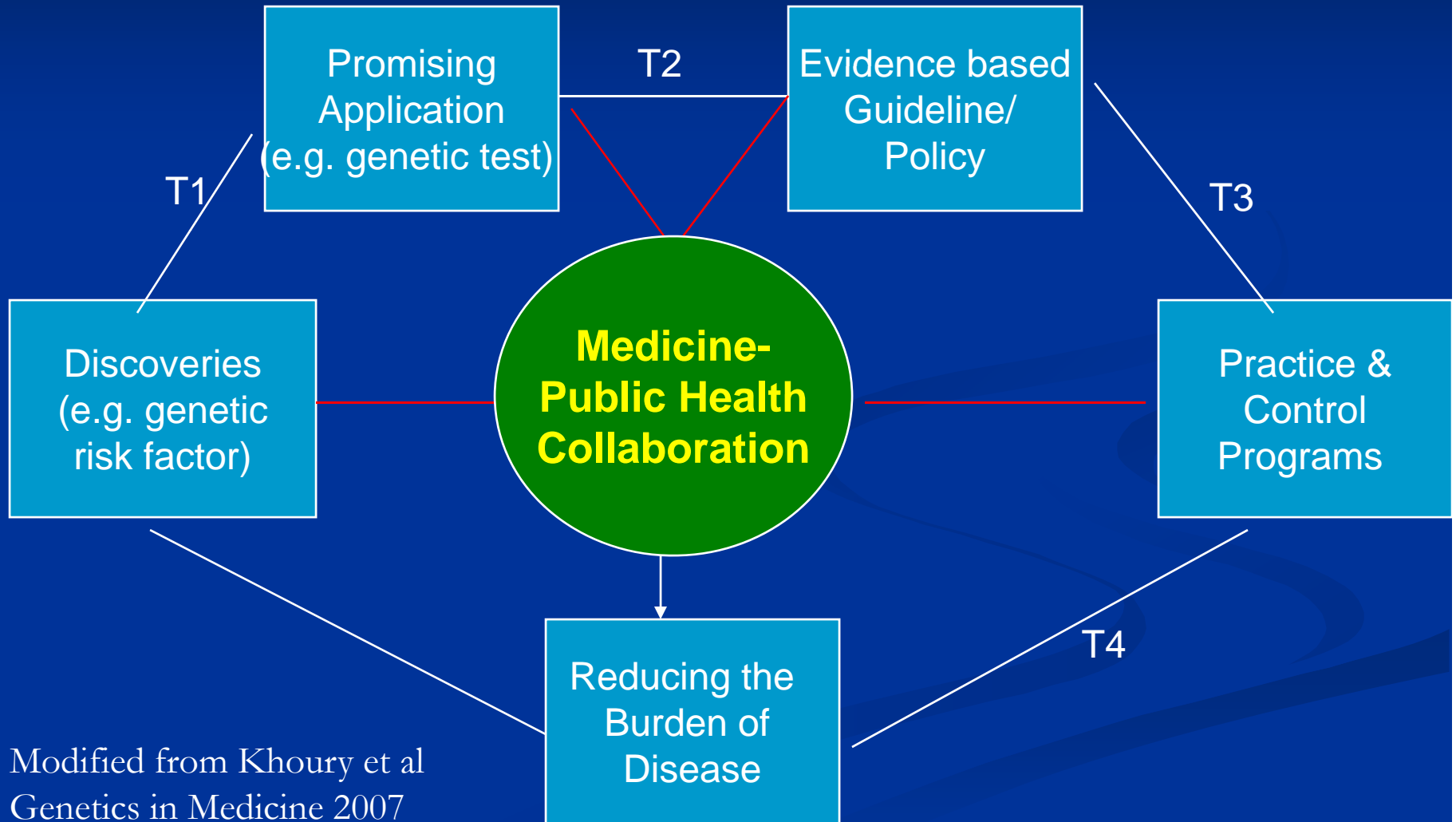
Letter to the Editor

Genomics, epidemiology, and common complex diseases: let's not throw out the baby with the bathwater!

