

A Scientific Foundation for Using Personal Genomics for Risk Assessment and Disease Prevention

Muin J. Khoury MD, PhD

Office of Public Health
Genomics

Centers for Disease Control
and Prevention

Perspective
JANUARY 10, 2008
NEJM

**Letting the Genome out of the Bottle —
Will We Get Our Wish?**

David J. Hunter, M.B., B.S., Sc.D., M.P.H., Muin J. Khoury, M.D., Ph.D., and Jeffrey M. Drazen, M.D.

It may happen soon. A patient, perhaps one you have known for years, who is overweight and does not exercise regularly, shows up in your office with an analysis of his whole genome at multiple single-nucleotide polymorphisms types. These studies rely on mi-

The test undergone by the patient described above is one of the products of this new knowledge. As of November 2007, two companies have made available direct-to-consumer “personal genome services” (www.23andme.com).



Outline

- Personal genomics 2009
- A scientific foundation for personal genomics
- Recommendations of NIH-CDC workshop
December 2008

2007-2009: GWAS!

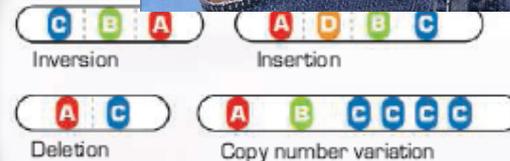
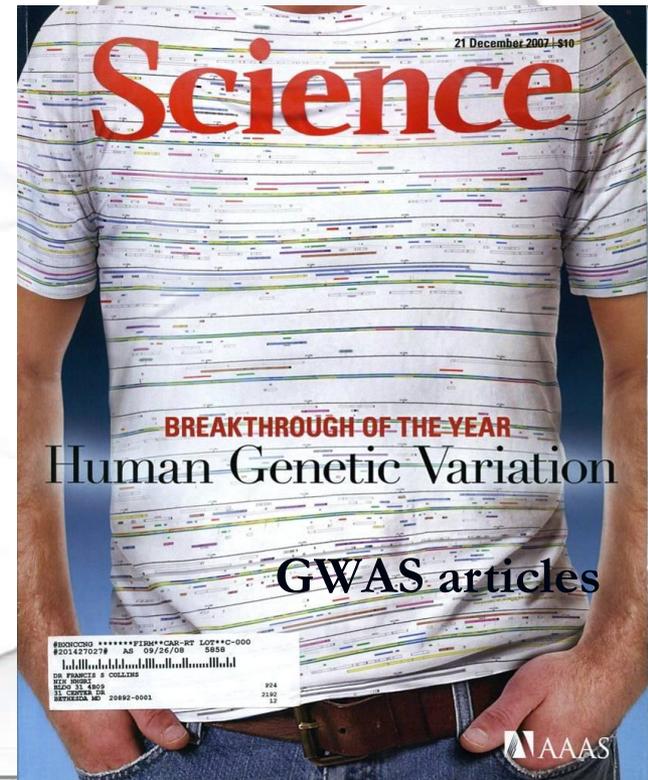
BREAKTHROUGH OF THE YEAR

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.



What makes us unique. Changes in the number and order of genes (A–D) add variety to the human genome.



2007-2009: GWAS!



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

Diseases and Traits with Published GWA Studies ($n = 87$, 3/4/09) *Ref T. Manolio*

- Macular Degeneration
- Exfoliation Glaucoma
- Lung Cancer
- Prostate Cancer
- Breast Cancer
- Colorectal Cancer
- Bladder Cancer
- Neuroblastoma
- Melanoma
- Basal Cell Cancer
- *TP53* Cancer Pred'n
- Ac/Ch Lym. Leukemia
- Thyroid Cancer
- Infl. Bowel Disease
- Celiac Disease
- Gallstones
- Hirschsprung Disease
- QT Prolongation
- Coronary Disease
- Coronary Spasm
- Atrial Fibrill'n/Flutter
- Stroke
- Intracranial Aneurysm
- Hypertension
- Hypt. Diuretic Rsp.
- Periph. Artery Disease
- Lipids/Lipoproteins
- Warfarin Dosing
- Ximelegatran Adv.Rsp.
- Parkinson Disease
- Amyotrophic Lat.Scler.
- Multiple Sclerosis
- MS Interferon- β Rsp.
- Prog. Supranuc. Palsy
- Tauopathies
- Alzheimer's Disease
- Var. Creutzfeldt-Jakob
- Cognitive Ability
- Memory
- Hearing, Otosclerosis
- Restless Legs Synd.
- Essential Tremor
- Nicotine Dependence
- Methamphet Depend.
- Pain
- Neuroticism
- Schizophrenia
- Sz. Iloperidone Rsp.
- Bipolar Disorder
- Family Chaos
- Narcolepsy
- ADHD
- Personality Traits
- Rheumatoid Arthritis
- RA Anti-TNF Rsp.
- Syst. Lupus Erythem.
- Juv. Idiop. Arthritis
- Psoriasis
- Kawaski Disease
- Sarcoidosis
- Pulmonary Fibrosis
- CF Severity
- Asthma
- Chr. Rhinosinusitis
- HIV Viral Setpoint
- Type 1 Diabetes
- Type 2 Diabetes
- Diabetic Nephropathy
- End-St. Renal Dis.
- Obesity, BMI, Waist
- IR, Metabolic Traits
- Height
- Osteoporosis
- Osteoarthritis
- Male Patt. Baldness
- Fetal Hemoglobin
- Platelet Volume
- Transferrin Levels
- C-Reactive Protein
- ICAM-1
- Total IgE Levels
- Urate Levels, Gout
- Protein Levels
- Vitamin B12 Levels
- β -Carotene Levels
- Recombination Rate
- Pigmentation

“Genomewide Association Studies and Human Diseases”

Hardy and Singleton NEJM 2009:April 23

Table 2. Benefits, Misconceptions, and Limitations of the Genomewide Association Study.

Benefits

- Does not require an initial hypothesis
- Uses digital and additive data that can be mined and augmented without data degradation
- Encourages the formation of collaborative consortia, which tend to continue their collaboration for subsequent analyses
- Rules out specific genetic associations (e.g., by showing that no common alleles, other than *APOE*, are associated with Alzheimer's disease with a relative risk of more than 2)
- Provides data on the ancestry of each subject, which assists in matching case subjects with control subjects
- Provides data on both sequence and copy-number variations

Misconceptions

- Thought to provide data on all genetic variability associated with disease, when in reality only common alleles with large effects are identified
- Thought to screen out alleles with a small effect size, when in reality such findings may still be very useful in determining pathogenic biochemical pathways, even though low-risk alleles may be of little predictive value

Limitations

- Requires samples from a large number of case subjects and control subjects and therefore can be challenging to organize
- Finds loci, not genes, which can complicate the identification of pathogenic changes on an associated haplotype
- Detects only alleles that are common (>5%) in a population
- Requires replication in a similarly large number of samples

Are we There Yet?

PERSPECTIVE

COMMON GENETIC VARIATION AND HUMAN TRAITS

Common Genetic Variation and Human Traits

David B. Goldstein, Ph.D.

The human genome has been only slightly a gene's expression would collectively generate a sub-

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PERSPECTIVE

GENOMEWIDE ASSOCIATION STUDIES — ILLUMINATING BIOLOGIC PATHWAYS

Genomewide Association Studies — Illuminating Biologic Pathways

Joel N. Hirschhorn, M.D., Ph.D.

Human geneticists seek to understand the basis of human biology aiming either to gain or to produce useful or predictive tests. In 2004, few genetic v

Genetic Risk Prediction — Are We There Yet?

Peter Kraft, Ph.D., and David J. Hunter, M.B., B.S., Sc.D., M.P.H.

A major goal of the Human Genome Project was to facilitate the identification of inherited genetic variants that increase or decrease the risk of complex diseases. The completion of the International HapMap Project and the development of new methods for genotyping individual DNA samples at 500,000 or more loci tests of genetic predisposition to important diseases would have major clinical, social, and economic ramifications. But the great majority of the newly identified risk-marker alleles confer very small relative risks, ranging from 1.1 to 1.5,² even though such analyses meet stringent statistical criteria (i.e., the identification of associations with disease that are the most relative risks are almost certainly overrepresented in the first wave of findings from genome-wide association studies, since considerations of statistical power predict that they will be identified first. However, a striking fact about these first findings is that they collectively explain only a very small proportion of the

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April 16, 2009

Genes Show Limited Value in Predicting Diseases

By [NICHOLAS WADE](#)

The era of personal genomic medicine may have to wait. The genetic analysis of common disease is turning out to be a lot more complex than expected.

