

GAPPNet

A Stakeholder-driven Collaboration to Translate Genome-based Discoveries into Health Benefits

Muin J. Khoury MD, PhD

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

The Human Genome at 10

nature

www.nature.com/nature

Vol 464 | Issue no. 7289 | 1 April 2010

The human genome at ten

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

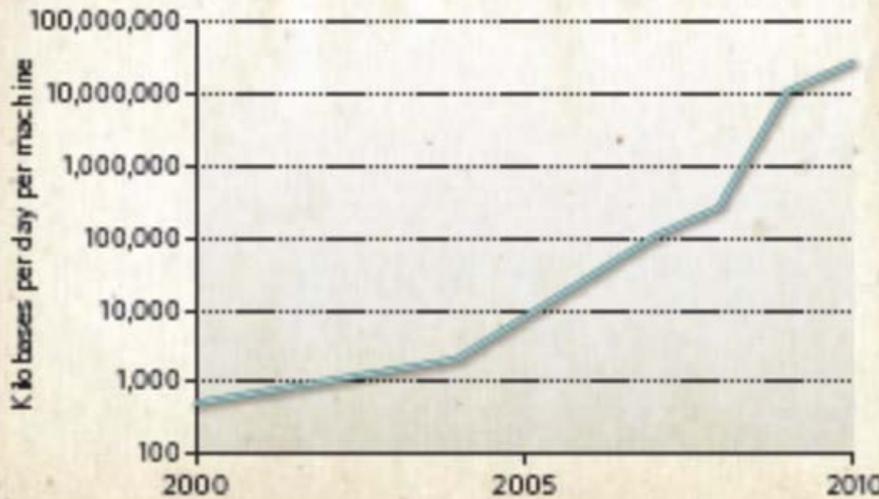
The race to complete the first human genome sequence had everything a story needs to keep its audience enthralled — right down to rivals. In the national, public for-profit com

ones (see page 670). Along the way, geneticists have such basic concepts as 'gene' and 'gene regulation' a

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SPEED READING

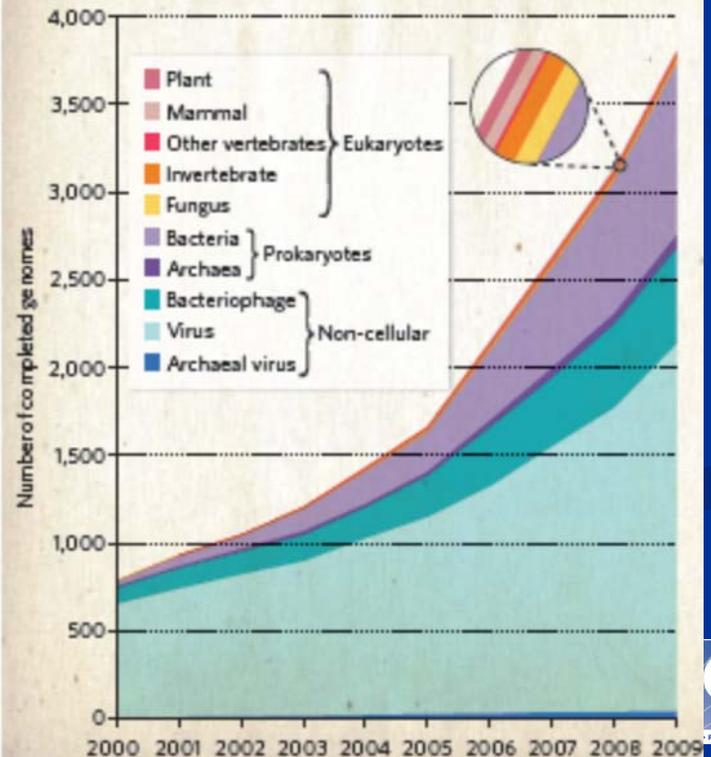
Genomes can now be sequenced around 50,000 times faster than in 2000.



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COMPLETED GENOMES*

More than 3,800 organisms have now had their genomes sequenced.



So What Do You Do With Genes When You Find Them?

TABLE 1. RESULTS OF GENETIC TESTING IN A HYPOTHETICAL PATIENT IN 2010.

CONDITION	GENES INVOLVED*	RELATIVE RISK	LIFETIME RISK (%)
Reduced risk			
Prostate cancer	<i>HPC1, HPC2, HPC3</i>	0.4	7
Alzheimer's disease	<i>APOE, FAD3, XAD</i>	0.3	10
Elevated risk			
Coronary artery disease	<i>APOB, CETP</i>	2.5	70
Colon cancer	<i>FCC4, APC</i>	4	23
Lung cancer	<i>NAT2</i>	6	40

BOOKS & ARTS

A reality check for personalized medicine

Bringing genetic information into health care is welcome but its utility in the clinic needs to be rigorously reviewed, caution **Muin J. Khoury, James Evans and Wylie Burke.**



Personal Genomics and Personalized Medicine
by Hamid Bolouri
Imperial College Press: 2010. 280 pp. £34

Excitement about how genomics will transform health care grows every time genes for com-

privacy issues — notably tests for psychiatric or behavioural traits. There is no reason to suppose that gene variants or protein markers associated with an increased risk of heart disease, macular degeneration or a host of other common conditions will require special protection, any more than non-genetic risk factors and biochemical markers do now.

tabulated in the book, only a few have withstood the rigour of evidence-based reviews.

Whenever new health technology is offered directly from the Internet or through clinical testing, it is tempting to think that the rules have changed. But they have not. It is important to remember that good ideas and scientific discoveries alone are insufficient to guide

Outline

- Genomics translation research: data urgently needed
- From translation research to actual translation: stakeholder perspectives
- The Genomic Applications in Practice and Prevention Network (GAPPNet)

Genomics Translation Research: From Bench to Population Health Impact

Discoveries
(e.g. genetic
risk factor)



Reducing the
Burden of
Disease

Genomics Translation Research: From Bench to Population Health Impact

Discoveries
(e.g. genetic
risk factor)

Health Affairs, 2009

The Evidence Dilemma In Genomic Medicine

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

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

STRACT: An ongoing dilemma in genomic medicine is balancing the need for scientific innovation with appropriate evidence thresholds for moving technology into practice. The current low threshold allows unsubstantiated technologies to enter into practice, with the potential to overwhelm the health system. Alternatively, establishing an excessively high threshold for evidence could slow the integration of genomics into practice and present disincentives for investing in research and development. Also, variable coverage and reimbursement policies can lead to differential access to technology, exacerbating health disparities. There is an urgent need for a collaborative process for appropriate identification of

COMMENTARY

JAMA Dec 3, 2008

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

Kathryn A. Phillips, PhD

NEW TESTING TECHNOLOGIES—INCREASINGLY BASED on genomic information—are essential in the shift toward personalized medicine and molecular targeted therapies. Considering the rapid proliferation of new tests, health care insurers and policy makers are interested in assessing evidence about their use and value.

It is critical to build an evidence base to support effective decision making related to testing technologies as they are

There is no consensus about optimal guidelines recommend using either test, with indeterminate results confirmed by fluorescence in situ hybridization (FISH), or FISH to determine HER2 status.¹ Although FISH is a better predictor of response to treatment, immunohistochemistry costs substantially less and is more easily performed in community laboratories.¹

Despite the clinical success of trastuzumab, there are concerns about the best methods for selecting patients for treatment. The accuracy and interpretation of HER2 tests have been highlighted by the results with overexpression of HER2



U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services

Report of the Secretary's Advisory Committee
on Genetics, Health, and Society

Technology Assessment



**Systematic Reviews on Selected
Pharmacogenetic Tests for
Cancer Treatment: CYP2D6 for
Tamoxifen in Breast Cancer,
KRAS for anti-EGFR antibodies
in Colorectal Cancer, and BCR-
ABL1 for Tyrosine Kinase
Inhibitors in Chronic Myeloid
Leukemia**

Burden of
Disease

PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY • SEPTEMBER 2008



Priorities for Personalized Medicine

Genomics Translation Research: From Bench to Population Health Impact

Discoveries
(e.g. genetic
risk factor)

“The personal genomics train has left the station...”
Mousses S et al. *Oncogene*, 2009;27:S58

TIME's Best Inventions of 2008

Invention of the Year

1. The Retail DNA Test

By Anita Hamilton



Top Stories on Time.com

- A Dismal Earnings Outlook on Wall Street
- TIME's Best Inventions of 2008
- The Ohio Republican County That Could Tip the Election
- GM Needs Bankruptcy, Not a Bailout

Invention Of the Year

Your genome used to be a closed book. Now a simple, affordable test can shed new light on everything from your intelligence to your biggest health risks. Say hello to your DNA—if you dare

BY ANITA HAMILTON

What Your Gene Test Can Tell You

Above-average odds of living to 100

Short-term memory is average

If she was breast-fed, her IQ is slightly higher than average

Above-average risk for glaucoma

4% chance of getting age-related macular degeneration

Has wet earwax

Can taste bitterness in broccoli and cabbage

Average odds of getting throat cancer

Less than 1.4% chance of getting melanoma, the most dangerous kind of skin cancer

If she is a smoker, she probably lights up a little less frequently than other smokers

0.8% chance of getting esophageal cancer

Because she metabolizes caffeine slowly, she is more sensitive to its stimulating effects

