Advancing Utility and Adoption of Clinical Genomic Diagnostics: A Public Health Perspective

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Questions

- What are your views of the described barriers to successful genomic test development?
- What are potential solutions?
- What are the obstacles to achieving those solutions?
- How can we overcome those obstacles?

Question 1

- What are your views of the described barriers to successful genomic test development?
  - Lack of a suitable oversight system for 21st century medicine (no need to evoke genetic exceptionalism)
  - The evidence gap in genomics
  - Stakeholders perspectives of the evidence gap
  - Less than optimal awareness and knowledge of consumers, providers and systems

U. S. System of Oversight of Genetic Testing

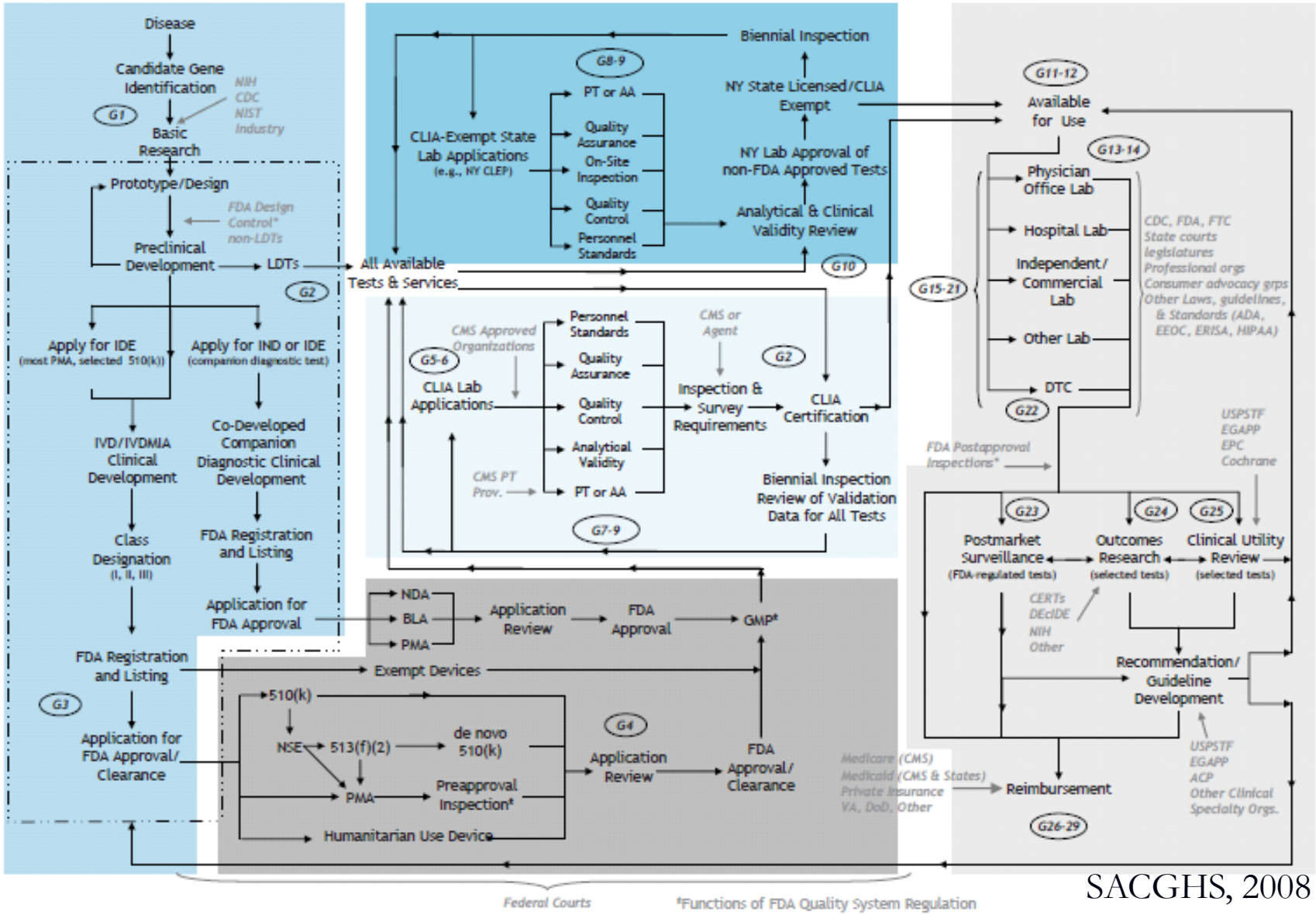
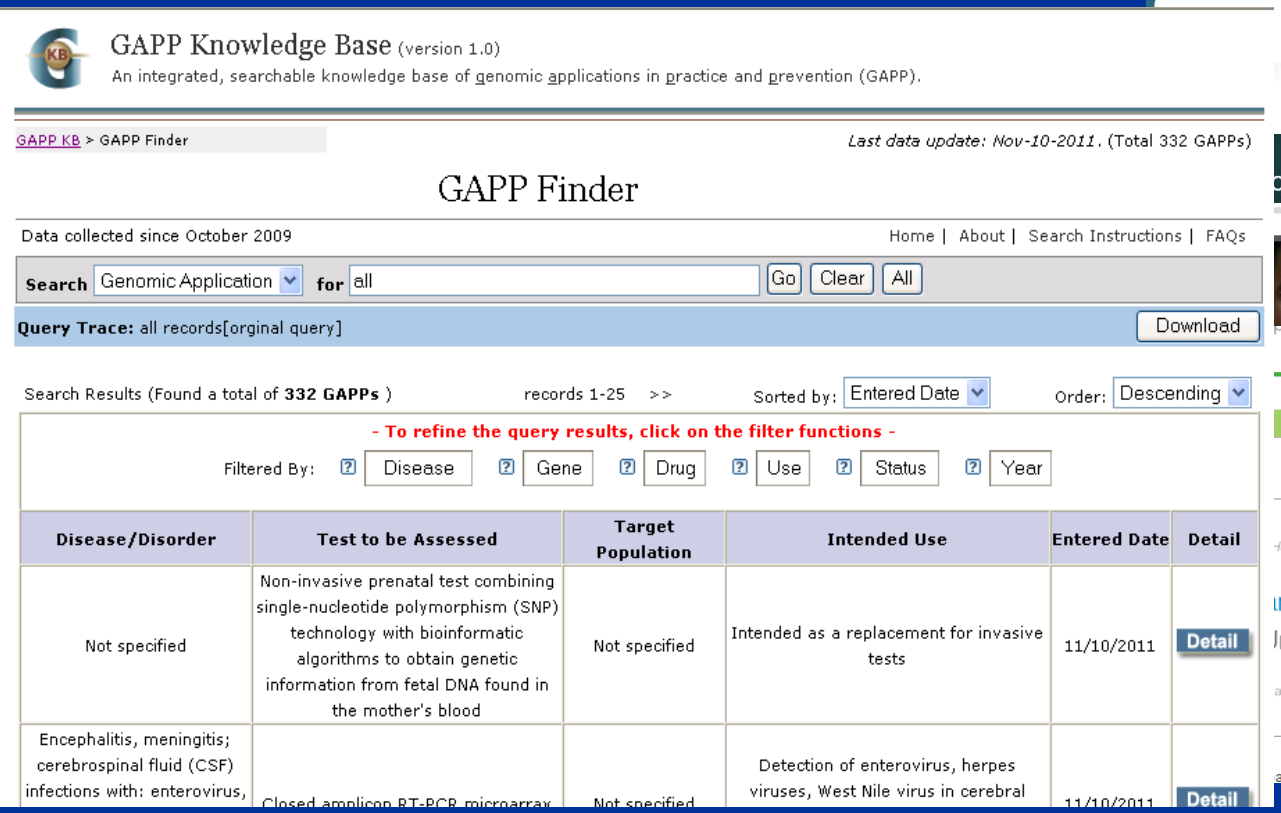