Since the human genome was decoded in 2003, researchers have been developing a powerful method for comparing the genomes of patients and healthy people, with the hope of pinpointing the DNA changes responsible for common diseases.

This method, called a genomewide association study, has proved technically successful despite many skeptics' initial doubts. But it has been disappointing in that the kind of genetic variation it detects has turned out to explain surprisingly little of the genetic links to most diseases.

A set of commentaries in this week's issue of The [New England Journal of Medicine](#) appears to be the first public attempt by scientists to make sense of this puzzling result.

One issue of debate among researchers is whether, despite the prospect of diminishing returns, to continue with the genomewide studies, which cost many millions of dollars apiece, or switch to a new approach like decoding the entire genomes of individual patients.

Should the Perfect be the Enemy of the Good?

- “One argument in favor of using the available genetic predictors is that some information is better than no information, and we should not let the perfect be the enemy of the good by refusing to make use of our knowledge until it is more complete. Why not begin testing for common genetic variants whose associations with susceptibility to disease have been established?”
- Kraft P and Hunter D. NEJM 2009;360:1701.

2008: Invention of the Year

TIME's Best Inventions of 2008

Invention of the Year

1. The Retail DNA Test

By Anita Hamilton

Before meeting with Anne Wojcicki, co-founder of a consumer gene-testing service called 23andMe, I know just three things about her: she's pregnant, she's married to Google's Sergey Brin, and she went to Yale. But after an hour chatting with her in the small office she shares with co-founder Linda Avey at 23andMe's headquarters in Mountain View, Calif., I know some things no Internet search could reveal: coffee makes her giddy, she has a fondness for sequined shoes and fresh-baked bread, and her unborn son has a 50% chance of inheriting a high risk for Parkinson's disease.

Learning and sharing your genetic secrets are at the heart of 23andMe's service — a \$399 saliva test that estimates your predisposition for more than 2,000 conditions ranging from baldness to blindness. Although 23andMe isn't selling DNA tests to the public, it does the best job of making them accessible and affordable. The 600,000 genetic markers that 23andMe identifies and

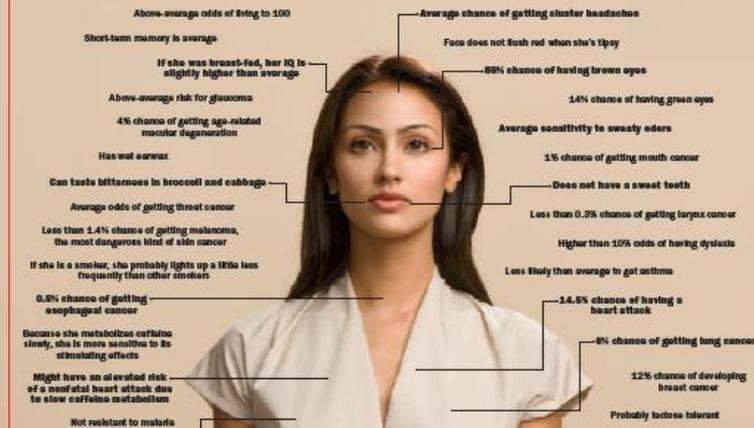
- ARTICLE TOOLS
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Invention Of the Year

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

What Your Gene Test Can Tell You



THE BEST INVENTIONS OF THE YEAR



IN DEPTH

Inflated expectations: At a September "spit party" hosted by 23andMe, invitees supply samples for free genetic testing

Time, November 10, 2008

And they must be able to analyze genetic data in light of each individual's entire medical history, including lifestyle choices and environmental exposures.

Consider the case of Mike Spear, communications director for Genome Alberta, a Canadian nonprofit. He recently got his genes read by 23andMe. "One of the things that stood out



Proliferation of Personal Genomic Tests

Genome wide	GWAS platforms Whole sequencing	23andme, decodeME, Navigenics Knome
Selected variants	Specific diseases or traits	Proactive Genetics, DNA Direct, Genelex
Other	Ancestry, nutritional, dermatologic, athletic	FamilyTree DNA Dermatogenetics, sciona, suracell

Outline

- Personal genomics 2009
- A scientific foundation for personal genomics
- Recommendations of NIH-CDC workshop
December 2008

Gene-Based Medicine in 2010? ***(now revised to 2020)***

■ Condition	Genes	RR	Lifetime
■ Prostate Ca	HPC1, 2, 3	0.5	7%
■ Alzheimer's	APOE,FAD3,XAD	0.3	10%
■ Heart disease	APOB,CETP	2.5	70%
■ Colon Cancer	FCC4,APC	4.0	23%
■ Lung Cancer	NAT2	6.0	40%

Collins FC, New Engl J Med 1999;341:28-37.

Gene-Based Medicine in 2010?

Prevention Strategies Based on Genetic information?

- Increased Risk for
 - Heart disease
 - Colon Cancer
 - Lung Cancer
- Prevention Strategies
 - **Tertiary:** Cholesterol drugs + Lifestyle changes
 - **Secondary:** Increased surveillance for early detection
 - **Primary:** Behavior modification for smoking cessation

Many Scientific Discoveries are “Lost in Translation”

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. Gouvas,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

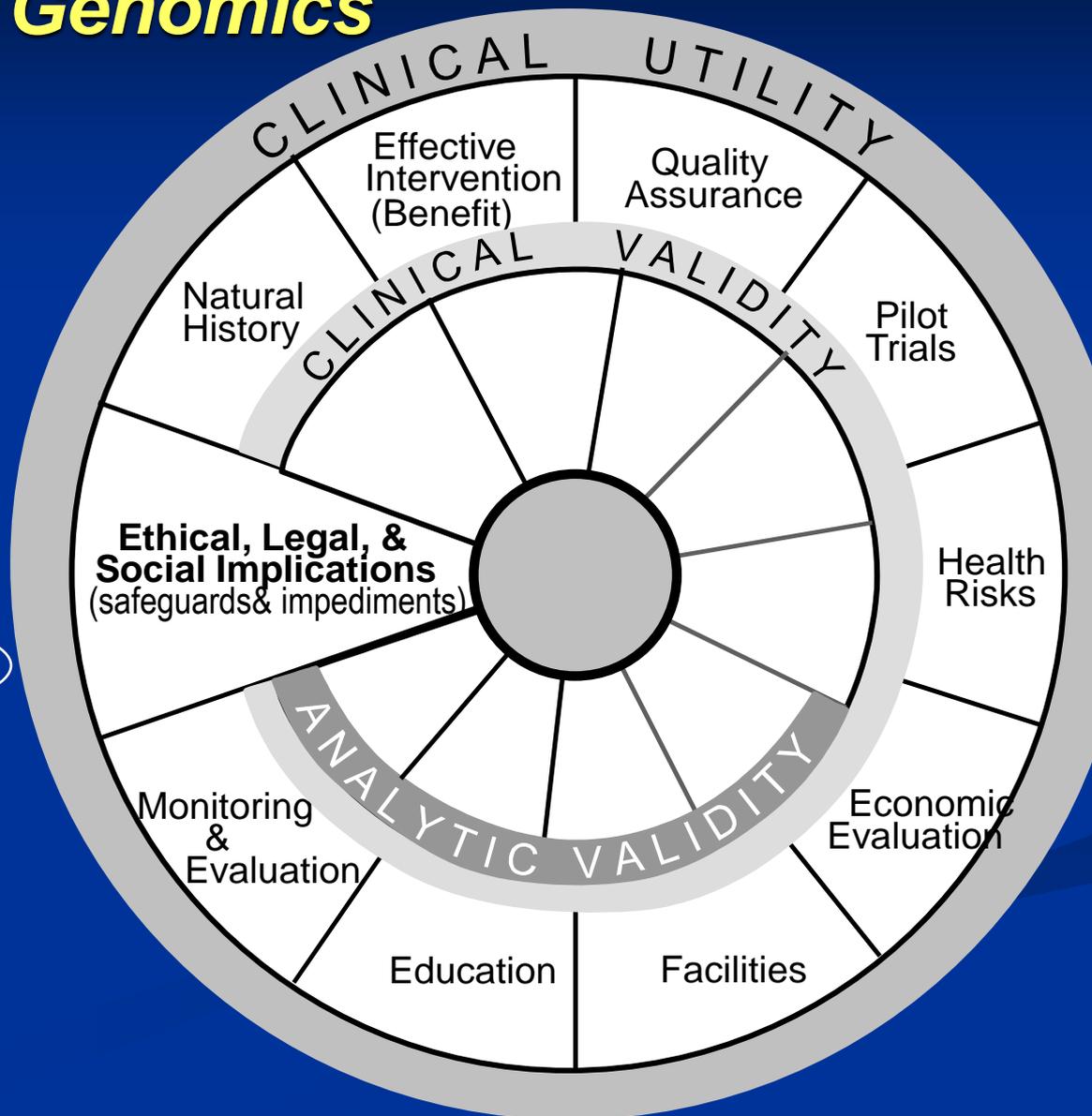
ineffective, as well as those assessing management strategies rather than specific interventions, and we selected only the earliest article whenever two or more highly cited studies with >1000 citations had been published on the same intervention and indication. Thirty-two interventions for specific 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