Might have an elevated risk of a nonfatal heart attack due to slow caffeine metabolism

Not resistant to malaria

Less than 1% chance of getting stomach cancer

Below-average odds of blood vessels narrowing as a result of peripheral artery disease

Drinking black or green tea is moderately likely to reduce her chance of getting breast cancer

Not resistant to HIV/AIDS

Average odds of having an irregular heartbeat due to atrial fibrillation

Slightly elevated odds of getting the autoimmune disorder Sjogren's syndrome, which affects up to 4 million Americans

10% to 20% chance of getting gallstones

10% lifetime chance of getting colorectal cancer

Average chance of getting cluster headaches

Face does not flush red when she's tipsy

88% chance of having brown eyes

Typical odds of remission from depression when treated with Zoloft or Paxil

0.08% chance of getting the bowel disease called Crohn's

28% to 70% chance of sexual dysfunction when taking certain antidepressants

The scientific foundation for personal genomics: recommendations from an National Institutes of Health–Centers for Disease Control and Prevention Multidisciplinary Workshop

Muin J. Khoury^{1,2}, Colleen McBride³, Sheri D. Schully², John P. A. Ioannidis⁴, W. Gregory Feero³, A. Cecile J. W. Janssens⁵, Maria Gwinn¹, Denise G. Simons-Morton⁶, Jay M. Bernhardt⁷, Michele Cargill⁸, Stephen J. Chanock², George M. Church⁹, Ralph J. Coates¹, Francis S. Collins³, Robert T. Croyle², Barry R. Davis¹⁰, Gregory J. Downing¹¹, Amy DuRoss⁸, Susan Friedman¹², Mitchell H. Gail¹, Geoffrey S. Ginsburg¹³, Robert C. Green¹⁴, Mark H. Greene², Philip Greenland¹⁵, Jeffrey R. Gulcher¹⁶, Andro Hsu¹⁷, Kathy L. Hudson¹⁸, Sharon L. R. Kardia¹⁹, Paul L. Kimmel²⁰, Michael S. Lauer⁶, Amy M. Miller²¹, Kenneth Offit²², David F. Ransohoff²³, Scott Roberts²⁴, Rebekah S. Rasooly²⁰, Kari Stefansson¹⁶, Sharon F. Terry²⁵, Steven M. Teutsch²⁶, Angela Trepanier²⁷, Kay L. Wanke²⁸, John S. Witte²⁹, and Jianfeng Xu³⁰

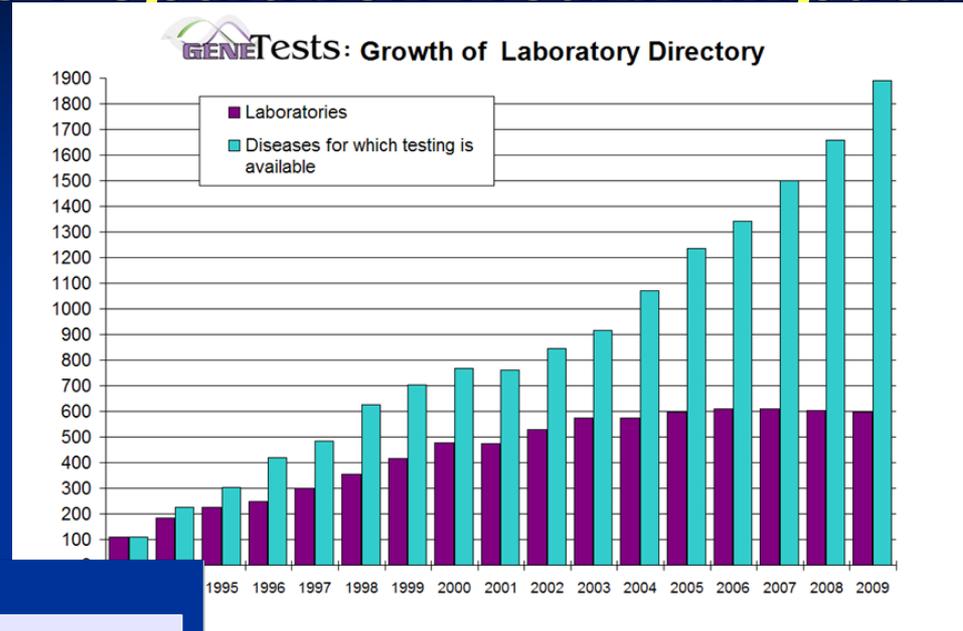
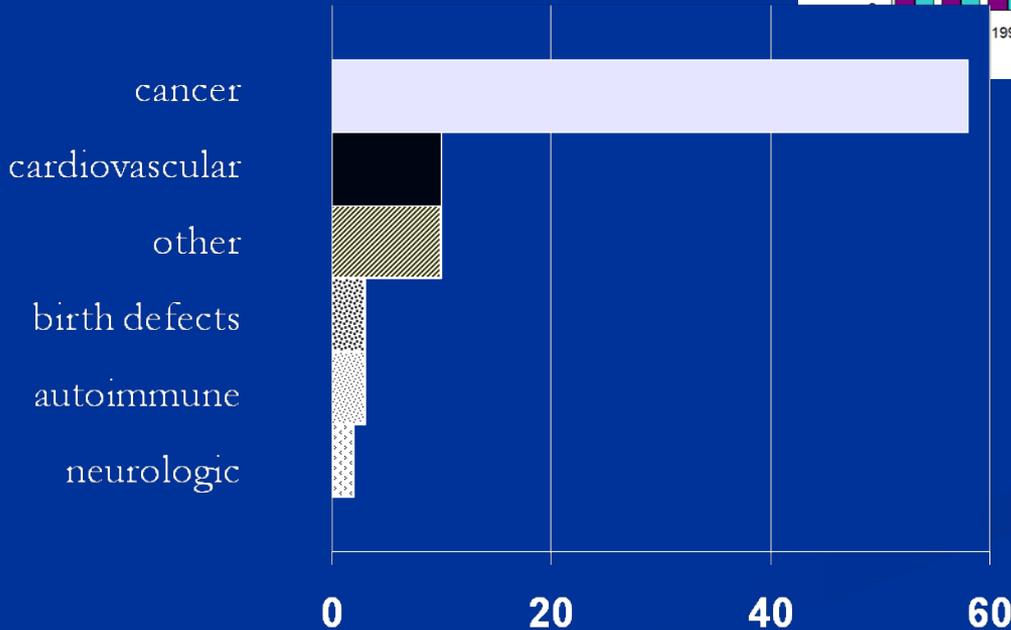
Genet Med 2009

Reducing the
Burden of
Disease

Genomics Translation Research: From Bench to Population Health Impact

Discoveries
(e.g. genetic
risk factor)

Horizon Scan for Candidate
Genomic Applications 4thQ/09
(SOURCE: CDC)

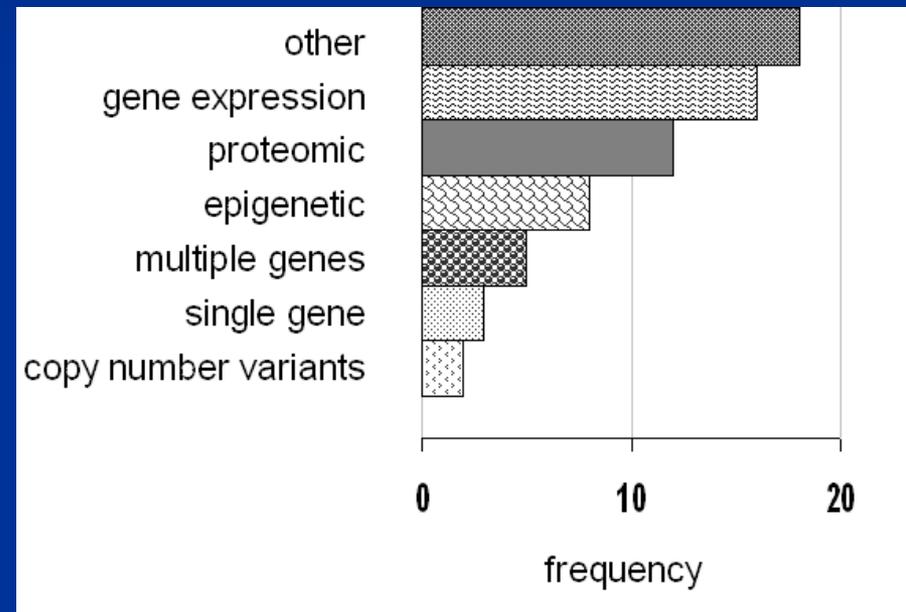
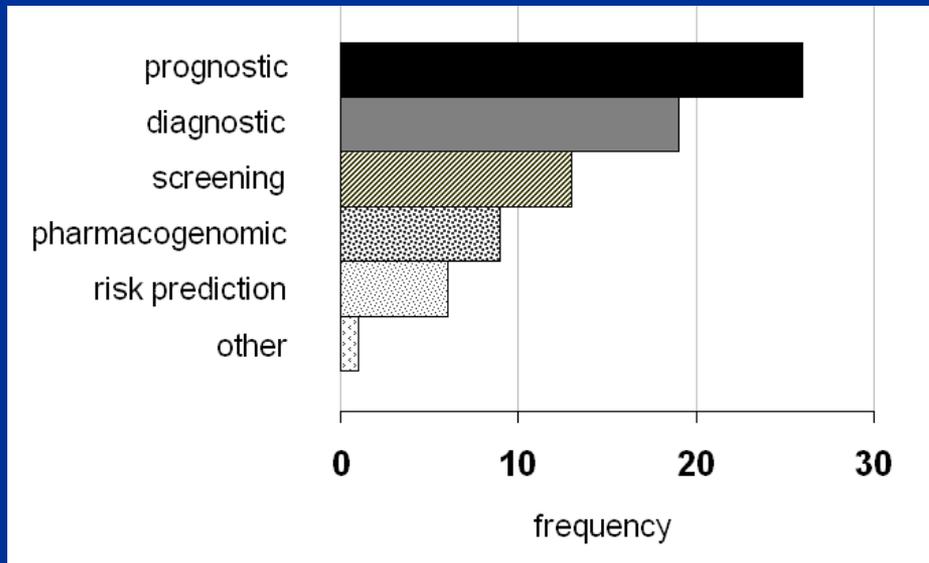