Figure 2–1. Map of the U.S. Oversight System for Genetic Testing

SACGHS, 2008

Current Genomics Translation Highway Allows for: "Premature Translation"

Bench (base pairs, etc) — T — Bedside (Diagnostics and Therapeutics)



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: Nov-10-2011. (Total 332 GAPPs)

GAPP Finder

Data collected since October 2009

Home | About | Search Instructions | FAQs

Search Genomic Application for all Go Clear All

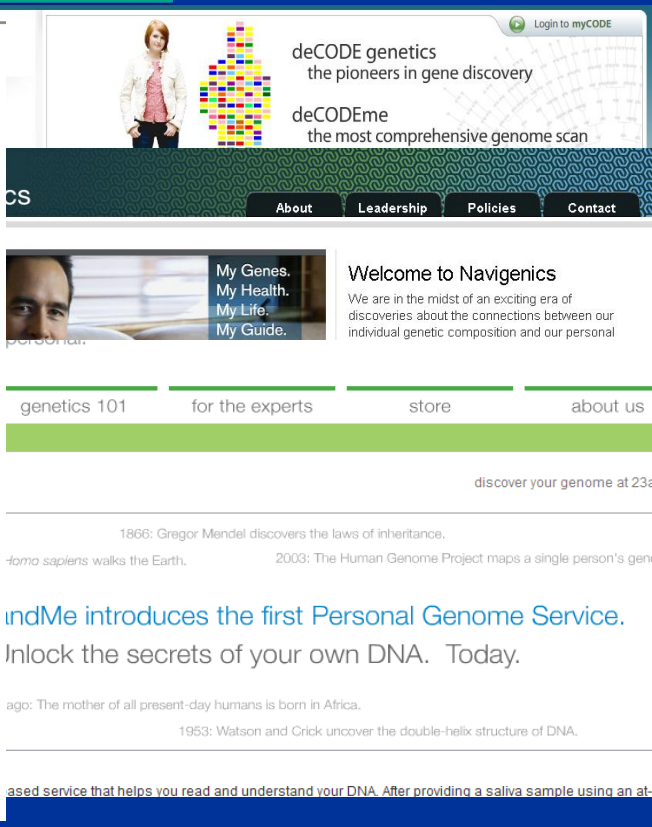
Query Trace: all records[orginal query] Download

Search Results (Found a total of **332 GAPPs**) records 1-25 >> Sorted by: Entered Date Order: Descending