From MUIN J KHOURY and MARTA GWINN

As public health professionals working to translate advances of genome-based research into population health benefits,[1,2] we found the article by Buchanan *et al.*[3] and associated commen- interventions to improve population health. Epidemiology is unique in offering a set of evolving tools and methods that are explicitly designed to observe disease variation in populations

Medicine-Public Health Collaboration in Genomics Translation

Promising Application (e.g. genetic test)

T2

Evidence based Guideline/ Policy

T1

Discoveries (e.g. genetic risk factor)

Medicine-Public Health Collaboration

Practice & Control Programs

T3

Reducing the Burden of Disease

T4

Modified from Khoury et al
Genetics in Medicine 2007
& Am J Prev Med 2007

"*Prevention is the Solution*" *The Cure for Healthcare in America*

New York Times January 22, 2007

- "It's been estimated that only four percent of America's $2.2 trillion dollars in annual healthcare spending is devoted to prevention"

- .."an investment of $10 per person per year in proven programs to increase physical activity, improve nutrition, and prevent smoking could save the country more than $16 billion annually within 5 years. This is a return of $5.60 for every $1 invested."

ISSUE REPORT

Prevention for a Healthier America:

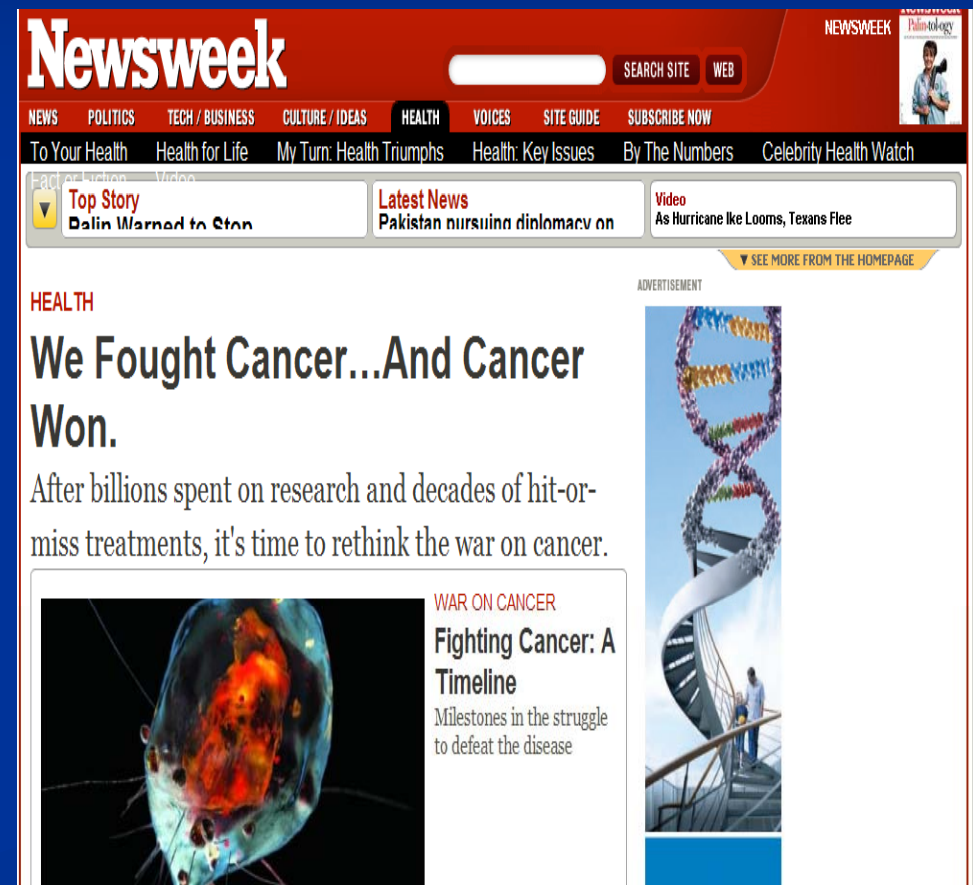INVESTMENTS IN DISEASE PREVENTION YIELD SIGNIFICANT SAVINGS, STRONGER COMMUNITIES

JULY 2008
PREVENTING EPIDEMICS.
PROTECTING PEOPLE.