Reducing the
Burden of
Disease

Genomics Translation Research: From Bench to Population Health Impact

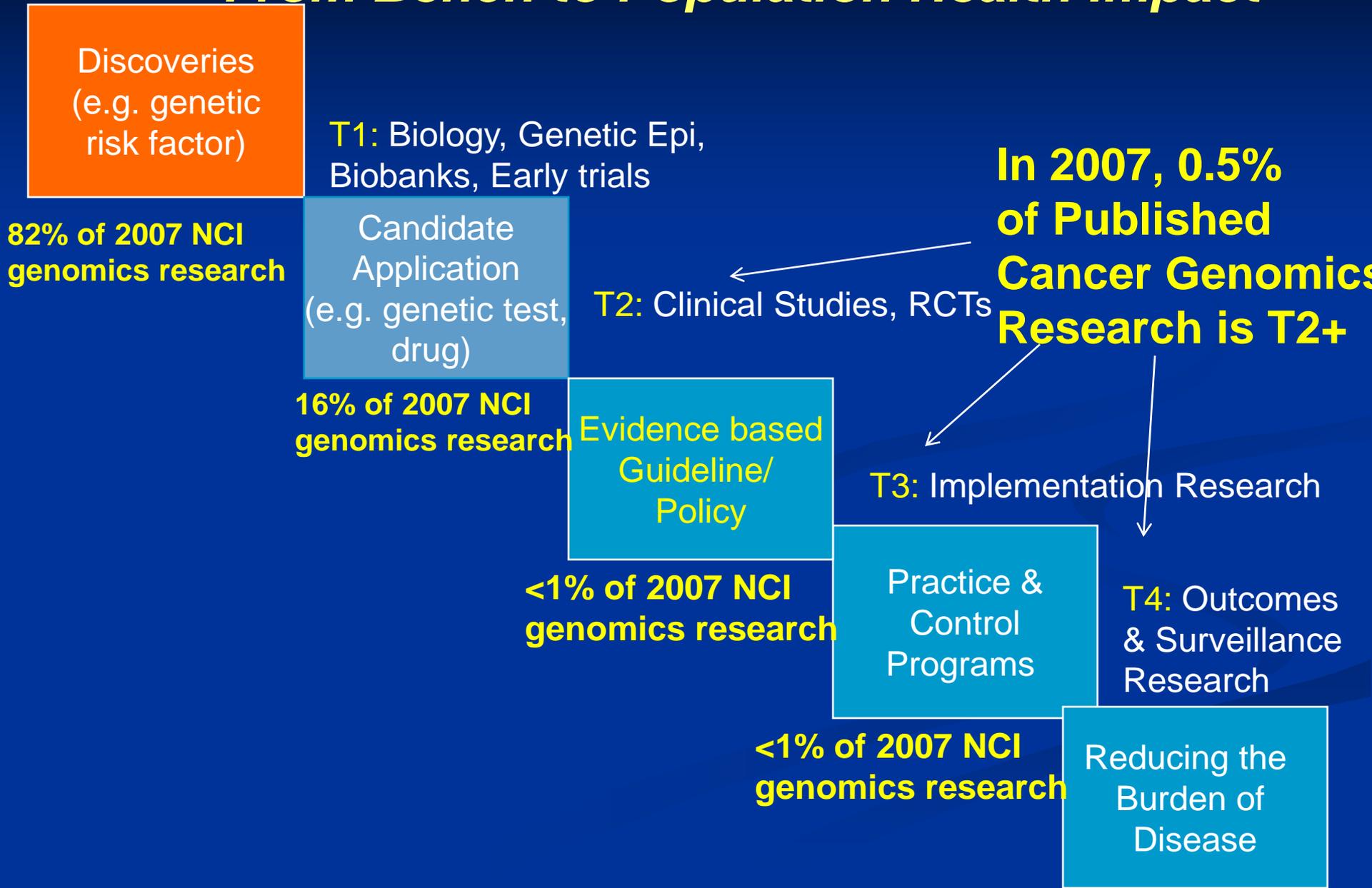
Discoveries
(e.g. genetic
risk factor)

Cancer Candidate
Genomic Applications 4thQ/09
(SOURCE: CDC)



Reducing the
Burden of
Disease

Genomics Translation Research: From Bench to Population Health Impact



Outline

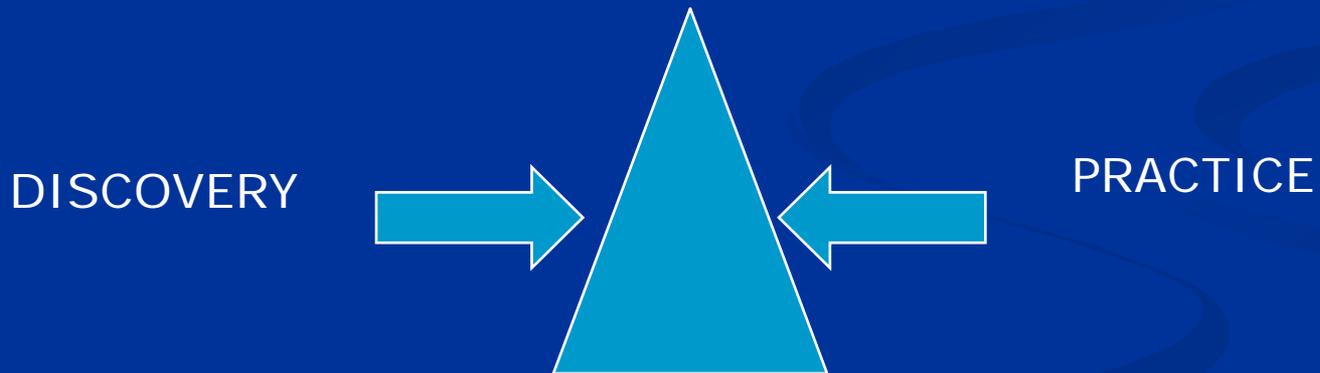
- Genomics translation research: data urgently needed
- From translation research to actual translation: stakeholder perspectives
- The Genomic Applications in Practice and Prevention Network (GAPPNet)

From Translation Research to Actual Translation: Stakeholder “Push and Pull Forces”

- Rapidly evolving technology
- Industry incentives for research and development
- Marketing
- Policy and oversight
- Consumer awareness and demand
- Professional clinical practice guidelines
- Clinical practice liability issues
- Differential access and disparities
- Coverage and reimbursement

Push and Pull Forces in Genomics Translation

Very Little Data from Translation Research



What Happens with Low Threshold for Translation into Practice? (Short T1/T2)