Multidisciplinary Evaluation of Personal Genomics

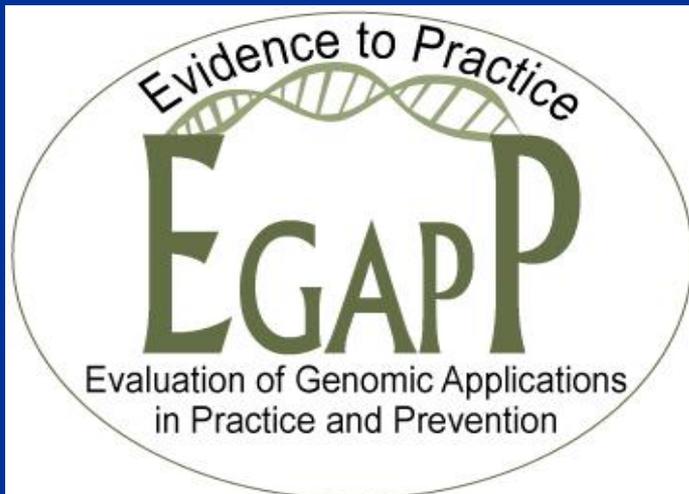
- Each intended use
- ACCE Framework
- Four components
 - Analytic Validity
 - **Clinical Validity**
 - Clinical Utility
 - ELSI



EGAPP Initiative

Evaluation of
Genomic
Applications in
Practice and
Prevention

- Independent multidisciplinary Working Group
- Evidence-based, transparent, and publicly accountable
- 4 components: horizon scan; systematic reviews; appraisal and recommendations; evaluation of impact



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Genetics in Medicine

Official Journal of the American College of Medical Genetics



Genetic Analysis of a Case
Jane Doe, medical geneticist, is called to assess the probability that her daughter might have inherited the genetic condition sickle cell disease. I understand that the DNA of Analysis is to be obtained from a blood cell sample or other methods. I also understand that the procedure is specific to the genetic condition mentioned and cannot determine the complete genetic makeup of an individual. Lack of cooperation by key relatives in providing blood samples may decrease the accuracy of the test result and for the ability to perform the test. An error in diagnosis may occur if there is anything incorrect in what I say about the biological relationship of relatives involved. I understand that

Dr. Reed Tuckson on EBM and genetics practice
Reducing mortality and morbidity in Lynch syndrome
Gene expression profiles in breast cancer

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On the cover...

"Based on the Evidence"
by Lori J. Oxendine, author, designer and graphic designer for M. Allen, incorporates manipulated conceptual and stock photo images. The artwork was inspired by the components of the evidence base in genetic medicine. Special thanks to Jeanne Lyons Dupuis at Dreamstime.com for providing the text.

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Contents

COMMENTARY

- 1 Challenges and opportunities for evidence-based genetics practice
Reed V. Tuckson, MD, FACP

ORIGINAL ARTICLE

- 3 The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative: methods of the EGAPP Working Group
Steven M. Teutsch, MD, MPH, Linda A. Bradley, PhD, Glenn E. Palomaki, BS, James E. Haddow, MD, Margaret Piper, PhD, Ned Calonge, MD, MPH, W. David Dotson, PhD, Michael P. Douglas, MS, and Alfred O. Berg, MD, MPH, Chair, on behalf of the EGAPP Working Group

EGAPP RECOMMENDATION STATEMENT

- 15 Recommendations from the EGAPP Working Group: can *UGT1A1* genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan?
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group

EVIDENCE REVIEW

- 21 Can *UGT1A1* genotyping reduce morbidity and mortality in patients with metastatic colorectal cancer treated with irinotecan? An evidence-based review
Glenn E. Palomaki, BS, Linda A. Bradley, PhD, Michael P. Douglas, MS, Katherine Kolor, PhD, and W. David Dotson, PhD

EGAPP RECOMMENDATION STATEMENT

- 35 Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives
Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group

EVIDENCE REVIEW

- 42 EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome
Glenn E. Palomaki, BS, Monica R. McClain, PhD, Stephanie Melillo, MPH, Heather L. Hampel, MS, and Stephen N. Thibodeau, PhD

(continued next page)

EGAPP Topics 2009				
Disorder/Effect	Test	Target Population	Intended Use	
Breast Cancer	<i>CYP2D6</i>	Individuals prior to treatment for BrCa	Treatment with Tamoxifen	Sel
Diabetes, Type II	<i>TCF7L2</i>	General population	Risk assessment	Plan
Cardiovascular Disease	Multigene panels	General population	Risk prediction; drug or nutritional/lifestyle management	In prog
Thrombophilia	<i>F5, F2</i>	Individuals with family history or clinical suspicion of thrombophilia	Prevention and management	In prog
Breast Cancer	Gene expression profiles	Women diagnosed with breast cancer	Treatment and recurrence risk	ER <input checked="" type="checkbox"/>
Colorectal Cancer (CRC)	<i>UGT1A1</i>	Individuals diagnosed with CRC	Treatment with Irinotecan	ER <input checked="" type="checkbox"/>
Hereditary Nonpolyposis Colorectal Cancer (HNPCC)	Mismatch repair gene mutations	Individuals diagnosed with CRC and their family members	Management of individuals and early detection/prevention for family members	ER <input checked="" type="checkbox"/>
Depression	<i>CYP450</i>	Individuals diagnosed with depression	Treatment with SSRI drugs	<input checked="" type="checkbox"/>
Ovarian Cancer	Genomic Tests	1) General population of women and; 2) women at increased risk for ovarian cancer	Detection and management	ER <input checked="" type="checkbox"/>

CypP450 Screening in Patients with Depression Treated with SSRI's

- **Non-psychotic depression**
 - Major cause of disability in the US
- **SSRIs** are first-line choices for drug
 - Choice/dose is highly empirical
 - SSRI's discontinued in 12 - 15% due to side effects
- **Cytochrome P450 (CYP450)** enzymes metabolize many drugs e.g. SSRI's
- **Genetic variants** result in extensive, intermediate and poor metabolizers

PRODUCTS

Roche Makes Waves with AmpliChip Launch

09/11/03—Reinforcing its position as a pharmacogenomics pioneer, diagnostic giant Roche launched in June a P450 chip measuring DNA markers for predicting patient responses to many common drugs.

The AmpliChip CYP450 test is based on the Affymetrix GeneChip DNA analysis platform. The chip detects variations in DNA that are known to affect genes controlling the body's mechanisms for processing drugs, and it is the first chip using Affymetrix technology that meets federal standards for clinical use. The test can be run only in reference laboratories, which must meet specific certification standards. In the future, though, it could become easier to use in a variety of settings.



What's the Evidence?

- Analytic validity
 - Does the test accurately and reliably measure CYP450 genotype?
→ Accuracy and reliability appear high
- Clinical validity
 - Does the test result correlate with the clinical outcomes: circulating drug levels, clinical response, side effects?
→ Study quality poor
→ No consistent association between CYP450 genotype and clinical response to SSRI treatment or side effects
- Clinical Utility
 - Does knowledge of the test result change patient management?
 - Does use of the test result in improved patient outcomes?
→ No evidence to support improved clinical outcomes

evidence review

December 2007 • Vol. 9 • No. 12

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

Mugdha Thakur, MD¹, Iris Grossman, PhD², Douglas C. McCrory, MD, MHS³, Lori A. Orlando, MD, MHS³, David C. Steffens, MD, MHS¹, Kathryn E. Cline, MHS³, Rebecca N. Gray, DPhil³, Jennifer Farmer, MD¹, Georgette DeJesus, MD¹, Cara O'Brien, MD³, Gregory Samsa, PhD³, David B. Goldstein, PhD², and David B. Matchar, MD^{3,4}

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL



Pharmacogenomics — Ready for Prime Time?