- To refine the query results, click on the filter functions -

Filtered By: Disease Gene Drug Use Status Year

Disease/Disorder	Test to be Assessed	Target Population	Intended Use	Entered Date	Detail
Not specified	Non-invasive prenatal test combining single-nucleotide polymorphism (SNP) technology with bioinformatic algorithms to obtain genetic information from fetal DNA found in the mother's blood	Not specified	Intended as a replacement for invasive tests	11/10/2011	Detail
Encephalitis, meningitis; cerebrospinal fluid (CSF) infections with: enterovirus,	Closed amplicon RT-PCR microarray	Not specified	Detection of enterovirus, herpes viruses, West Nile virus in cerebral	11/10/2011	Detail



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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

genetics 101 for the experts store about us

discover your genome at 23a

1866: Gregor Mendel discovers the laws of inheritance.

Homo sapiens walks the Earth. 2003: The Human Genome Project maps a single person's gen

ndMe introduces the first Personal Genome Service.

Unlock the secrets of your own DNA. Today.

ago: The mother of all present-day humans is born in Africa.

1953: Watson and Crick uncover the double-helix structure of DNA.

ased service that helps you read and understand your DNA. After providing a saliva sample using an at-

Current Genomics Translation Highway Allows for: the Phenomenon of "Lost in Translation"

Will genomics widen health disparities?

Genetics in Medicine 2011

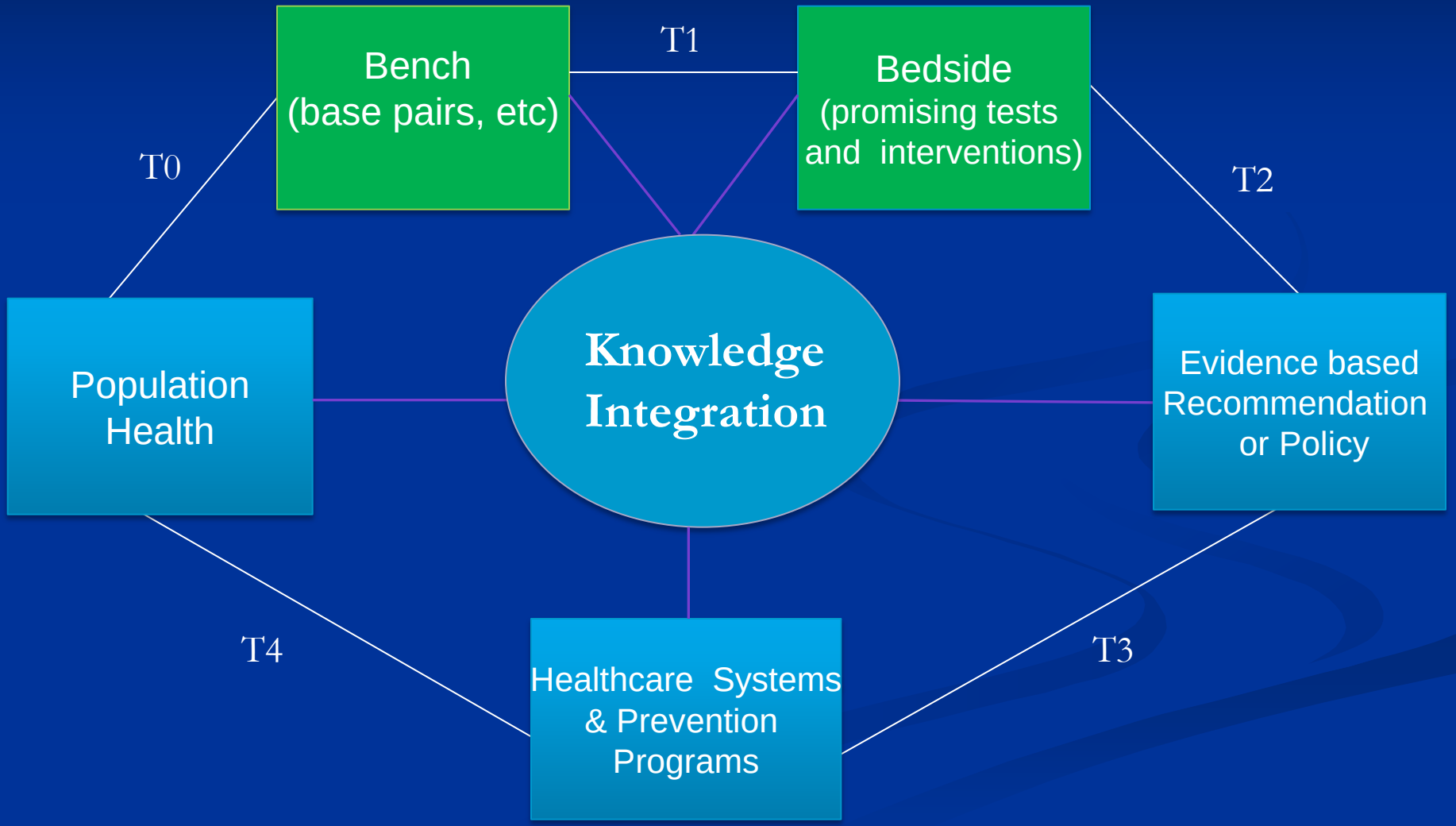
Underutilization of *BRCA1/2* testing to guide breast cancer treatment: Black and Hispanic women particularly at risk