Very Little Data from Translation Research



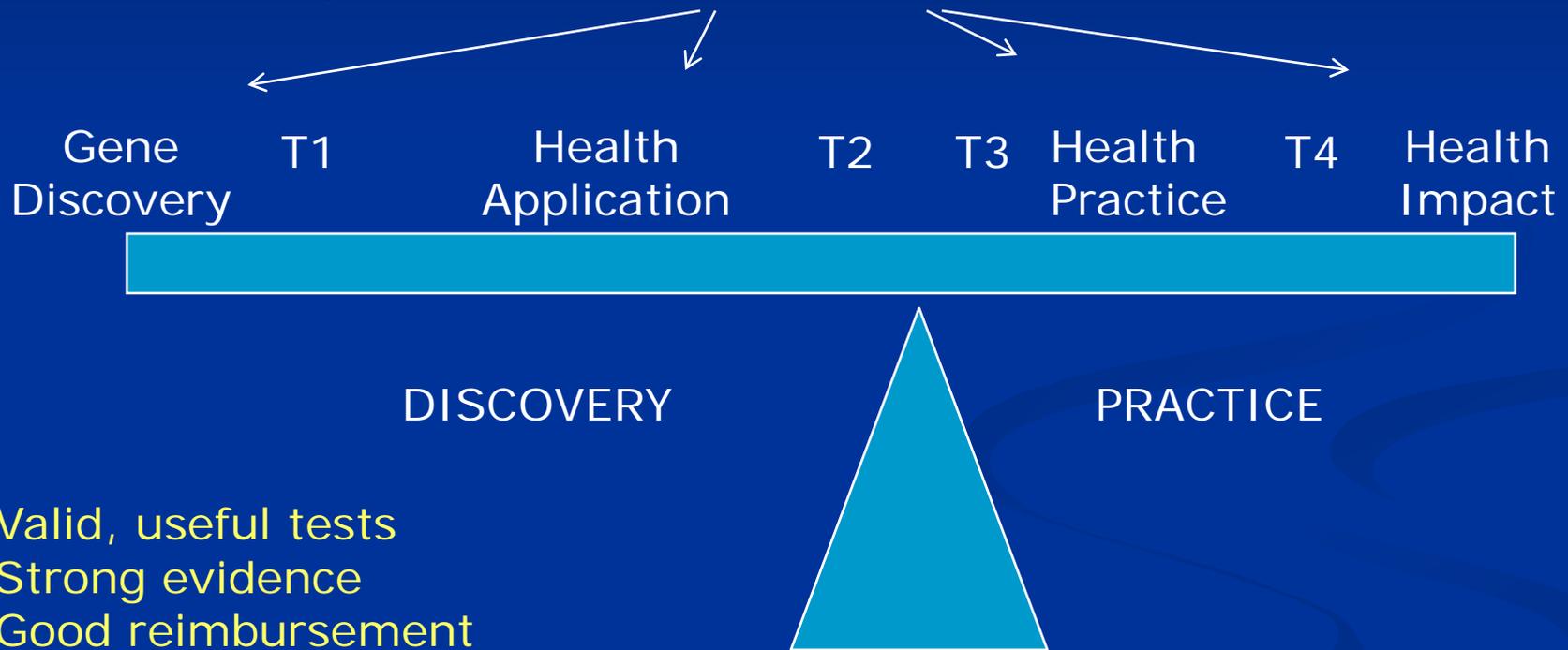
DISCOVERY

PRACTICE

Little information on clinical validity
No information on clinical utility
Potentially no coverage
Potential for increased harms
Potential for increased benefits
Use based on expert opinion
Stimulate innovation

What Happens with High Threshold for Translation into Practice? (Long T1/T2)

Very Little Data from Translation Research



Valid, useful tests
Strong evidence
Good reimbursement
Lower incentive for innovation
Diminished potential for harms
But Potential for diminished benefits

Challenges in Translating Genomics into Population Health Benefits

- Premature translation: low threshold
- “Lost in translation”: high threshold
- **What we need**
 - The knowledge and wisdom to know the difference and act accordingly
 - The will, capacity, policies and resources to act

Outline

- Genomics translation research: data urgently needed
- From translation research to actual translation: stakeholder perspectives
- The Genomic Applications in Practice and Prevention Network (GAPPNet)

What is GAPPNet?

- Collaboration of individuals and organizations interested in validating and translating genome-based applications into practice and prevention

REVIEW

Genetics in Medicine August 2009 The Genomic Applications in Practice and Prevention Network

Muin J. Khoury, MD, PhD¹, W. Gregory Feero, MD, PhD², Michele Reyes, PhD¹, Toby Citrin, JD³, Andrew Freedman, PhD⁴, Debra Leonard, PhD⁵; and the GAPPNet Planning Group: Wylie Burke, MD, PhD⁶, Ralph Coates, PhD¹, Robert Croyle, PhD³, Karen Edwards, PhD⁷, Sharon Kardia, PhD², Colleen McBride, PhD², Teri Manolio, MD, PhD², Gurvaneet Randhawa, MD⁸, Rebekah Rasooly, MD⁹, Jeannette St. Pierre, MPH¹, and Sharon Terry, MS¹⁰

Abstract: The authors describe the rationale and initial development of a new collaborative initiative, the Genomic Applications in Practice and Prevention Network. The network convened by the Centers for Disease Control and Prevention and the National Institutes of Health includes multiple stakeholders from academia, government, health care, public health, industry and consumers. The premise of Genomic Applications in Practice and Prevention Network is that there is an unaddressed chasm between gene discoveries and demonstration of their clinical validity and utility. This chasm is due to the lack of readily accessible information about the utility of most genomic applications and the lack

ered factors and clinical outcomes (clinical validity), and the costs, benefits, and harms of genome-based technologies in real world settings (clinical utility).⁴ Furthermore, the process should facilitate the development of evidence-based guidelines for the use of genomic applications⁵; and appropriate implementation of these applications in practice, including protection of individuals and communities against discrimination based on genetic information.⁶ Importantly, advances in genomics should be considered in the context of the larger forces affecting health care delivery in the United States, including escalating costs, differential access to quality health care, and a growing number

GAPPNet Mission

- To accelerate and streamline the effective translation of validated genomic knowledge into the practice of medicine and public health in the United States, by empowering research and evaluation, and disseminating high quality information on promising genomic applications in practice and prevention

The screenshot shows the GAPPNet website homepage. At the top is the GAPPNet logo, which includes a stylized network diagram. To the right of the logo are four circular images: a doctor and patient, a woman with a child, a person in a lab coat, and a group of people. Below these is a navigation bar with links: Home, About Us, Genomic Applications, Project Locator, Get Involved, and Contact Us. The main content area features three news items, each with a small image and a text box. The first item is titled 'First GAPPNet Meeting' and mentions it was held in Ann Arbor, Michigan, in October 2009. The second item is titled 'Three New EGAPP Recommendations' and mentions specific genetic tests for breast and colorectal cancer. The third item is titled 'BRCA1/2 Testing in Practice' and mentions identifying individuals at increased risk for hereditary breast or ovarian cancer. On the right side of the page, there is a search bar and a sidebar with links: What's New, Get Involved, Join Public Discussion, For GAPPNet Interest Groups, and Contact Us.

The Genomic Applications in Practice and Prevention Network (GAPPNet™) aims to accelerate and streamline effective and responsible use of validated and useful genomic knowledge and applications, such as genetic tests, technologies, and family history, into clinical and public health practice. [Learn more.](#)

First GAPPNet Meeting
Held in Ann Arbor, Michigan, October 29-30, 2009

Three New EGAPP Recommendations
On specific genetic tests for breast and colorectal cancer

BRCA1/2 Testing in Practice
For identifying individuals at increased risk for hereditary breast or ovarian cancer

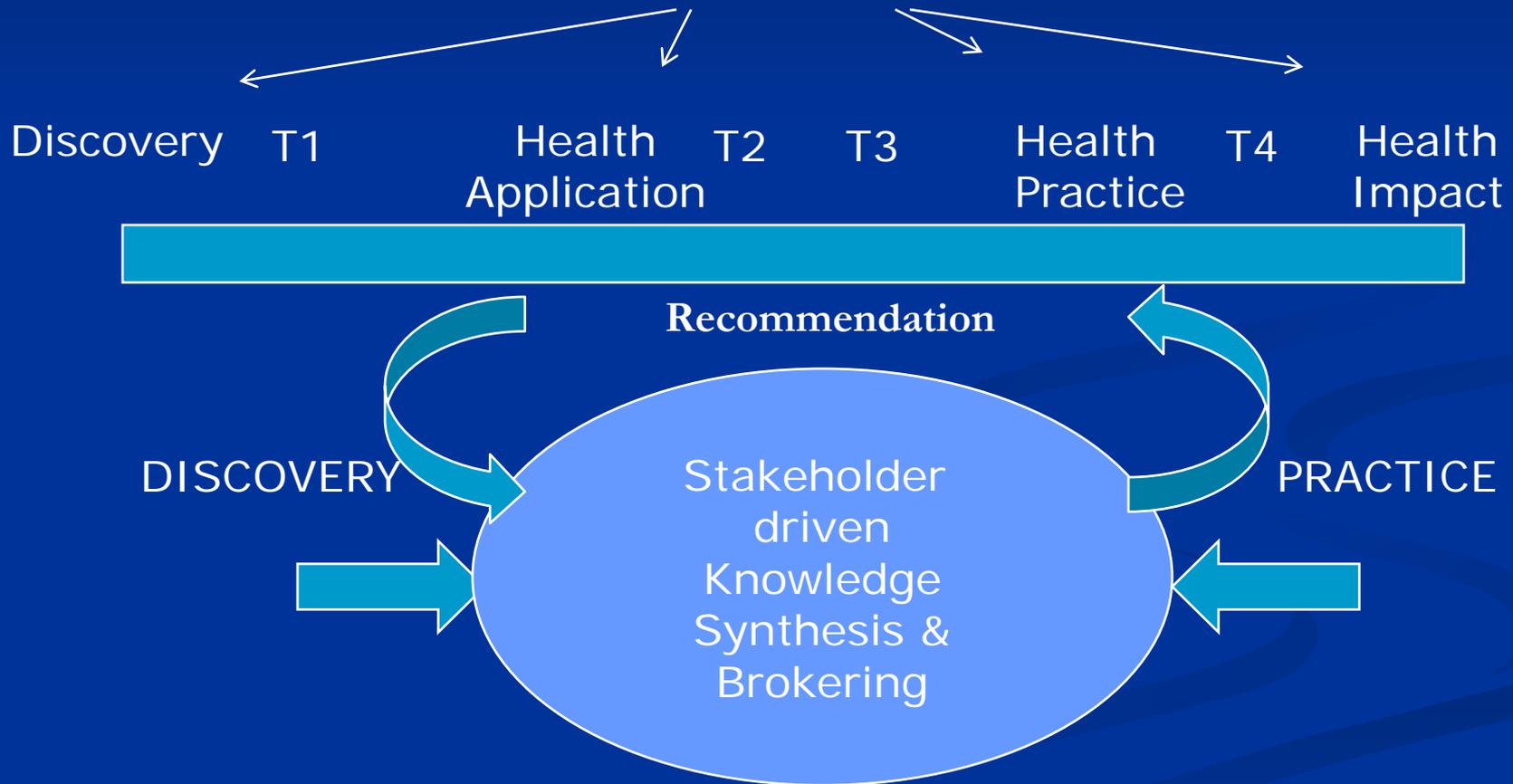
Two Overarching GAPPNet Themes

- Theme 1: Empowering research through the translation continuum
 - Fill knowledge gaps
- Theme 2: Linking stakeholders to information from translation research
 - Enhance evidence-based translation