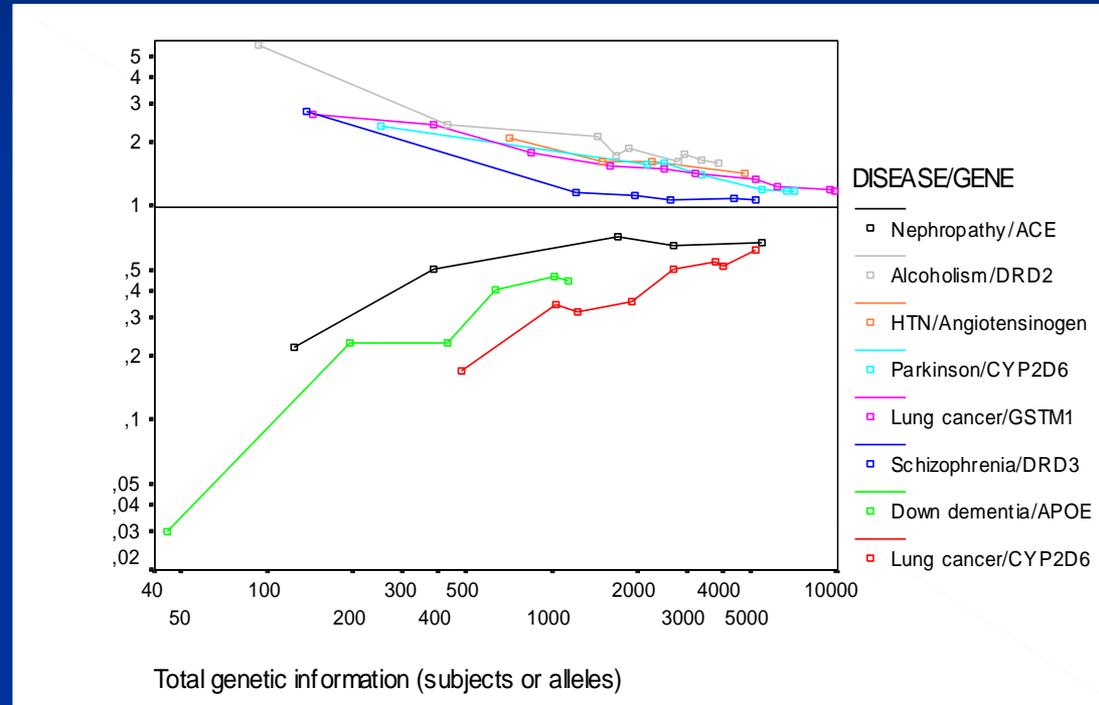
Susan B. Shurin, M.D., and Elizabeth G. Nabel, M.D.

Steps in Clinical Validity

- Establishing credible genetic associations
- The importance of what we do not know
- Evaluating the clinical relevance of associations

Methodologic Challenges in Human Genome Epidemiology

- Publication bias
- False positives
- Selection bias
- Confounding
- Exposure misclassification
- Genotype misclassification
- Lack of power



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 Seminara¹⁸ and Muin J Khoury¹⁹

Accepted 9 July 2007

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 development are needed to develop an integrated model for combining epidemiological and biological evidence in the rapidly evolving field of investigation of genetic factors.

Keywords Epidemiologic methods, genetics, genomics, causality, evidence

Grading the evidence: the Venice criteria

AAA	ABA	ACA
AAB	ABB	ACB
AAC	ABC	ACC

First letter = amount
Second letter = replication
Third letter = protection from bias

BAA	BBA	BCA
BAB	BBB	BCB
BAC	BBC	BCC

- Strong evidence
- Moderate evidence
- Weak evidence

CAA	CBA	CCA
CAB	CBB	CCB
CAC	CBC	CCC

Steps in Clinical Validity

- Establishing credible genetic associations
- The importance of what we do not know
 - Gene-Environment interaction
 - The problem of hidden heritability
 - Other sources of heterogeneity
 - Biological mechanisms: pathways, gene expression, epigenomics, and so on

Importance of Gene-Environment Interaction

(From Khoury et al. Am J Hum Genet 1988;42:89-95)

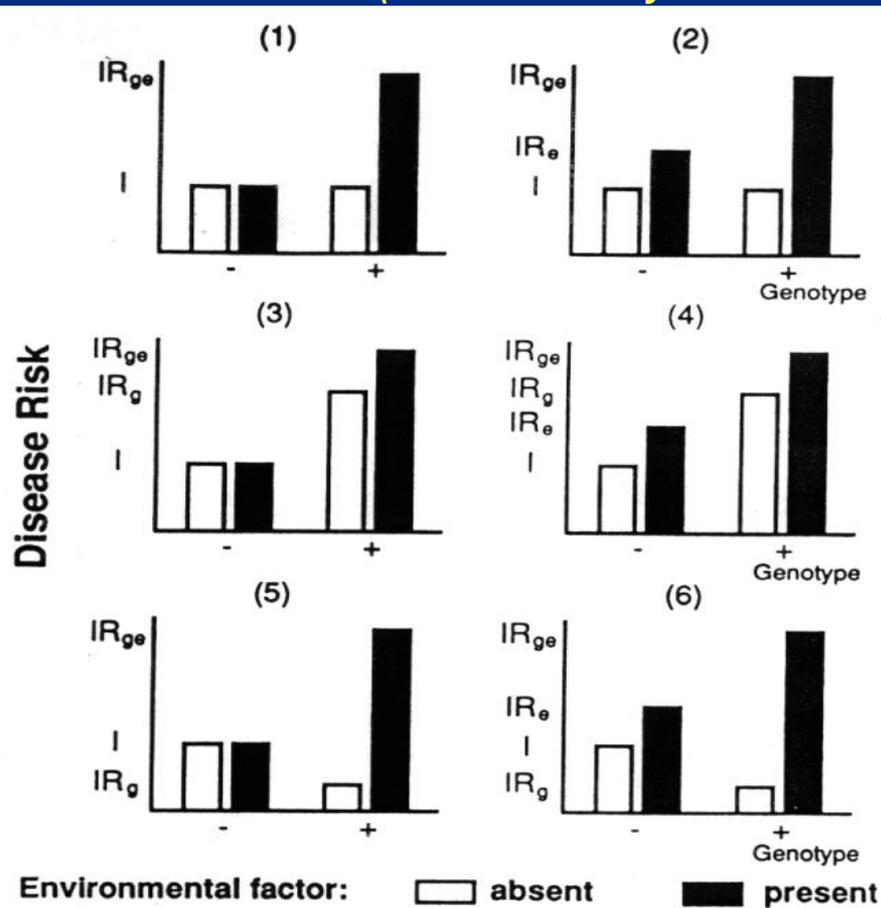


Table 5-13. Relative risks associated with a susceptibility genotype in type 1 interaction, by exposure frequency and the magnitude of interaction R_{ge}

Exposure frequency	R_{ge}		
	5	10	100
0.001	1.004	1.009	1.099
0.01	1.04	1.09	1.99
0.10	1.40	1.90	10.9
0.50	3.0	5.5	50.5
1.0	5.0	10.0	100.0