Douglas E. Levy, PhD[1,2,3], Stacey D. Byfield, PhD, MPH[4], Catherine B. Comstock, MPH,[5] Judy E. Garber, MD, MPH[3,6], Sapna Syngal, MD, MPH[3,6,7], William H. Crown, PhD[4], and Alexandra E. Shields, PhD[1,2,3]

Purpose: Women with early-onset (age ≤40 years) breast cancer are at high risk of carrying deleterious mutations in the *BRCA1/2* genes; genetic assessment is thus recommended. Knowledge of *BRCA1/2* mutation status is useful in guiding treatment decisions. To date, there has been no national study of *BRCA1/2* testing among newly diagnosed women. **Methods:** We used administrative data (2004–2007) from a national sample of 14.4 million commercially insured patients to identify newly diagnosed, early-onset breast cancer cases among women aged 20–40 years (n = 1474). Cox models assessed *BRCA1/2* testing, adjusting for covariates and differential lengths of follow-up. **Results:** Overall, 30% of women aged 40 years or younger received *BRCA1/2*

to assess risk of hereditary breast and ovarian cancer (HBOC) is among the most established genetic tests in clinical use.[1–3] Guidelines and commercial testing for *BRCA1/2* mutations have been available for more than a decade,[4] and most health insurers now reimburse at least partially for these tests in individuals at high risk for mutations.[5] National guidelines recommend that women diagnosed with early-onset breast cancer receive *BRCA1/2* testing to guide treatment decisions.[6] Among patients newly diagnosed with cancer, a positive test result will often prompt more aggressive surgical treatment (e.g., bilateral salpingo oophorectomy or prophylactic contralateral mastectomy)

Genomics Translation Highway: The "Public Health Genomics" Model Allows for the "Right Balance"



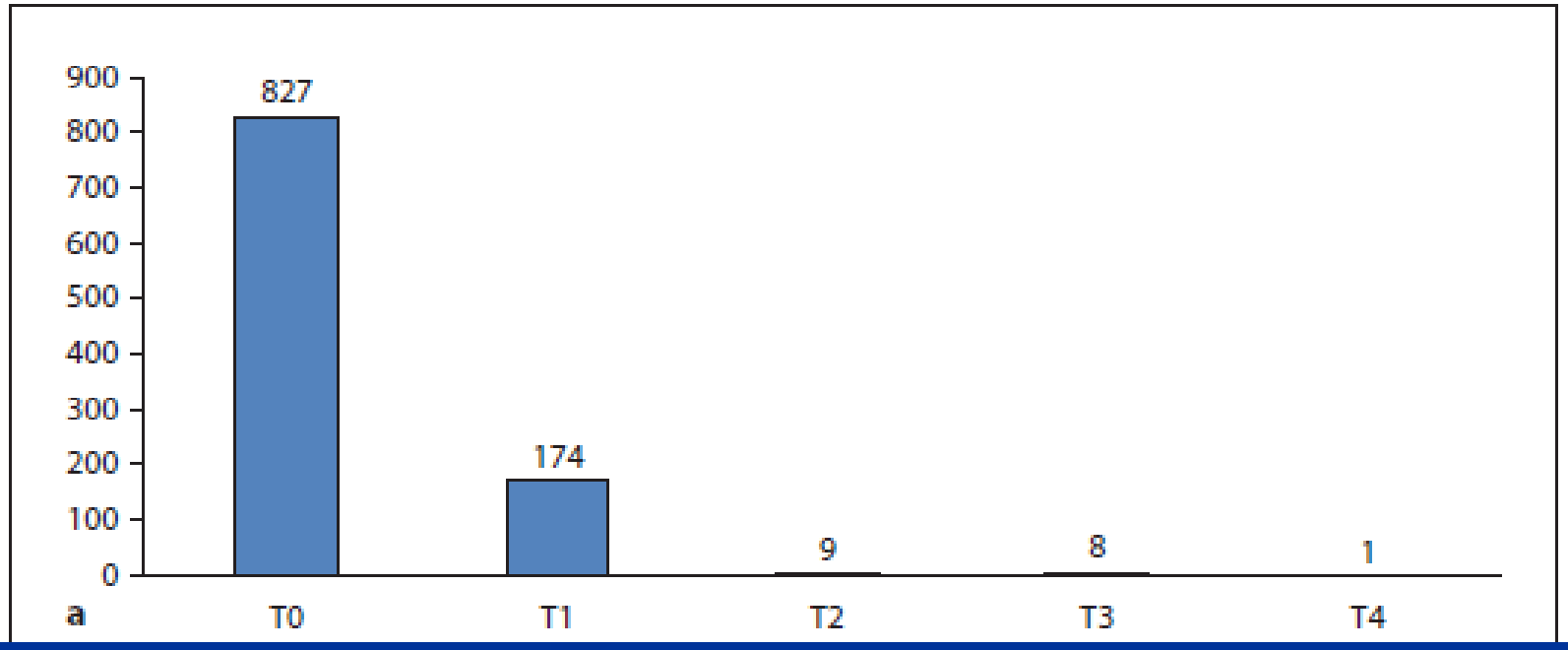
Genomics Translation Beyond Bench to Bedside: The Road Less Traveled