GAPPNet

*Putting Stakeholders “in the Same Room”
and Connecting them to Data*

Theme 1-Building the Data from Translation Research



Theme 2- Dealing with Stakeholder Forces Affecting Translation

Knowledge Synthesis and Brokering

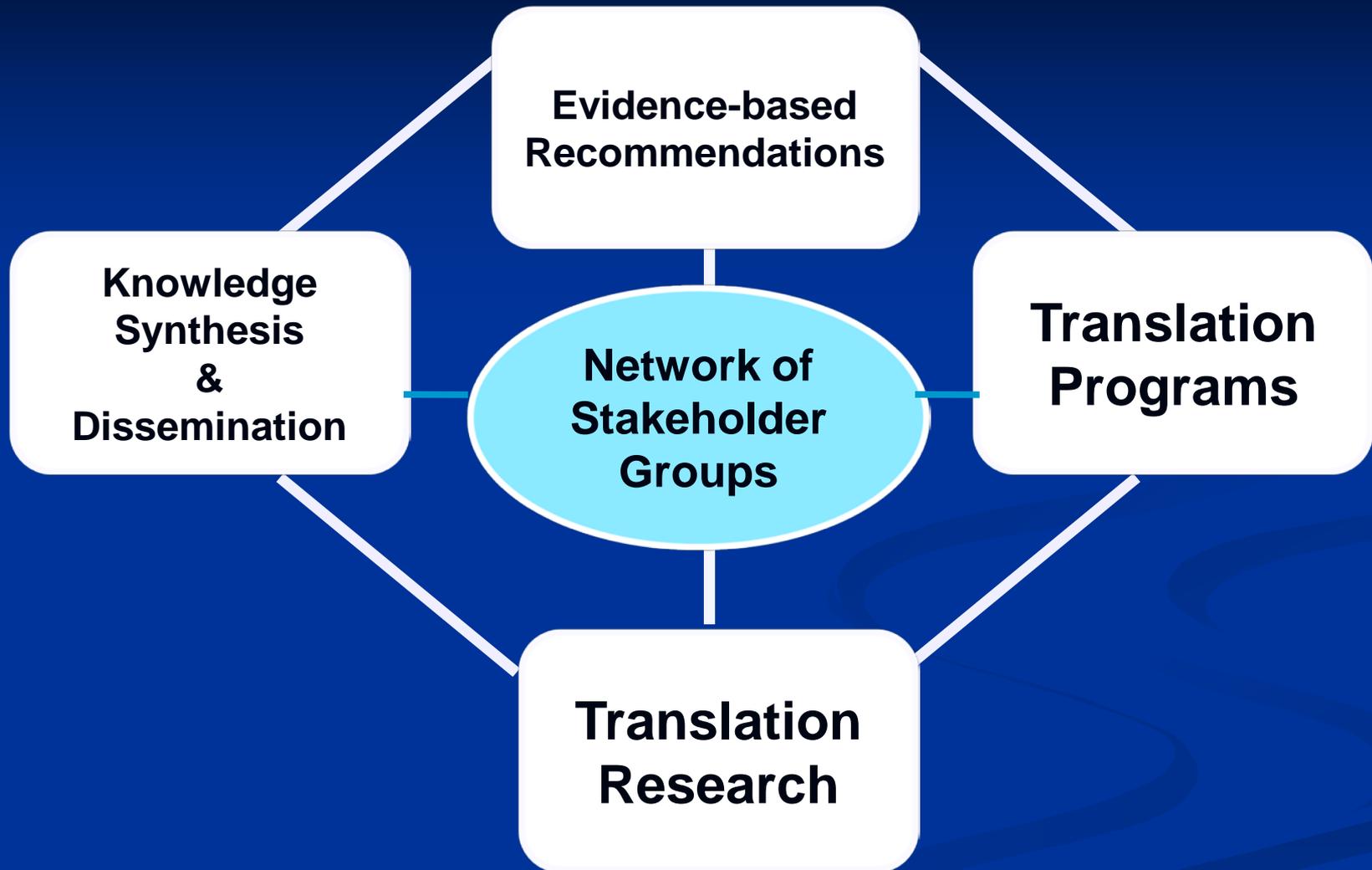
- **Knowledge Synthesis**
 - **Conducting systematic reviews and evidence synthesis on the health impact of using specific applications in practice**

- **Knowledge Brokering**
 - **Facilitating interactions of stakeholders so that they can better understand one another's goals and cultures.**

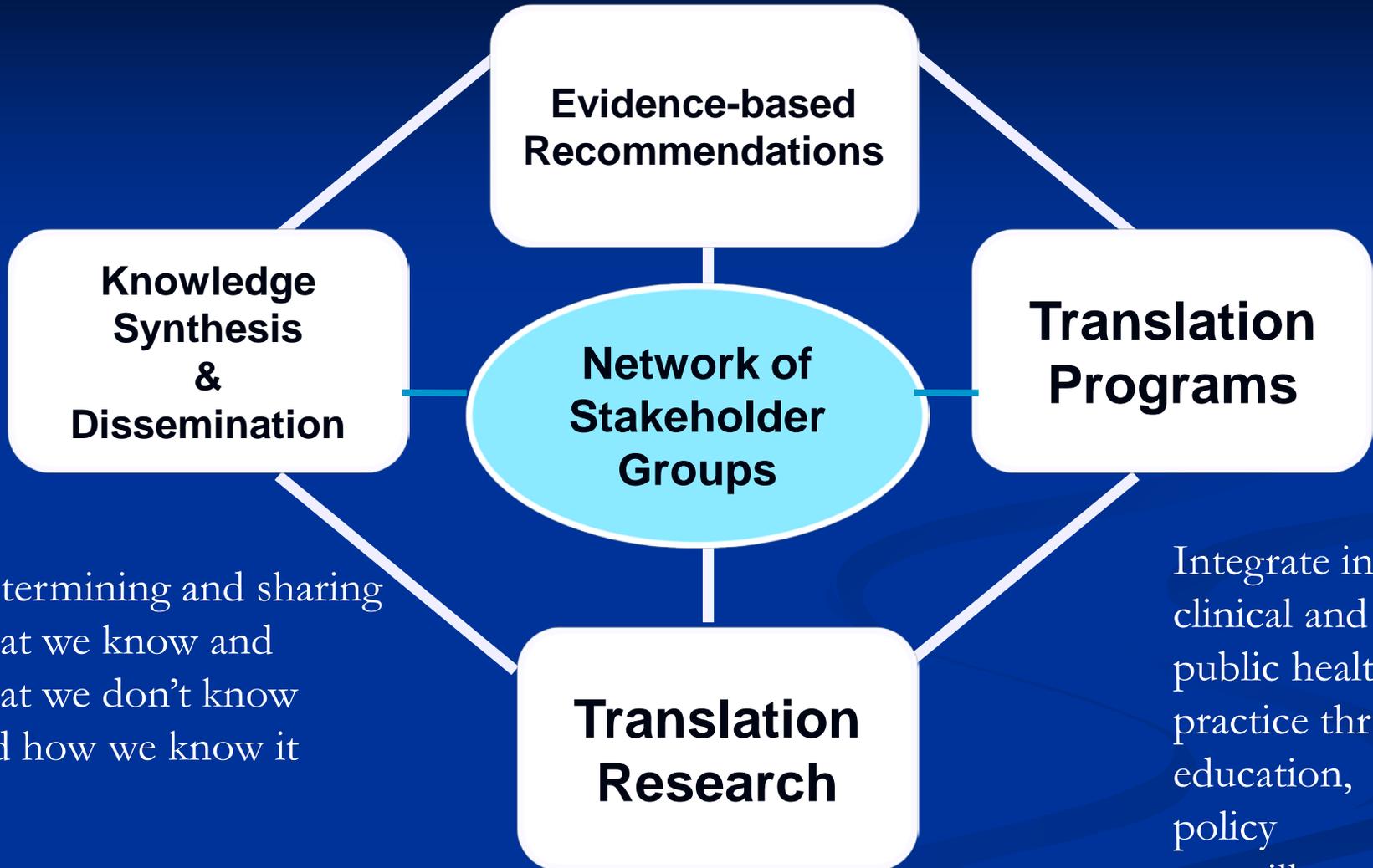
GAPPNet Inaugural Meeting October 29-30, 2009 - Ann Arbor, Michigan



What are the 4 Domains of GAPNet?