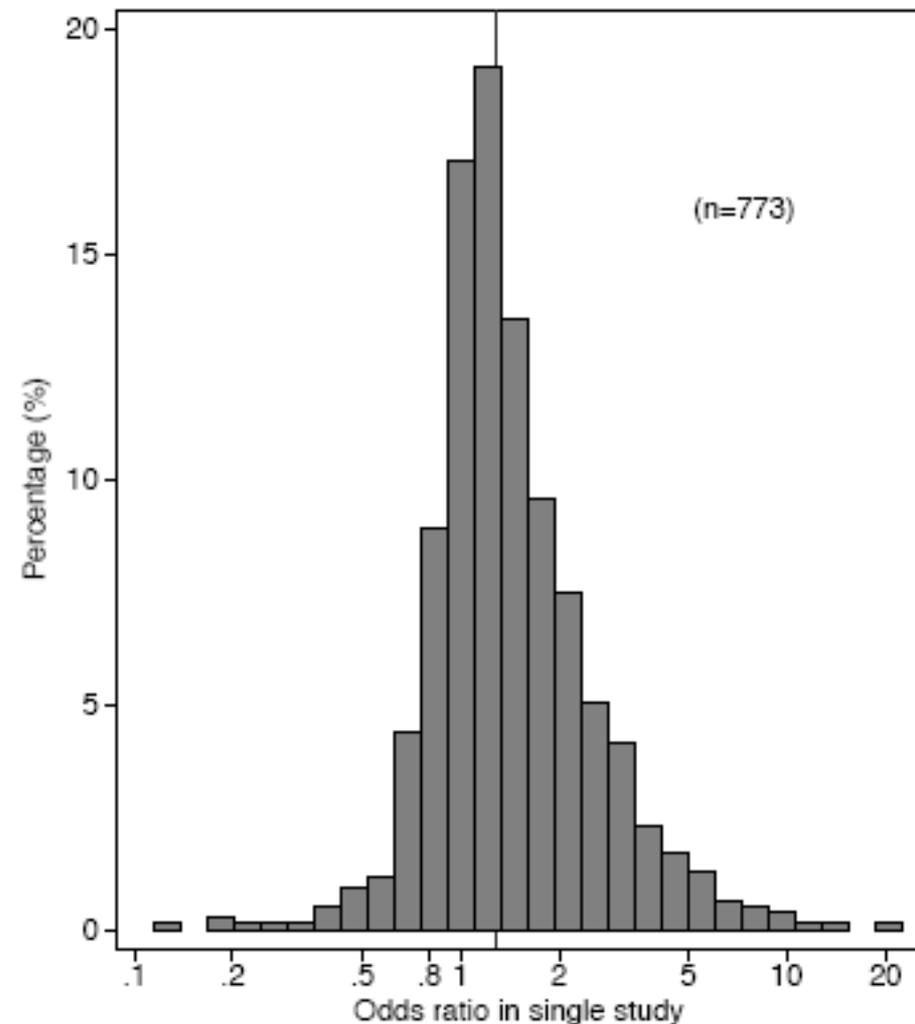
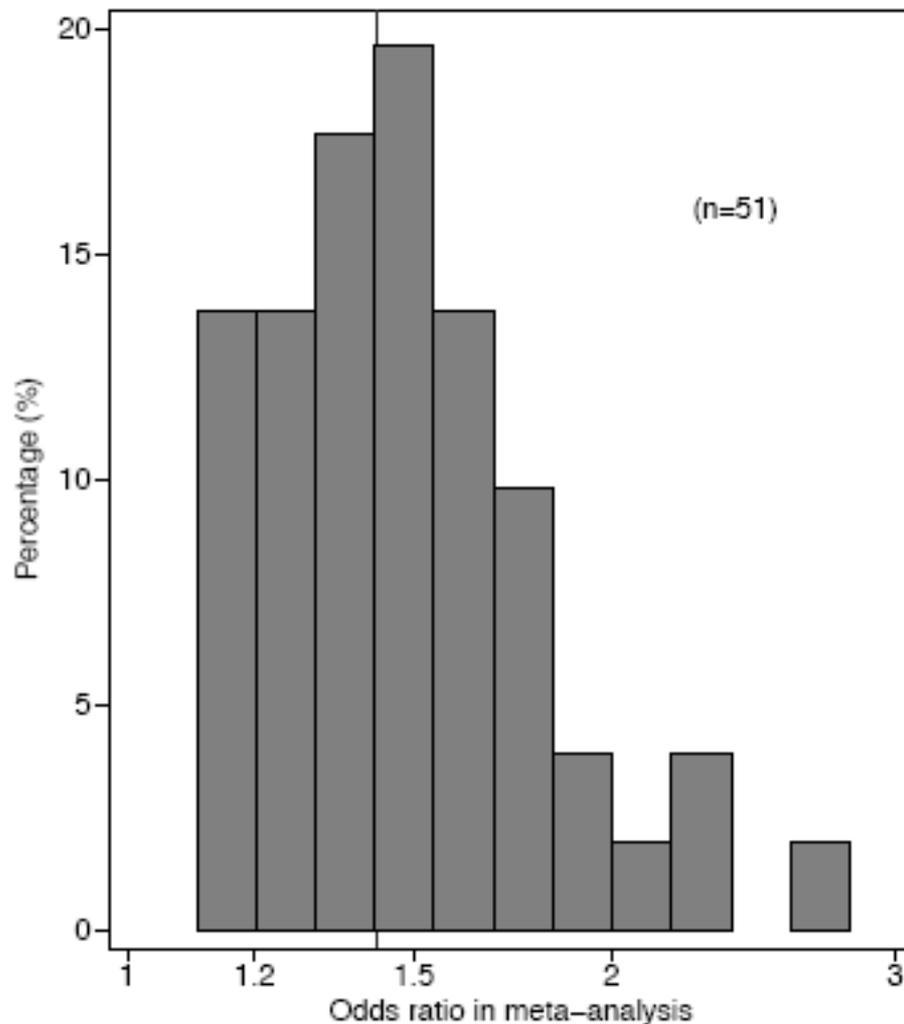
From Khoury et al. (1988a).

Disregarding interactions weakens gene-disease associations

Figure 5-3. Patterns of genotype-environment interaction.

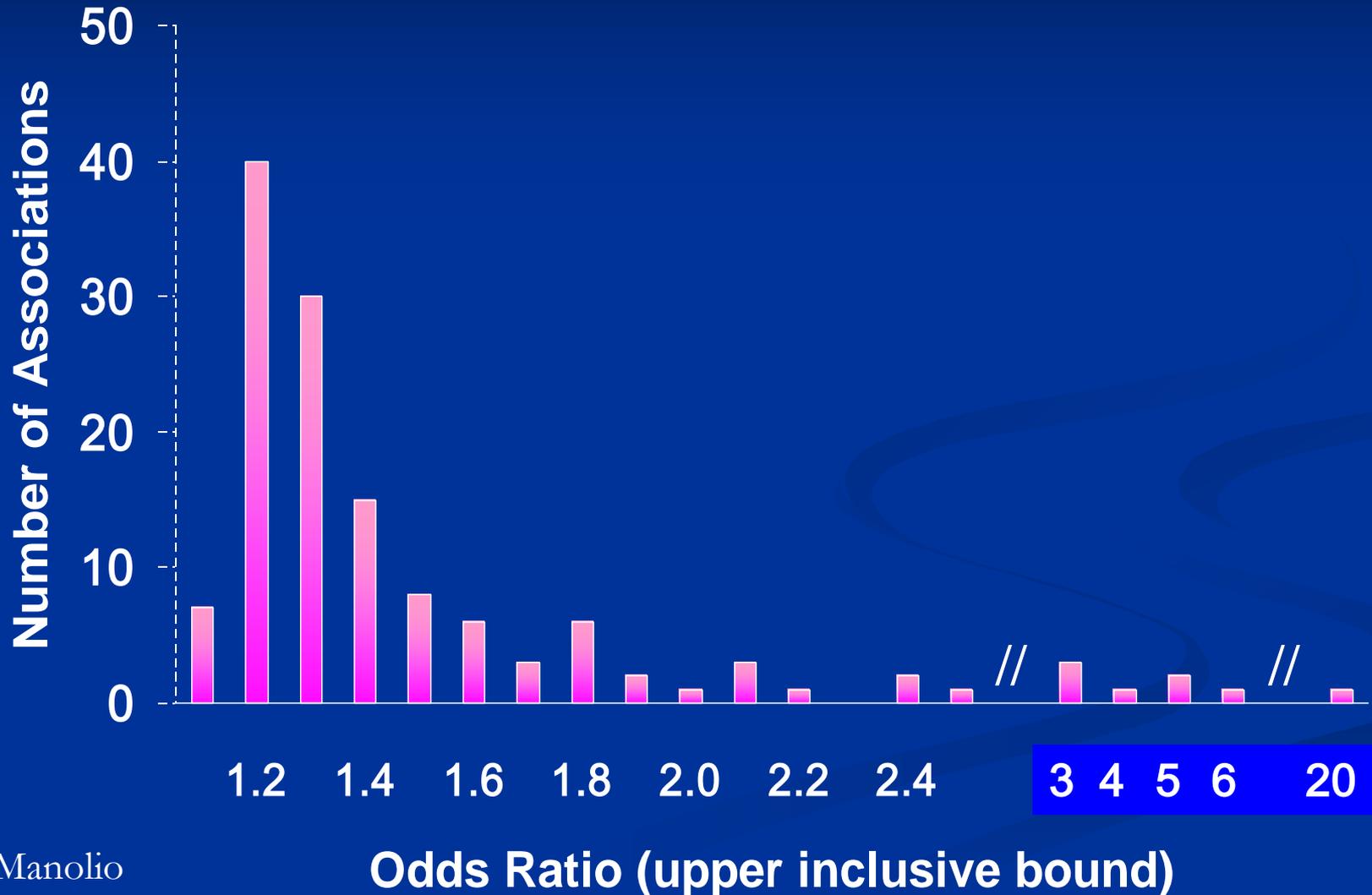
Empirical Evidence on Effect Sizes for Validated Genetic Associations of Complex Diseases