Public Health Genomics 2010

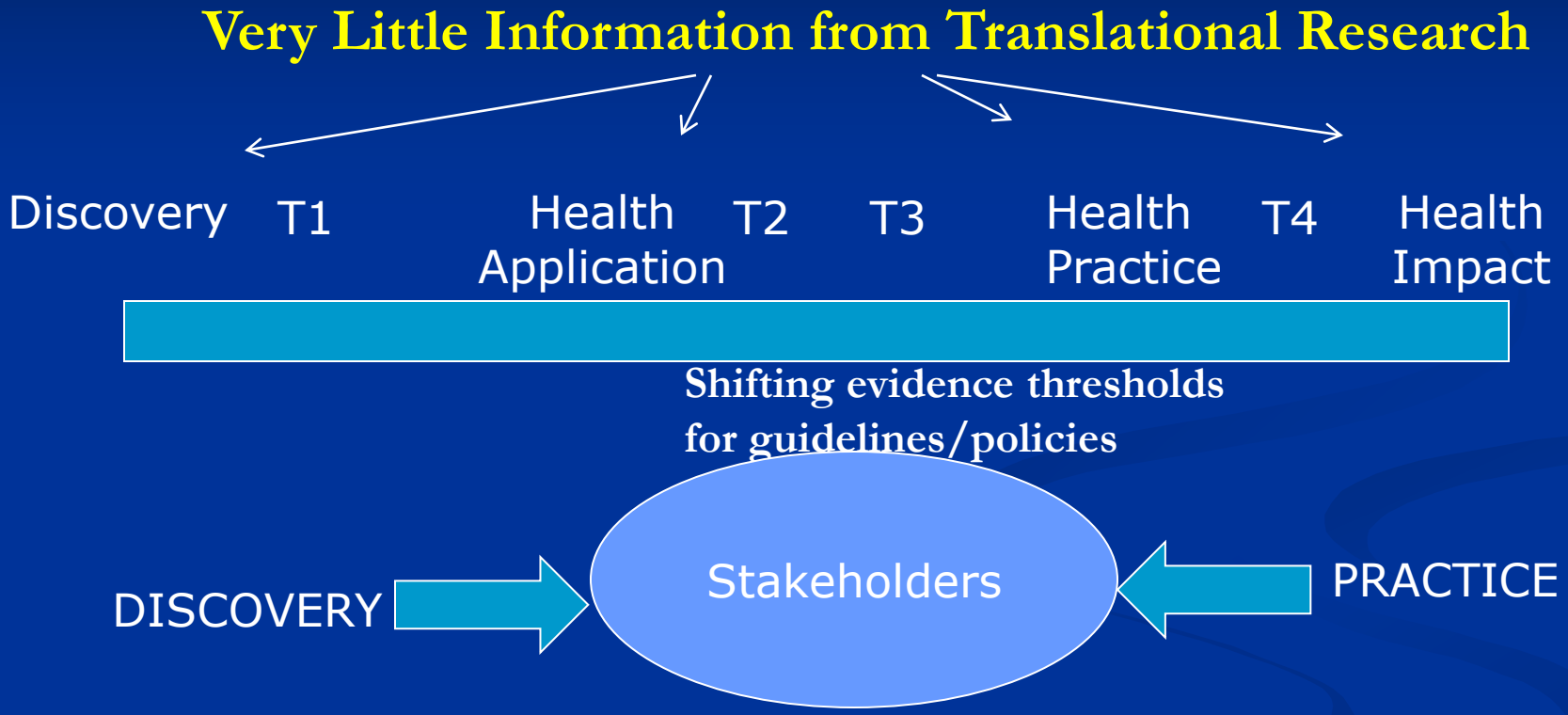
Translational Research in Cancer Genetics: The Road Less Traveled

S.D. Schully[a] C.B. Benedicto[b] E.M. Gillanders[a] S.S. Wang[c] M.J. Khoury[a, d]

[a]Division of Cancer Control and Population Sciences and [b]Office of Workforce Development, National Cancer Institute, Bethesda, Md., [c]Division of Etiology, Department of Population Sciences, City of Hope, Duarte, Calif., and



Stakeholder "Push" and "Pull" Forces in Genomics Translation



- "Ultimately clinicians and health care systems will have to decide which evidentiary frameworks are best suited for their needs" Beitelshees & Veenstra, JAMA 2011

Question 2

- What are potential solutions?
  - We need a 21st Century “model” oversight system
  - Public and private funding of T2+ research
  - We need a knowledge integration enterprise involving knowledge synthesis and stakeholder convening & brokering (EGAPP and GAPPNet concepts)
  - We need to increase awareness and knowledge of consumers, providers and systems

Knowledge Synthesis
EGAPP "Model Process"

www.egappreviews.org

- Since 2005, independent multidisciplinary working group
- Developed methods and outcomes processes
- Conducted systematic reviews
- Developed recommendations
- Pointed to evidence gaps
- Tackling evidentiary standards for whole genome sequencing

Evidence to Practice
EGAPP
Evaluation of Genomic Applications in Practice and Prevention