Linking evidence to practice
in a credible and transparent way



Determining and sharing
what we know and
what we don't know
and how we know it

Integrate into
clinical and
public health
practice thru
education,
policy
surveillance &
evaluation

Research to fill gaps
and how to implement

GAPPNet Network of Stakeholder Groups (A Network of Networks)

- Personalized Medicine Coalition
- NCHPEG
- Genetic Alliance
- Government partners
- APHA Genomics Forum
- IOM Roundtable on Genomics Translation
- Others



The screenshot displays the GAPPNet website interface. At the top, the GAPPNet logo is accompanied by a series of circular images showing diverse people. Below the logo is a navigation menu with links for Home, About Us, Genomic Applications, Project Locator, Get Involved, and Contact Us. The main content area is titled "GAPPNet™ Stakeholder Organizations" and provides an overview of the network's mission. It lists various stakeholder organizations categorized into Academia and Research Institutions, Government, and National Institutes of Health. A search bar and additional navigation links are visible on the right side of the page.

GAPPNet™ Stakeholder Organizations

GAPPNet™ is made up of stakeholder organizations, including academia, government, health care, public health, industry, policy institutions, and community and consumer groups. GAPPNet™ stakeholders share a common interest in the field of genomic medicine and realizing the benefits of using validated genomic knowledge and applications, such as genetic tests, technologies, and family history, in health care and disease prevention. These organizations are working together to provide greater support for the [major GAPPNet™ functions](#). Learn more about [general activities](#) in these areas that the stakeholders and members may work on independently to meet their own organization's goals, or collaboratively as part of GAPPNet.

Academia and Research Institutions

- [Center for Genomics and Healthcare Equality, University of Washington](#) 
- [Center for Genomics and Public Health, University of Washington](#) 
- [Center for Public Health and Community Genomics, University of Michigan](#) 
- [Center for Translational and Policy Research on Personalized Medicine, University of California, San Francisco](#) 
- [Institute for Genome Sciences and Policy Center for Genomic Medicine, Duke University](#) 
- [Pharmacogenomics Knowledge Base, Stanford University](#) 

Government

- [Agency for Healthcare Research and Quality](#) 
- Centers for Disease Control and Prevention
 - [Office of Public Health Genomics](#) 
 - [Division of Laboratory Sciences](#) 
 - [Division of Laboratory Systems](#) 
- [Department of Veterans Affairs, Office of Research and Development](#) 
- National Institutes of Health
 - [Division of Cancer Control and Population Sciences, National Cancer Institute](#) 
 - [GeneTests](#),  [National Center for Biotechnology Information](#)
 - [National Human Genome Research Institute](#) 
 - [National Institute of Diabetes and Digestive and Kidney Diseases](#) 

GAPPNet Domain 1: Knowledge Synthesis & Dissemination GAPP Knowledge Base



GAPP Knowledge Base (beta version)

An integrated, searchable knowledge base of genomic applications in practice and prevention (GAPP).

[Home](#) | [About](#) | [GAPPNet™](#) | [Contact](#)

GAPP KB

[GAPP Finder](#) ?

[EGA Journal](#) ?

[GAPPNet](#) ?

[EGAPP](#) ?

Spotlight

NOPHG/CDC launches the GAPP KB: The National Office of Public Health Genomics (NOPHG) launched the GAPP KB, an on-line resource providing access to information on genomic applications in practice and prevention. [Read more about GAPP KB](#)

About GAPP KB

GAPP KB is a resource serving the information needs of diverse stakeholders in the responsible translation of genomic research into applications for use in public health and health care... [more](#)

Related Links

[AHRQ](#)

[FDA](#)

[GeneTests](#)

News related to genomic applications in practice and prevention

- Medical News Today, April 13: [Scientists find new genetic clue for multiple myeloma diagnosis, treatment](#)
- Baltimore Sun, April 12: [Genetic tests can unravel the mysteries of your DNA](#)

GAPPNet Domain 1: Knowledge Synthesis & Dissemination GAPP Finder



GAPP Knowledge Base (version 1.0)

An integrated, searchable knowledge base of genomic applications in practice and prevention (GAPP).

[GAPP KB](#) > GAPP Finder

Last data update: Apr-07-2010. (Total 153 GAPPs)

GAPP Finder

Data collected since July 2009

[Home](#) | [About](#) | [Search Instructions](#) | [FAQs](#)

Search

GAPP

for

Go

Clear

All

- Enter search terms into the text box.
- Search terms can include disease, test, gene, drug, company name, trade name, etc.
- Simple Boolean operators are allowed (such as AND or OR).

The GAPP Finder is a searchable database of genetic tests and genomic applications in transition from research to clinical and public health practice. The search query can include disease, genes, drug, test, etc. The results can be further refined using the filtering feature.

Note: Database includes genomics applications identified since July 2009.

Disclaimer: The GAPP Finder is supported by CDC's National Office of Public Health Genomics; however, the information and links in this knowledge base do not constitute an endorsement by CDC or the federal government, and none should be inferred.

GAPPNet Domain 1: Knowledge Synthesis & Dissemination GAPP Finder

Search Results (Found a total of **153 potential GAPPs**) records 1-25 >> Sorted by: Order:

- To fine-tune the query results, use these filter functions -

Filtered By: Disease Gene Drug Application Summary Status Year

Disease/Disorder	Test to be Assessed	Target Population	Intended Use	Entered Date	Detail
Alzheimer's disease	Gene expression signature (blood sample)	Patients presenting with mild cognitive symptoms	To be used in conjunction with a patient's clinical data and results from other tests in order to establish a probable Alzheimer's disease diagnosis	03/31/2010	Detail
Breast cancer	80-gene expression signature for molecular subtyping (tumor biopsy specimen)	Women diagnosed with breast cancer	To classify breast cancer into Basal-type, Luminal-type and ERBB2-type cancers following a risk assessment with MammaPrint.	03/31/2010	Detail
Autism spectrum disorders	Chromosomal microarray analysis (CMA) (tissue sample not specified)	Not specified	To obtain a genetic diagnosis for a child suspected of having autism spectrum disorder	03/24/2010	Detail
Cancer	92-gene molecular cancer classifier (variety of tissue specimens including FFPE blocks from surgical resections, excisional biopsies, fine needle aspirates (FNA) and biopsy, core needle biopsies, cell blocks (pleural effusions, ascites, and FNAs), and bone marrow)	Metastatic cancer patients whose primary tumor is either poorly differentiated or undifferentiated following assessment using conventional diagnostic tests	To identify the primary tumor type in order to select optimal therapies and potentially improve treatment outcomes	03/24/2010	Detail
Gastric cancer	An immunohistochemistry (IHC) assay used to identify patients with HER2-positive metastatic cancer (tumor sample)	Individuals with stomach/gastric cancer	To select patients with metastatic stomach (gastric) cancer who may benefit from Herceptin treatment.	03/24/2010	Detail

GAPPNet Domain 1: Knowledge Synthesis & Dissemination EGA Journal



<http://www.cdc.gov/genomics/>

Search Toolkit

Search

Search this collection Search all knols

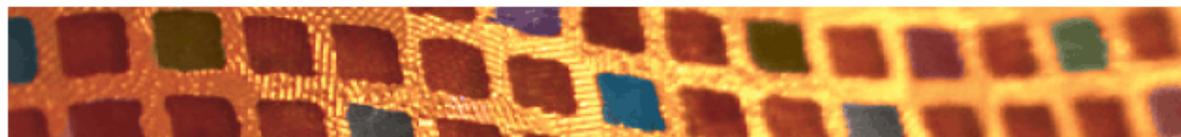
There are no pending collection submissions

Evidence for Genomic Applications

A moderated collection for open sharing of systematic reviews and summaries with researchers and the public.

Health-related applications of genomic research are increasingly available to practitioners and the public but information on their validity and utility is often fragmented. Evidence for Genomic Applications aims to provide updated, systematic reviews and summaries of available data and to highlight gaps. Evidence for Genomic Applications content is moderated by an expert group of researchers in genetics and knowledge synthesis.

[Link](#) [Citation](#) [Email](#) [Print](#) [Favorite](#)



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[GAPPNet](#)

Your rating:



No rating

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[Moderator-centric collection](#)

[Moderated collaboration](#)

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Version: 46

Last edited: 6 hours ago.

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GAPPNet also wrote

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[Submitting an Article to Evidence for Genomic Applications](#)

GAPPNet Domain 1: Knowledge Synthesis & Dissemination EGA Journal

DRAFT: CYP2D6 testing to predict response to tamoxifen in women with breast cancer

Pharmacogenomic

Tamoxifen, a selective estrogen receptor modulator, is the standard of care for premenopausal women with estrogen or progesterone receptor-positive breast cancer and a valid option for treating postmenopausal women. However, a substantial number of tamoxifen-treated patients relapse following surgical resection, while remain disease-free for many years. It appears that the primary effectors of tamoxifen activity are its active metabolites, rather than tamoxifen itself. Cytochrome P450 (CYP) enzymes, CYP2D6 in particular, play a major role in the metabolism of tamoxifen to active metabolites. More than 75 germline CYP2D6 variants have been identified.

A test predicting lack of response to tamoxifen could supplement information used by clinicians and patients in treatment decision-making. For example, physicians and patients may opt to switch to an alternative therapy upfront.