Trust for America's Health
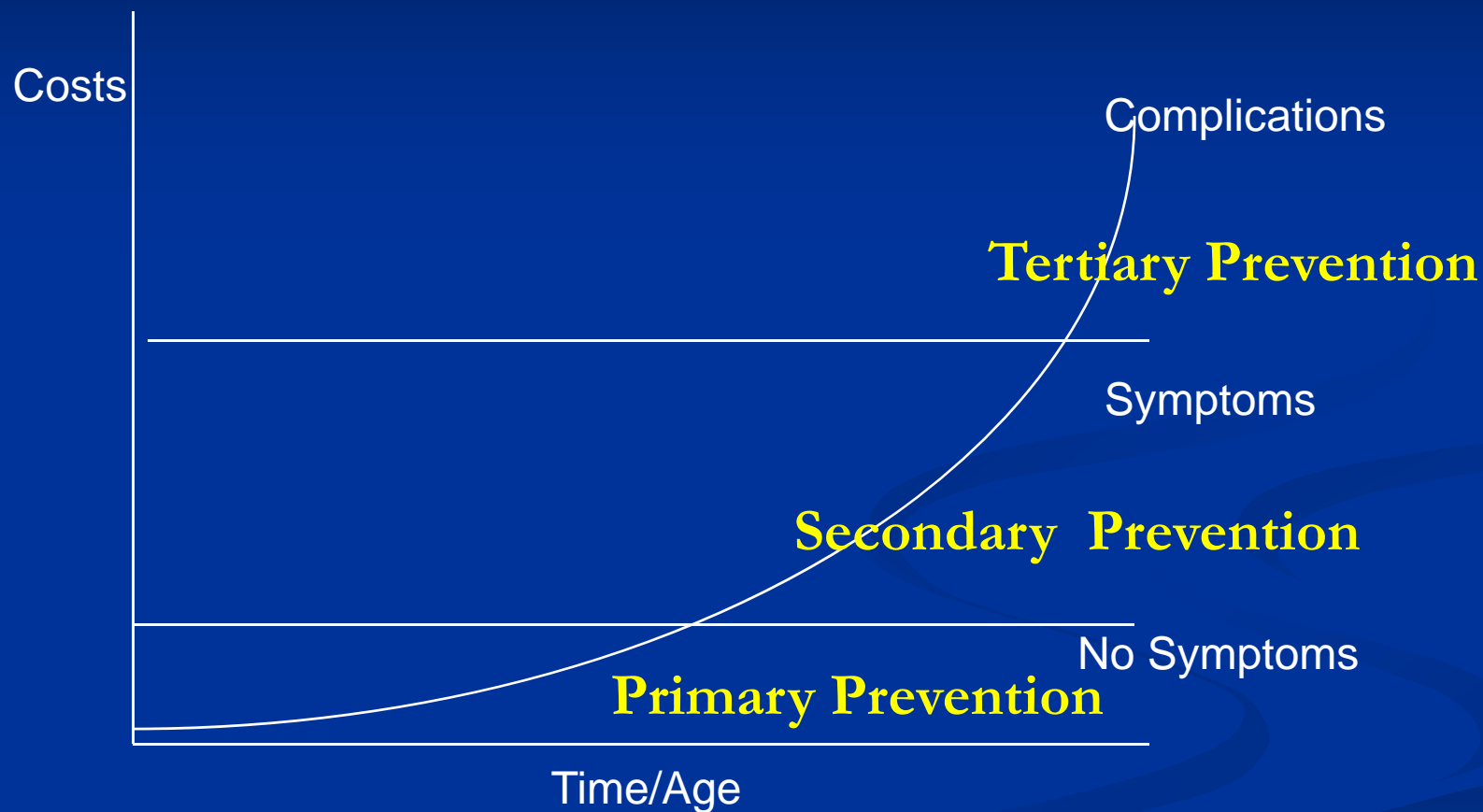WWW.HEALTHYAMERICANS.ORG

From Discovery to Cancer Control: Focus on Prevention

- This is a propitious time to consider the missed opportunities of the first 37 years of the war on cancer. Surely the greatest is prevention
- The huge majority of funding for cancer has gone into the search for ways to eradicate malignant cells rather than to keep normal cells from becoming malignant

  - S Begley, Newsweek, 9/15/08

Health Care Costs for Common Diseases by Stages of Prevention Will Genomics Help or Hurt?