Not All "Genomic Diagnostics" Are Used for "Diagnosis" Measuring Validity and Utility by Intended Use

Application of test	Clinical validity	Clinical utility
Diagnosis (symptomatic patient)	Association of marker with disorder	Improved clinical outcomes[a]—health outcomes based on diagnosis and subsequent intervention or treatment Availability of information useful for personal or clinical decision-making End of diagnostic odyssey
Disease screening (asymptomatic patient)	Association of marker with disorder	Improved health outcome based on early intervention for screen positive individuals to identify a disorder for which there is intervention or treatment, or provision of information useful for personal or clinical decision making
Risk assessment/susceptibility	Association of marker with future disorder (consider possible effect of penetrance)	Improved health outcomes based on prevention or early detection strategies
Prognosis of diagnosed disease	Association of marker with natural history benchmarks of the disorder	Improved health outcomes, or outcomes of value to patients, based on changes in patient management
Predicting treatment response or adverse events (pharmacogenomics)	Association of marker with a phenotype/metabolic state that relates to drug efficacy or adverse drug reactions	Improved health outcomes or adherence based on drug selection or dosage

[a]Clinical outcomes are the net health benefit (benefits and harms) for the patients and/or population in which the test is used.

Teutsch S. et al (EGAPP) Genet Med 2009

FDA Boxed Warning is Generally Based on Clinical Validity

FDA Boxed Warning on Clopidogrel

Warning: Diminished Effectiveness in Poor Metabolizers

- Effectiveness of clopidogrel depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19
- Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

PLAVIX (clopidogrel bisulfate) tablets PI.

FDA warnings on more than 80 gene-drug pairs

Recommendations for Use (and Reimbursements) Are Usually Based on Clinical Utility

ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning". A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association

David R. Holmes, Jr, Gregory J. Dehmer, Sanjay Kaul, Dana Leifer, Patrick T. O'Gara and C. Michael Stein

Circulation published online Jun 28, 2010;

2. Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can

Clinical validity

5. The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. In

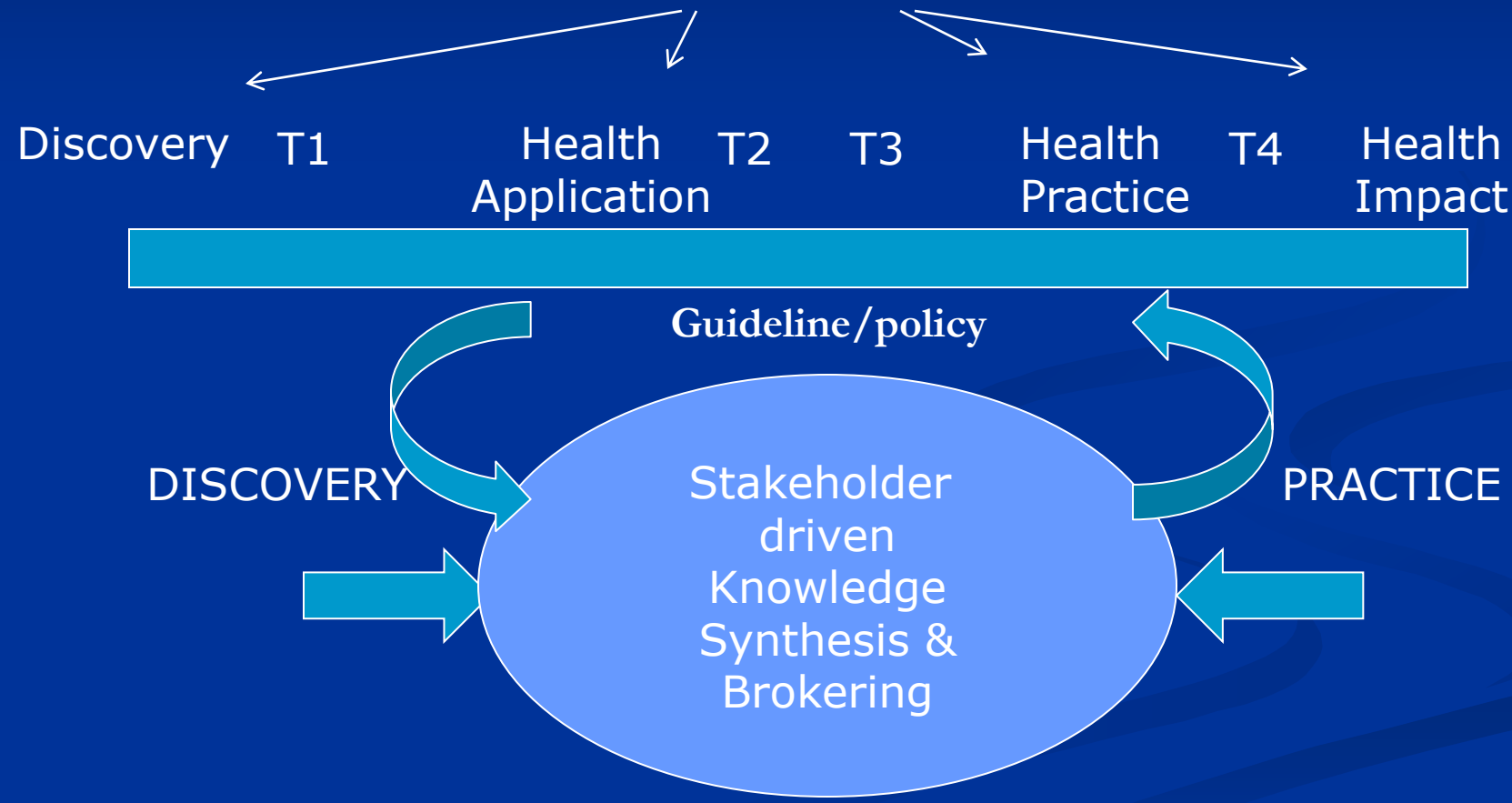
Clinical utility

From David Veenstra

GAPPNet (The Concept)