Contents

- [Clinical Scenario](#)
- [Test Description](#)
- [Public Health Importance](#)
- [Published Reviews, Recommendations and Guidelines](#)
- [Evidence Overview](#)
- [Links](#)

Edit this knol

Write a knol



[GAPPNet](#)

Your rating:



No rating

Is this knol as good or better than the top 10 search results on its topic?

[No](#) [Yes](#) [Neutral](#)

[Moderated collaboration](#)

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Version: 21

Last edited: Mar 25, 2010 1:33 PM [Versions](#)

Reviews

GAPPNet Domain 1: Knowledge Synthesis & Dissemination EGA Journal

Clinical Scenario

Testing of women with non-metastatic breast cancer to predict those who will not respond to tamoxifen therapy could inform decisions regarding choice of alternative treatment strategies including chemotherapy or the use of aromatase inhibitors (for post-menopausal women in particular [1]).

Test Description

- Analysis of multiple single nucleotide polymorphisms, deletions or duplications in CYP2D6 by DNA-based methods.
- Genotype-based prediction of CYP2D6 enzymatic activity ([2][3][4]; see also Links section) categorizes patients into:
 - Ultra metabolizers (carrying multiple or duplicated functional alleles)
 - Extensive metabolizers (carrying “normal” function alleles)
 - Intermediate metabolizers
 - Slow metabolizers (carrying only no-or low-function alleles)

Public Health Importance

GAPPNet also wrote

[Board of Expert Moderators](#)

[About this Collection](#)

[Template: \[Title indicating type of test and intended use\]](#)

[Submitting an Article to Evidence for Genomic Applications](#)

[DRAFT2: Tumor gene expression profiling in women with breast cancer](#)

[\(9 knols and collections\)](#)

Knol translations

Help [translate this knol](#) into your language.

Search for uses of this page ▼

Categories

[+ Add a category](#)

Learn more about categories

GAPPNet Domain 1: Knowledge Synthesis & Dissemination EGA Journal

Published Reviews, Recommendations and Guidelines

Systematic evidence reviews

Agency for Healthcare Research and Quality (AHRQ), Evidence Report/Technology Assessment (Draft Technology Assessment) [6].

Recommendations by independent group

There are no recommendations by an independent group.

Guidelines by professional groups

American Society of Clinical Oncology clinical practice guideline update on the use of pharmacologic interventions including tamoxifen, raloxifene, and aromatase inhibition for breast cancer risk reduction: "Given the limited evidence, CYP2D6 testing is currently not recommended in the preventive setting" [7].

Evidence Overview

Analytic Validity: Test accuracy and reliability in measuring [indicate analytes or other entities measured] (analytic sensitivity and specificity).

- Based on an AHRQ Evidence Report on antidepressants (includes reference to 2 FDA documents on the Roche Amplichip®) [8]:
 - Very limited published data on few CYP2D6 polymorphisms, and with important methodological shortcomings.



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Clinical Validity: Test accuracy and reliability in [supporting clinical or public health assessment] (predictive value).

- Based on an AHRQ Draft Technology Assessment that included 13 studies [6].
 - Large between-study variability in classifying genotypes to extensive, intermediate or slow metabolizers.
 - Most studies evaluated surrogate endpoints, such as disease- or recurrence free survival. Results were inconsistent in direction and formal statistical significance.
 - A few evaluated overall survival. None demonstrated any significant differences in overall survival by *CYP2D6* status.
 - Most reviewed studies had methodological shortcomings.
- Based on an earlier-published systematic review of 10 studies (included in the above review):
 - Study results on the association between *CYP2D6* status and breast cancer recurrence are “widely heterogeneous with relative-risk estimates outside the range of reasonable bounds”[3].
- Recent additions to the literature include:
 - A cohort of 1325 post-menopausal women with breast cancer who received tamoxifen following surgery demonstrated that carrying two functional *CYP2D6* alleles is associated with significantly improved event- and disease-free survival, but did not find significant associations with overall survival [9]. This study partially overlaps with studies included in the aforementioned reviews [10].
 - A study of 282 women receiving tamoxifen monotherapy demonstrated that recurrence-free survival

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Clinical Utility: Net benefit of test in improving health outcomes.

- No clinical trial has evaluated the net benefit of testing versus no testing in improving health outcomes
- We did not identify any modeling analysis that compared the expected benefits and harms of patient management strategies that are informed by *CYP2D6* testing versus patient management strategies that are not informed by such testing.

Links

- Human Cytochrome P450 (CYP) Allele Nomenclature Committee, CYP2D6 allele nomenclature (<http://www.cypalleles.ki.se/cyp2d6.htm>, last accessed: March 15th, 2010).

Last updated: *March 15, 2010*

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005 May 14-20;365(9472):1687-717. PubMed PMID: 15894097.

GAPPNet Domain 2: Evidence based Recommendations



Evaluation of Genomic Applications in Practice and Prevention (EGAPP)

Home

About EGAPP

Working Group »

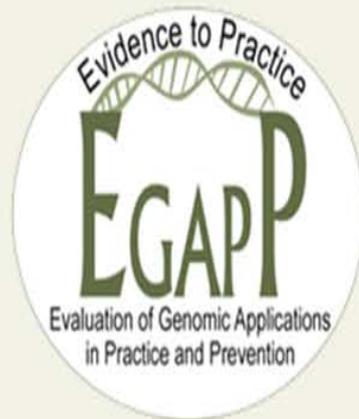
Understanding EGAPP

Topics

Methods

Evidence Reports

Recommendations



Evaluation of Genomic Applications in Practice and Prevention (EGAPP) is an initiative launched in 2004 to support a coordinated, systematic 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.

The EGAPP Working Group was established in 2005 to support the development of a systematic process for assessing the available evidence regarding the validity and utility of rapidly emerging genetic tests for clinical practice. This independent, multidisciplinary panel prioritizes and selects tests, reviews CDC-commissioned evidence reports and other contextual factors, highlights critical knowledge gaps, and provides guidance on appropriate use of genetic tests in specific clinical scenarios.

GAPPNet Domain 3: Translation Programs

- Translation programs on candidate applications
- Sponsored by CDC, NIH, AHRQ and other groups including private sector
- Develop and evaluate decision support tools
- Assess utilization, barriers and health impact

GAPPNet Domain 4: Translation Research

- Translation research on genomic candidate health applications
- Sponsored by CDC, NIH, AHRQ and other groups including private sector
- Comparative effectiveness research

Comparative Effectiveness Research and Genomic Medicine!

- CER is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers and policy makers to make informed decisions that will improve health care at both the individual and population levels



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Duke University

Clinical Validity and
Utility of Genomic
Targeted
Chemoprevention of
PCa
Wake Forest University

Developing Information
Infrastructure Focused
on Cancer Comparative
Effectiveness
Moffitt Cancer Center

COMMENTARY

Comparative effectiveness research and genomic medicine: An evolving partnership for 21st century medicine

Mu'in J. Khoury^{1,2}, Eugene C. Rich³, Gurbaneet Randhawa⁴, Steven M. Teutsch⁵, and John Niederhuber²

Abstract: The American Recovery and Reinvestment Act has provided resources for comparative effectiveness research that will lead to evidence-based decisions about health and health care choices. Some have voiced concerns that evidence-based comparative effectiveness research principles are only relevant to "average" patients and not as much to individuals with unique combinations of genes, exposures and disease outcomes, and intrinsic to genomic medicine. In this commentary, we argue that comparative effectiveness research and genomic medicine not only can and should coexist but also they will increasingly benefit from each other. The promise and success of genomic medicine will depend on rigorous comparative effectiveness research methods to compare outcomes for genome-based applications in practice to traditional non-genome-based approaches. In addition, the success of comparative effectiveness research will depend on developing new methods and clinical research infrastructures to integrate genome-based personalized perspectives into point of care decisions by patients and providers. There is a need to heal the apparent schism between genomic medicine and comparative effectiveness research to enhance knowledge-driven practice of medicine in the 21st century. *Cancer Med*

will increasingly benefit from each other. The promise and success of GM will depend on rigorous CER methods to compare outcomes for genome-based applications in practice to traditional non-genome-based approaches. However, the success of CER will depend on developing new approaches, and building the capacity to integrate genome-based personalized perspectives into point of care decisions by patients and providers. Although we do not present any novel concepts in this article, we aim to clarify the issues that have led to an apparent schism between GM and CER and highlight recent initiatives that will strengthen and link GM and CER to enhance knowledge-driven practice of medicine in the 21st century.

What is comparative effectiveness research?