Costs

Complications

Tertiary Prevention

Symptoms

Secondary Prevention

No Symptoms

Primary Prevention

Time/Age

Adapted from Zerhouni

The Emergence of Public Health Genomics

The population health approach provides the best strategy for the appropriate applications of genomics in health practice in the 21st century

Emergence of "Public Health Genomics"

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

commentary

The path from genome-based research to population health: Development of an international public health genomics network

Wylie Burke, MD, PhD[1], Muin J. Khoury, MD, PhD[2], Alison Stewart, PhD[3], and Ronald L. Zimmern, MA, FFPHM[4]
for the Bellagio Group[5]

The health benefits of the Human Genome Project have been widely anticipated. Experts predict a new era of individualized disease prevention based on testing for genetic susceptibilities,[1] and safer, more effective use of drugs based on

Which vision of the future should the prudent clinician believe: A cornucopia of healthcare innovations based on genomic research, or a stream of genetically-based interventions that fail to deliver value to the public? We argue that both visions are

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Am J Prev Med 2007

Review and Special Articles

Will Genomics Widen or Help Heal the Schism Between Medicine and Public Health?

Muin J. Khoury, MD, PhD, Marta Gwinn, MD, MPH, Wylie Burke, PhD, MD, Scott Bowen, MPH, Ron Zimmern, MA, FRCP, FFPHM

Abstract: We discuss the "schism" between medicine and public health in light of advances in genomics and the expected evolution of health care toward personalized treatment and prevention. Undoubtedly, genomics could deepen the divide between the two worlds, but it also represents an important and perhaps unique opportunity for healing the schism, given the volume of new scientific discoveries and their potential applications in all areas of health and disease. We argue that the integration of genomics into health care and disease prevention requires a strong medicine–public health partnership in the context of a population approach to a translational research agenda that includes four overlapping areas: (1) a joint focus on prevention—a traditional public health concern but now a promise of genomics in the realm of individualized primary prevention and early detection, (2) a population perspective, which requires a large amount of population-level

Areas of Collaboration

1. Prevention
2. Population sciences
3. Evidence-based practice!!
4. Collect data in the real world

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- 2008: science and expectations

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Role of Clinical and Population Disciplines

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.
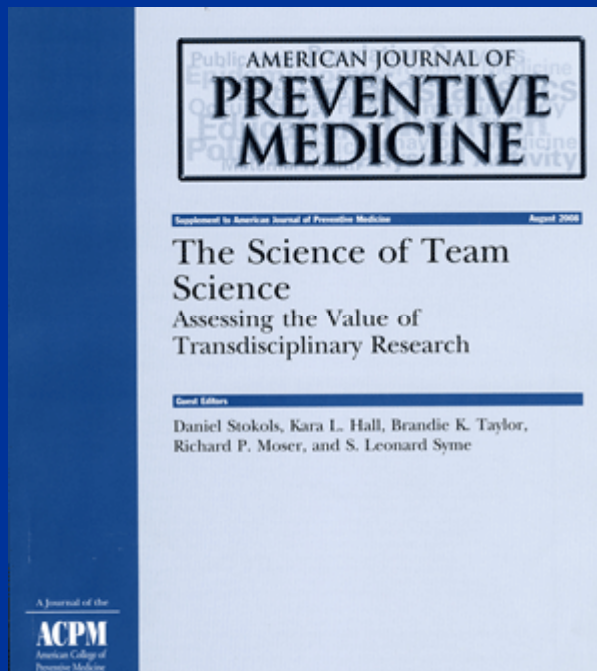
Perhaps the most breathtaking recent advances relevant to personalized medicine come from the current explosion of genome-wide association studies. These studies are based on the ability to search the genomes of large numbers of individuals in an unbiased way for statistical associations between the 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-