Putting Stakeholders "in the Same Room" and Connecting them to Data

Theme 1-Building the Information from Translational Research



Theme 2- Dealing with Stakeholder Forces Affecting Translation

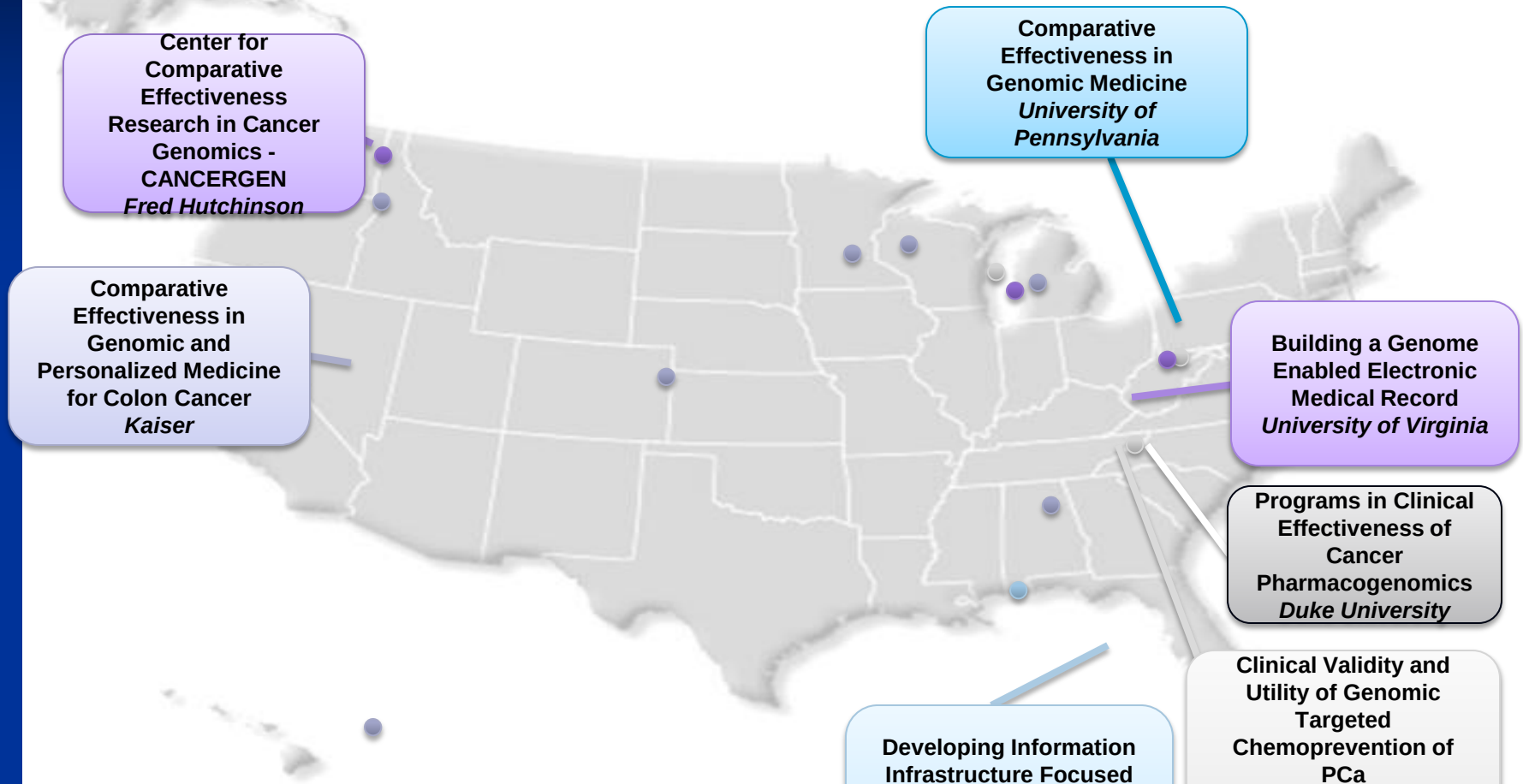
Question 3

- What are the obstacles to achieving those solutions?
  - Politics/incentives in health and healthcare (no need to evoke genetic exceptionalism)
  - No incentives for public and private funding of T2+ research
  - No incentives for knowledge synthesis and stakeholder convening
  - No incentives for public and provider education