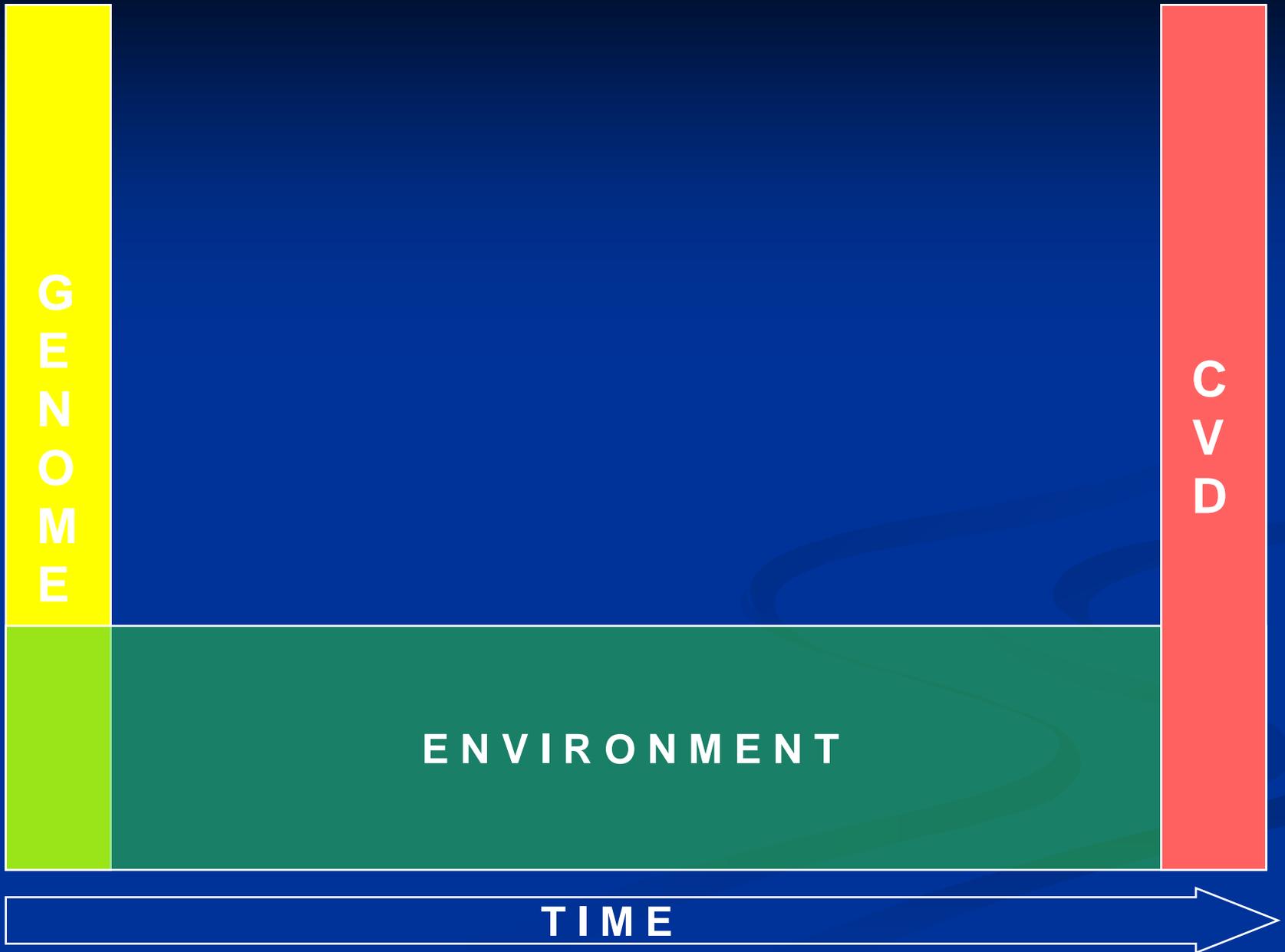
J PA. Ioannidis, TA. Trikalinos, MJ Khoury. AJE 2006