- **Multiple disciplines**

- Epidemiology-Get the numbers
- Behavioral research
- Intervention trials
- Communication research
- Outcome research
- Economic research
- Surveillance
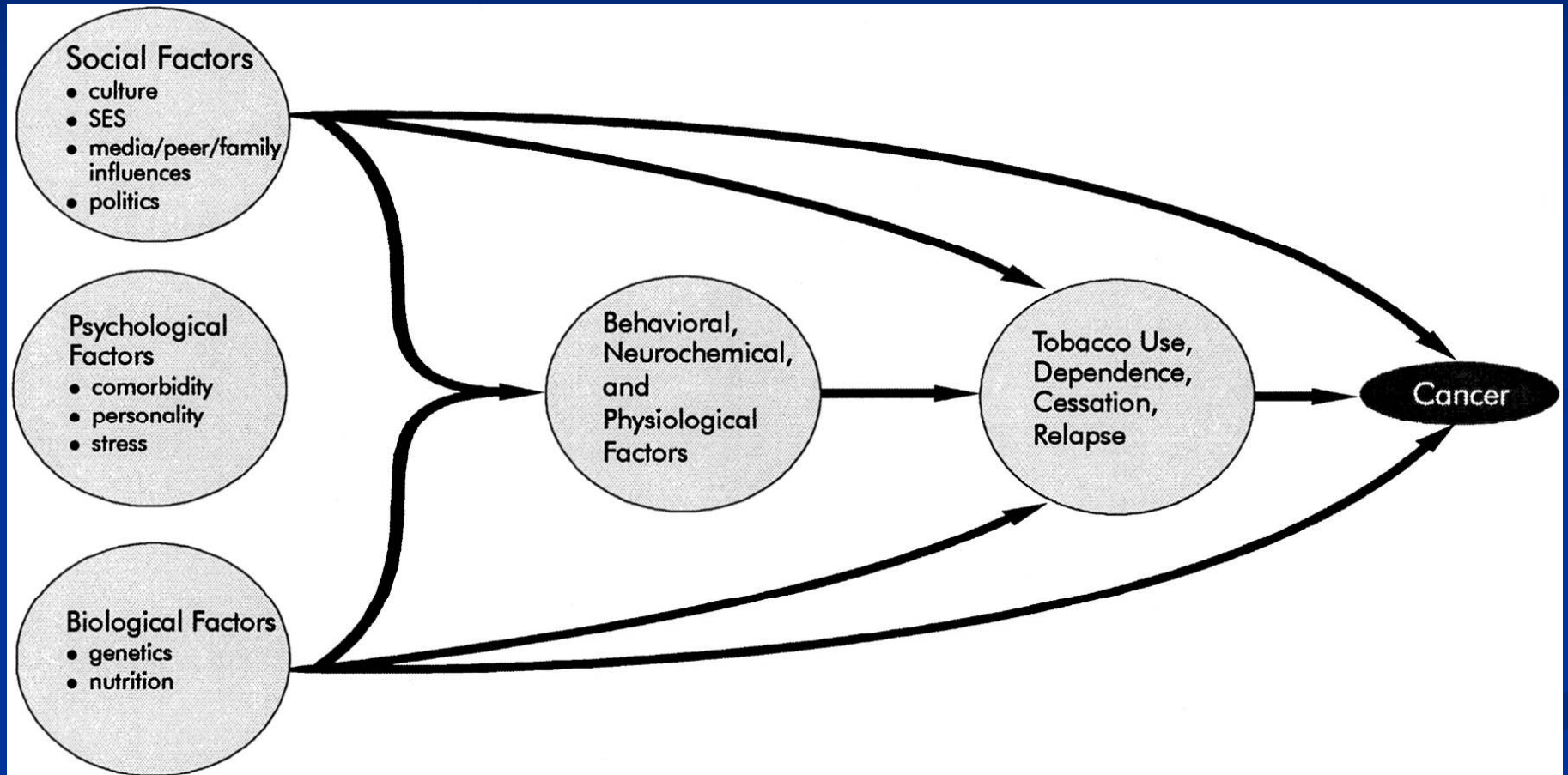- Health services research
- ELSI…..