CER has been defined in many ways.¹⁰⁻¹³ The Congressional Budget Office defines CER as the rigorous evaluation of the impact

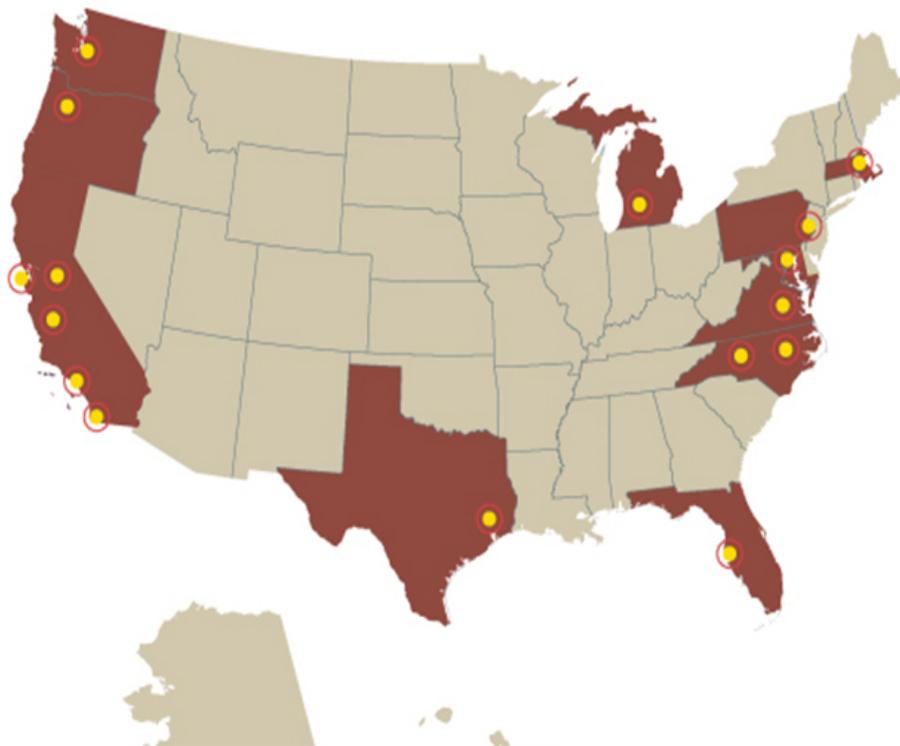
GAPPNet Translation Research and Programs: Connecting the Dots

Project Locator: Active Genomic Translation Projects

Click on the yellow dots in the map below to find genomic translation projects that are currently being conducted by academic and research institutions, and state health departments. Read more about [genomics translation projects](#) and [view projects by funding agency](#).

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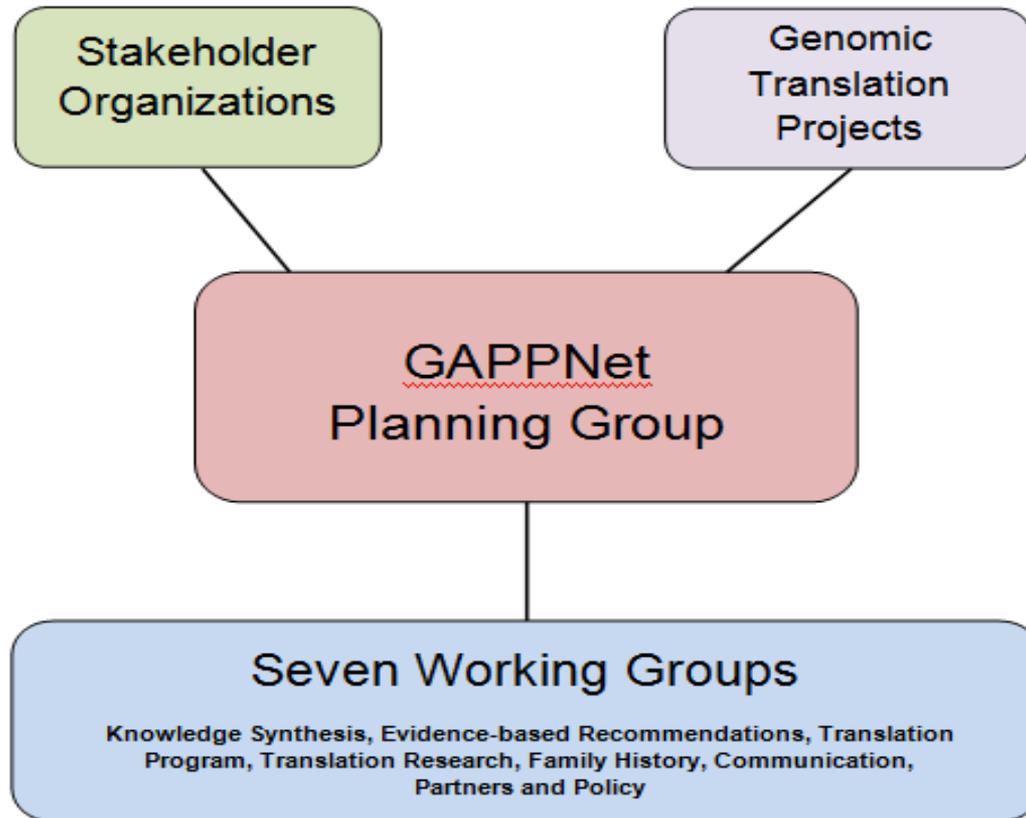
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[Facilitating Informed Decisions for MSI Testing](#)

[Prophylactic surgery in carriers of BRCA 1/2 mutations](#)

[Comparative Effectiveness in Genomic Medicine](#)

GAPPNet Current Structure



Database of Genomic Applications, Reviews,
Recommendations and Projects

GAPPNet

Putting Stakeholders “in the Same Room” and Connecting them to Data

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Genomic Applications in Practice and Prevention Network (GAPPNet)

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Wednesday



4th National Conference on Genomics and Public Health: Using Genomic Information to Improve Health Now and in the Future

December 8, 2010 to December 10, 2010 - Bethesda, Maryland

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Translation
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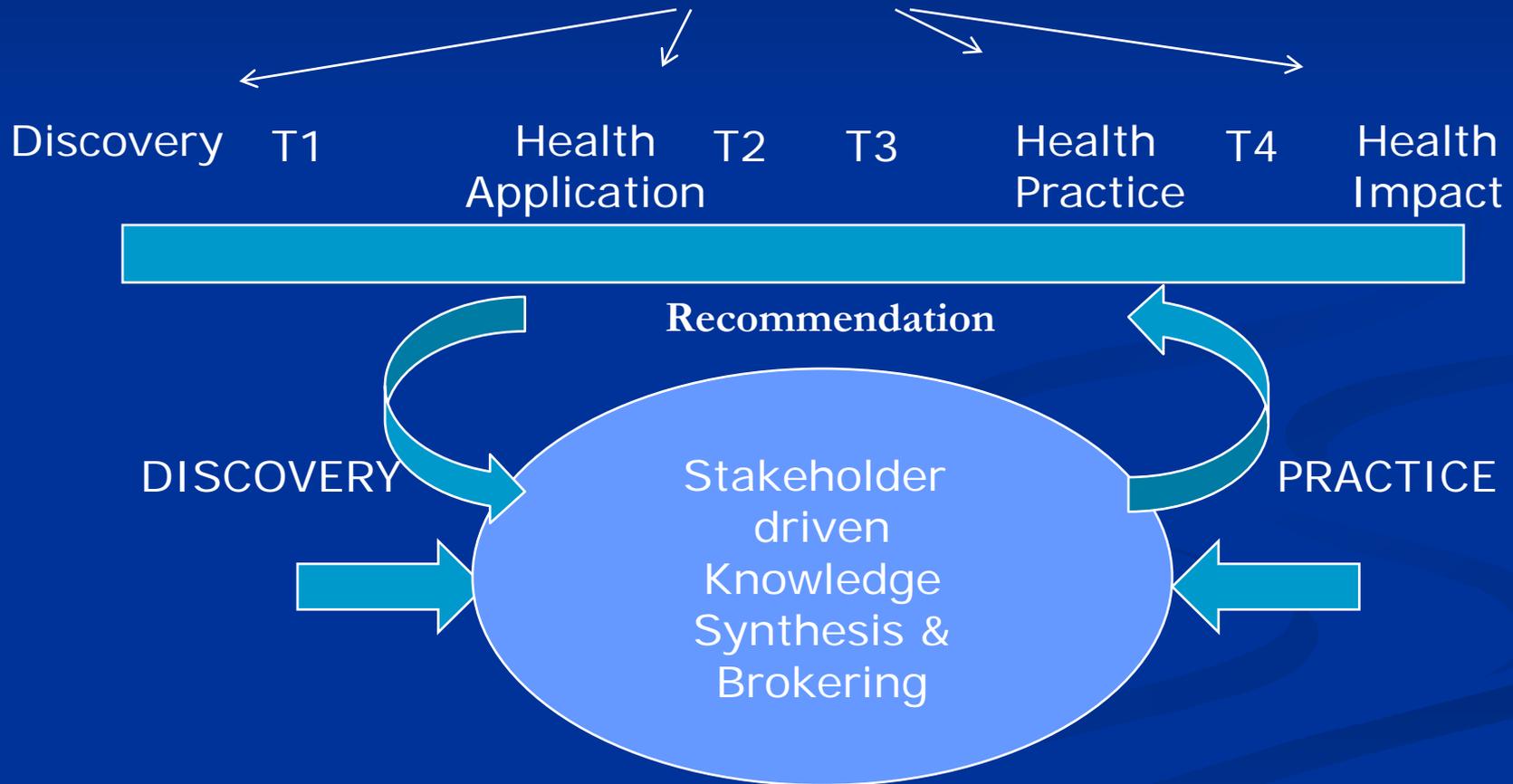
Genetic Test
Registry

Comparative Effectiveness &
Implementation Research

GAPPNet

*Putting Stakeholders “in the Same Room”
and Connecting them to Data*

Theme 1-Building the Data from Translation Research



Theme 2- Dealing with Stakeholder Forces Affecting Translation