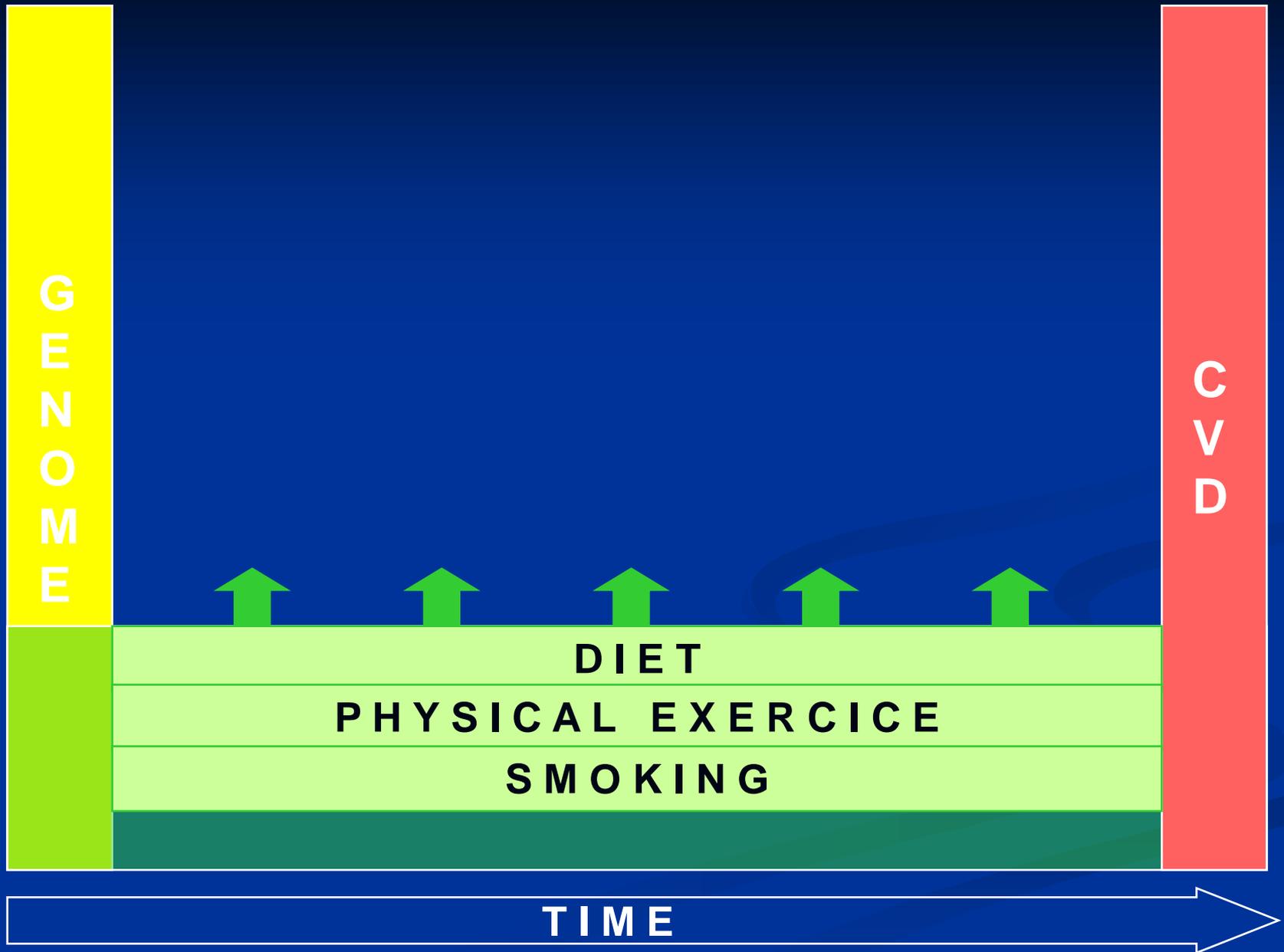
Odds Ratios of Associations from GWAS

<http://www.genome.gov/gwastudies/>

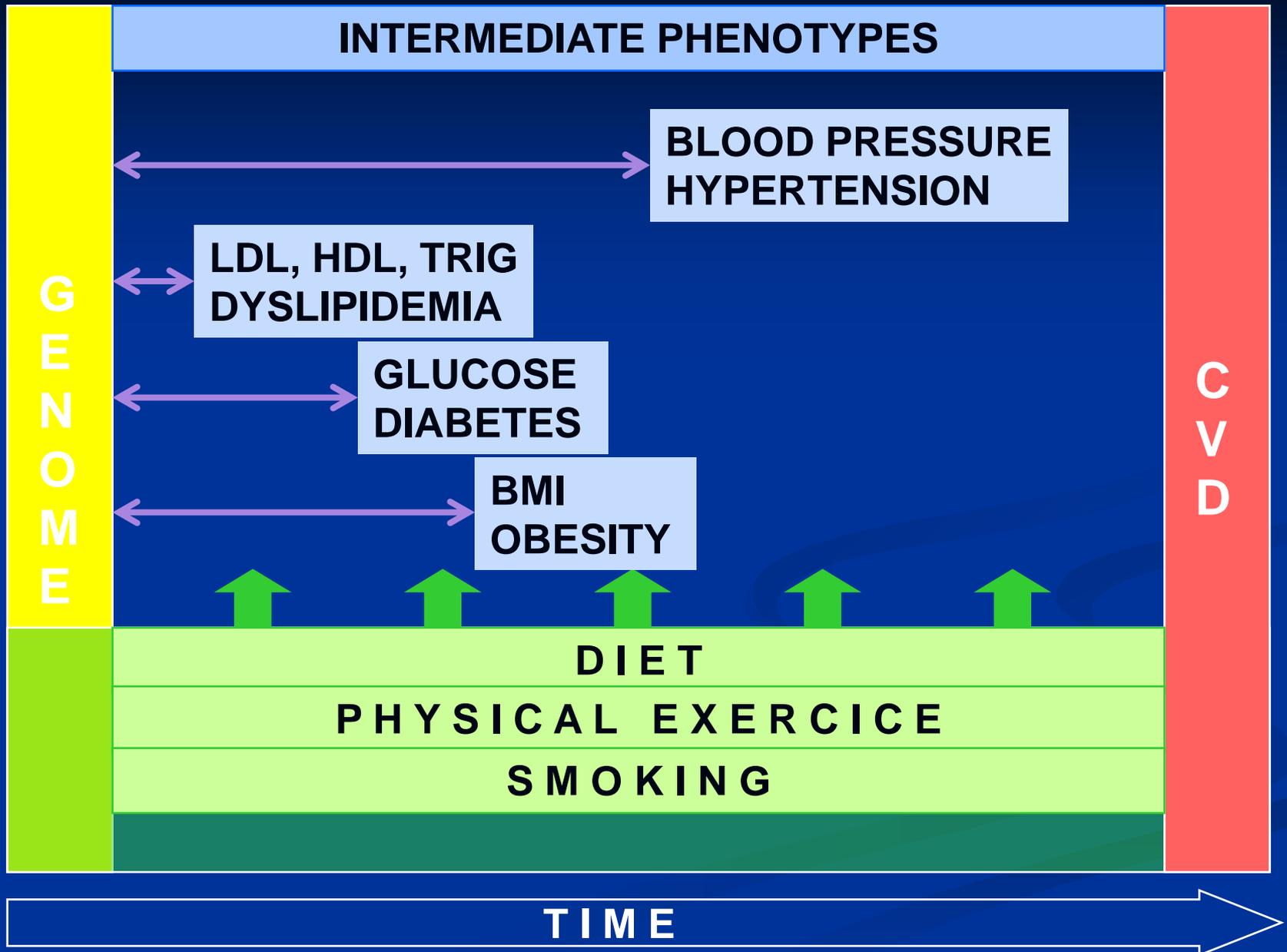




From M Bouchud



From M Bouchud



From M Bouchud

NATIONAL INSTITUTES OF HEALTH

Genes, Environment and Health Initiative (GEI)

Determining Genetic and Environmental Roots of Common Diseases

**G
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[GEI Home Page](#)

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[Exposure Biology Program](#)

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The Genes, Environment and Health Initiative (GEI)

On February 8, 2006 Health and Human Services Secretary Michael O. Leavitt announced that the President's 2007 budget proposal includes \$40 million for the National Institutes of Health to plan and implement a Genes and Environment Initiative (GEI). If approved by Congress, federal funding will begin in fiscal year 2007 and continue for four years, with \$26 million annually going to genetic analysis and \$14 million annually designated for the development of new tools to measure

What's New

[GEI Genetics Program](#)

The Genetics Program is a pilot program for analyzing genetic variation in groups of patients with specific illnesses.

**C
V
D**



DIET

PHYSICAL EXERCISE

SMOKING

TIME



The UK Biobank

A study of genes, environment and health

Frequently asked questions

Why is this needed and what are the benefits?

What's new

Status and history

Organisation and management

Ethics and governance

Consultation

Science

Press office

Jobs

Welcome to the UK Biobank

The UK Biobank project will be the world's biggest resource for the study of the role of nature and nurture in health and disease.

Up to half a million participants aged between 45 and 69 years will be involved in the study. They will be asked to contribute a blood sample, lifestyle details and their medical histories to create a national database of unprecedented size.

Many disorders, including cancer, heart disease, diabetes and Alzheimer's disease are caused by complex interactions between genes, environment and lifestyle. Researchers will use the UK Biobank resource to uncover the genetic and environmental factors that lead to these common conditions.

GENOME

CVD



DIET

PHYSICAL EXERCISE

SMOKING

TIME



**G
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N
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M
E**



**C
V
D**



DIET

PHYSICAL EXERCISE

SMOKING

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Prevalence of Genetic Variants in the United States: NHANES III (1991-1994)



Chang MH¹, Lindegren ML², Butler MA³, Chanock SJ⁴, Dowling NF¹, Gallagher M⁵, Moonesinghe R¹, Moore CA⁶, Ned RM¹, Reichler M², Sanders CL⁷, Welch R⁸, Yesupriya A¹, Khoury MJ¹ for the CDC/NCI NHANES III Genomics Working Group

¹National Office of Public Health Genomics, Coordinating Center for Health Promotion, CDC; ²National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC; ³National Institute for Occupational Safety and Health, CDC; ⁴National Cancer Institute, NIH; ⁵National Center for Environmental Health, CDC; ⁶National Center on Birth Defects and Developmental Disabilities, CDC; ⁷National Center for Health Statistics, CDC; ⁸Core Genotyping Facility, Division of Cancer Epidemiology and Genetics, Advanced Technology Program, SAIC Frederick, Inc. NCI

Background

Background

- Allele and genotype frequencies are important for understanding the contribution of genetic variation to human disease susceptibility, progression, and outcomes.
- Population-based prevalence estimates provide the basis for epidemiologic studies of gene-disease associations, for estimating population attributable fractions, and for informing health policy and clinical and public health practice.
- Study aim**
 - Determine prevalence of genotypes of public health importance by sex, age, and race/ethnicity in the U.S. population

First population-based estimates of allele and genotype frequencies for the U.S.