"The Science of Team Science"
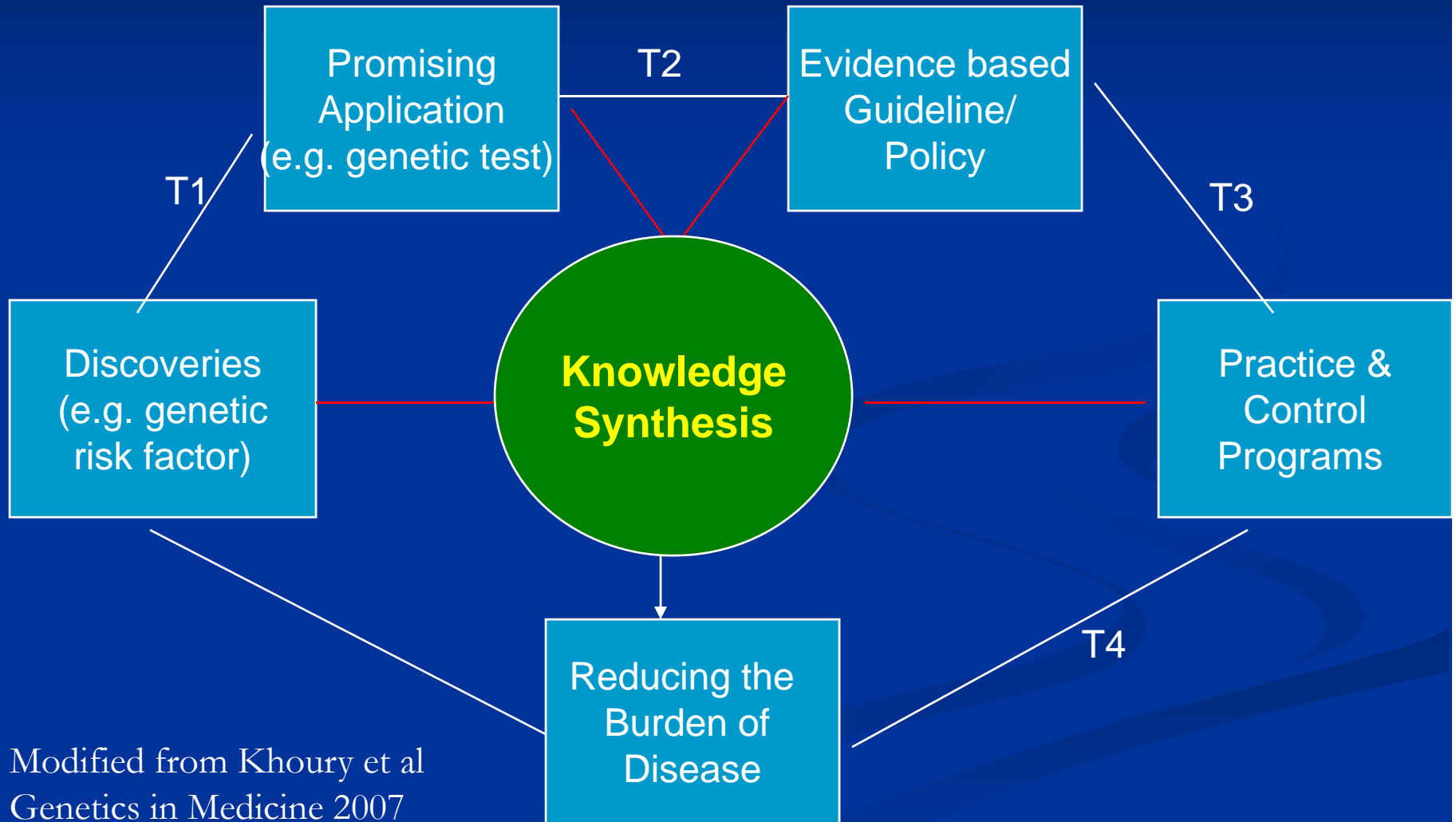### *D. Stokols et al. Am J Prev Med 2008;35:77-89*

- Unidisciplinarity
- Multidisciplinarity
- Interdisciplinarity
- Transdisciplinarity

- "Integrative process in which researchers work jointly on a framework that synthesizes and extends discipline-specific theories, concepts and methods to create new models to address a common research problem"

AMERICAN JOURNAL OF
PREVENTIVE MEDICINE

Supplement to American Journal of Preventive Medicine   August 2008

The Science of Team Science
Assessing the Value of Transdisciplinary Research

Guest Editors
Daniel Stokols, Kara L. Hall, Brandie K. Taylor,
Richard P. Moser, and S. Leonard Syme

A Journal of the
ACPM
American College of
Preventive Medicine

A New Strategy for Cancer Control Research Biobehavioral Model for Nicotine Addiction Allowing Interplay Among Numerous Factors

Public Health Genomics

Promising Application (e.g. genetic test)

T2

Evidence based Guideline/ Policy

T1

Discoveries (e.g. genetic risk factor)

Knowledge Synthesis

T3

Practice & Control Programs

Reducing the Burden of Disease

T4

Modified from Khoury et al
Genetics in Medicine 2007
& Am J Prev Med 2007

Welcome to the Public Health Genomics Interest Group

- Accelerate the integration of genomics into clinical and population sciences to improve population health

- Activities
  - Information sharing, education, collaborations, scientific initiatives, listserv, website
  - In addition to monthly seminars, the group can….