Question 4

- How can we overcome those obstacles?
  - Develop and apply pilot oversight “experiments” that deal “insufficient evidence” (no need for genetic exceptionalism)
  - Public and private T2+ initiatives (ARRA, GAPPNet, PCORI, etc..)
  - Develop a stakeholder-driven knowledge integration enterprise that explores novel methods of synthesis, decision analysis and modeling
  - Develop “ dose appropriate” consumer and provider education programs

Comparative Effectiveness Research in Genomics and Personalized Medicine



Through ARRA, the NCI funded 7 groups to conduct CER in GPM and develop a collaborative road map

Exploring New Knowledge Integration Tools and Methods

- Value of research (VOR) analyses
- Risk-benefit modeling
- Stakeholder engagement
- Binning genomic information into actionable components (return of results in WGS)

Categories of Genomic Applications by Levels of Evidence and Uncertainty: Use of Modeling

Figure 3. Risk-Benefit Policy Matrix

Risk-Benefit Profile	Uncertainty: High	Uncertainty: Moderate	Uncertainty: Low
Favorable	Use with evidence-development	Consider use in clinical practice	Appropriate for use in clinical practice
Neutral	Do not use, conduct additional research	Use with evidence-development	Consider use in clinical practice
Unfavorable	Do not use, conduct additional research	Do not use	Do not use

Veenstra D et al. Genet in Medicine 2010

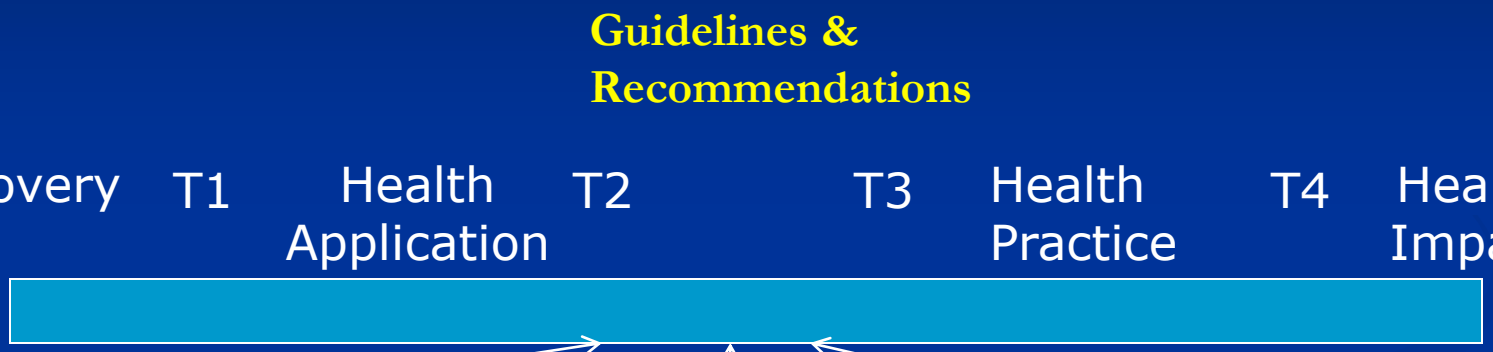
Three-Tier Classification of Recommendations on Genomic Applications

- Tier 1: Ready for implementation (per evidence-based recommendation on clinical utility)
- Tier 2: Informed decision making (adequate information on analytic and clinical validity, promising but not definitive information on clinical utility)
- Tier 3: Discourage use (no or little information on validity or utility; or evidence of harm)
  - Khoury MJ et al. Genetics in Medicine 2010

Binning the Human Genome
Based on Evidence base and type of Application
(Berg et al, Genet Med 2011)

	Criteria:	*Clinical Utility*	*Clinical Validity*			*Unknown Clinical Implications*
Genes	Bins:	**Bin 1 Medically actionable incidental information**	**Bin 2A Low risk incidental information**	**Bin 2B Medium risk incidental information**	**Bin 2C High risk incidental information**	**Bin 3**
	Examples:	*BRCA1/2* *MLH1, MSH2* *FBN1* *NF1*	PGx variants and common risk SNPs	*APOE* Carrier status for recessive Mendelian disorders	Huntington Prion diseases ALS (SOD1)	**All other loci**
	Estimated number of genes/loci:	10s	10s (eventually 100s – 1000s)	1000s	10s	~20,000
	Alleles that would be reportable (YES) or not reportable (NO) in a clinical context					
Variants	Known deleterious	YES	YES/NO [1]	YES/NO [1]	YES/NO [1]	N/A [2]
	Presumed deleterious	YES	N/A [3]	YES/NO [1]	YES/NO [1]	NO [4]
	VUS	NO	N/A [3]	NO	NO	NO [4]
	Presumed benign	NO	N/A [3]	NO	NO	NO
	Known benign	NO	NO	NO	NO	NO

A Public Health Genomics Model:
to Accelerate Transition from Research to Practice



- AV: Analytic Validity
- CV: Clinical Validity
- CU: Clinical Utility
- ELSI: Contextual Factors

Tier 3:
AV: Unknown or Poor
CV: Unknown Or Poor
CU: Unknown Or Poor

Don't Use

Tier 2:
CV: Established & Rationale For CU

Promote Informed/ Shared Decision Making
(Labeling +/- Coverage with Evidence based Practice)

Tier 1
CU Established

Use in Practice (With Coverage)