Materials and Methods

- DNA samples**
 - 7,159 participants aged ≥ 12 years in the NHANES III DNA bank (1991-1994)
- 90 variants in 50 genes available**
- Statistical analysis**
 - Conducted analysis with SAS-Callable SUDAAN 9.01 and SAS 9.1
 - Used NHANES III genetic sample weights due to complex survey design
 - Reported allele frequency and genotype prevalence by race/ethnicity, age, and sex
 - Tested differences in allele and genotype frequency using χ^2 test at $p < 0.05$

50 Genes in Major Cellular

Apoptosis, Cell cycle, Cellular growth and differentiation GPN16, IL10, IL12, IL4, IL4R, ITGB2, PPAR2, TGFBI, TNF, VDR	DNA R OGG1, X
Blood pressure regulation, Cardiac function ACE, ADRB1, ADRB2, NOS3A, NOS3	Hemos F2, F3, F5B, ITGA2, SERP
Cellular adhesion, Cell migration/motility CCL4, CCR2, CXCL12, F2, F5B, ITGA2, ITGB3, SERPINE1	Immunity and CCL4, CCR2, CXCL12, IL4, IL4R, MBL2, NOS3, TLR4, TN

American Journal of Epidemiology Advance Access published October 20, 2008



American Journal of Epidemiology
 Published by Oxford University Press 2008.
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Doi:10.1093/aje/kwn286

Original Contribution

Prevalence in the United States of Selected Candidate Gene Variants

Third National Health and Nutrition Examination Survey, 1991–1994

Man-huei Chang, Mary Lou Lindegren, Mary A. Butler, Stephen J. Chanock, Nicole F. Dowling, Margaret Gallagher, Ramal Moonesinghe, Cynthia A. Moore, Renée M. Ned, Mary R. Reichler, Christopher L. Sanders, Robert Welch, Ajay Yesupriya, and Muin J. Khoury for the CDC/NCI NHANES III Genomics Working Group

Initially submitted December 11, 2007; accepted for publication August 14, 2008.

Genotype-Phenotype Studies



Effects of Stage of Reproduction, Nutrients, and Genes on Serum Total Homocysteine Concentrations in Reproductive Age Women (17-44 Years) in the United States from the Third National Health and Nutrition Examination Survey DNA Bank



S.K. Shapira¹, A. Yesupriya², J. Robitaille¹, R. Fisk Green¹, H.C. Hamner¹, J.E. Kimmons³, and K.S. Crider¹ for the CDC/NCI NHANES III Genomics Working Group
¹NCBDDD, ²NOPHG, and ³NCCDPHP, Centers for Disease Control and Prevention

Polymorphisms in immune response and inflammation genes are associated with chronic kidney disease in the U.S. population: data from NHANES III

Renée Ned¹, Ajay Yesupriya¹, Giuseppina Imperatore², Diane Smelser¹, and Ramal Moonesinghe¹ for the CDC/NCI NHANES III Working Group on Genomics

1) National Office of Public Health Genomics, CDC

2) Division of Diabetes Translation, National Center for Chronic Disease Prevention and Health Promotion, CDC

The Association of Moderate/Severe Periodontitis (MSP), Pregnancy, and Two Single Nucleotide Polymorphisms (SNPs) in the Vitamin D Receptor (VDR) Gene: NHANES III, 1988-1994

Karon Abe¹, Ajay Yesupriya², Althea Grant³, Paul Eke⁴, Man-Huei Chang², Renee Ned², Nicole Dowling², Glen Satten¹

¹NCCDPHP, Division of Reproductive Health; ²National Office of Public Health Genomics; ³National Center on Birth Defects and Developmental Disabilities, Division of Hereditary Blood Disorders; ⁴NCCDPHP, Division of Oral Health



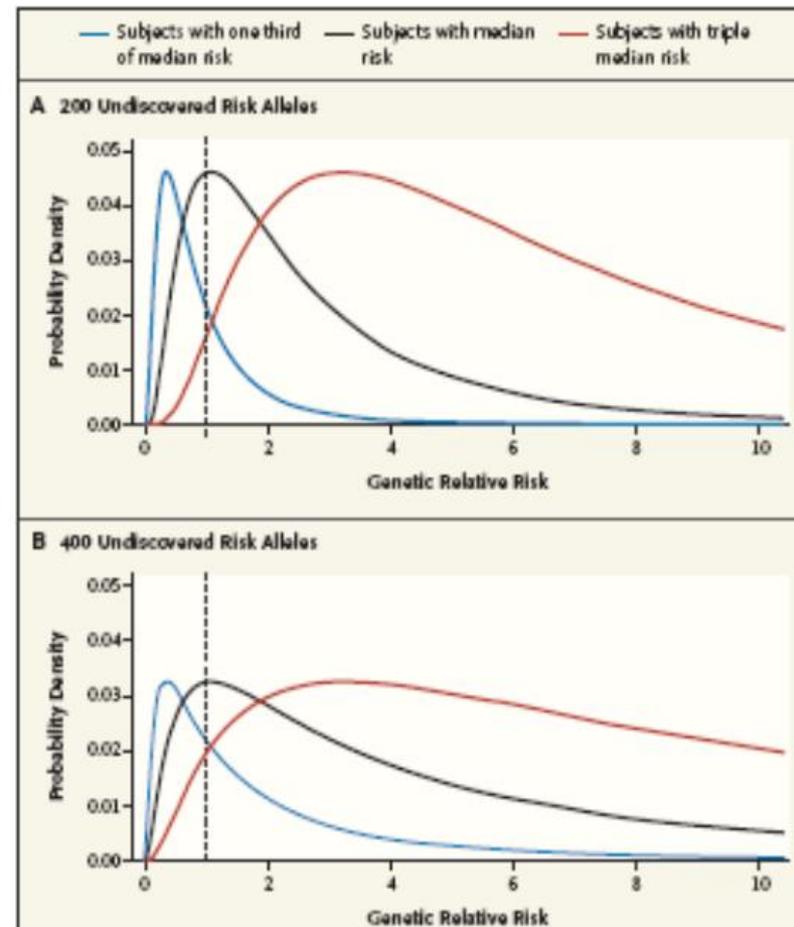
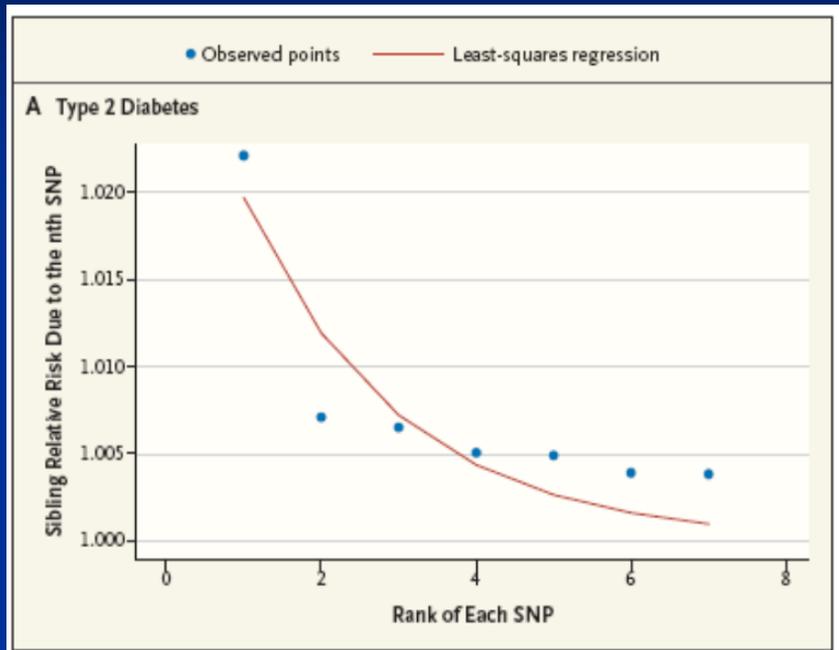
The Association of Candidate Gene Variants with Blood Lipids in NHANES III (1991-1994)

Man-huei Chang¹, Ajay Yesupriya¹, Renée M. Ned¹, Nicole F. Dowling¹, Patricia W. Mueller²
for the CDC/NCI NHANES III Genomics Working Group

¹National Office of Public Health Genomics, CDC; ²National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC



The Problem of Hidden Heritability



Number of Risk Alleles Needed to Produce a Sibling Relative Risk of 1.5, 2.0, or 3.0.*

Relative Risk Per Allele	Sibling Relative Risk		
	1.5	2.0	3.0
		<i>no. of risk alleles</i>	
1.10	203–507	347–867	550–1374
1.20	51–135	87–231	138–367

* The number of risk alleles was calculated over a range of allele frequencies (10 to 90%); the minimum and maximum numbers are presented. All alleles were assumed to have the same frequency and relative risk and to be independent.

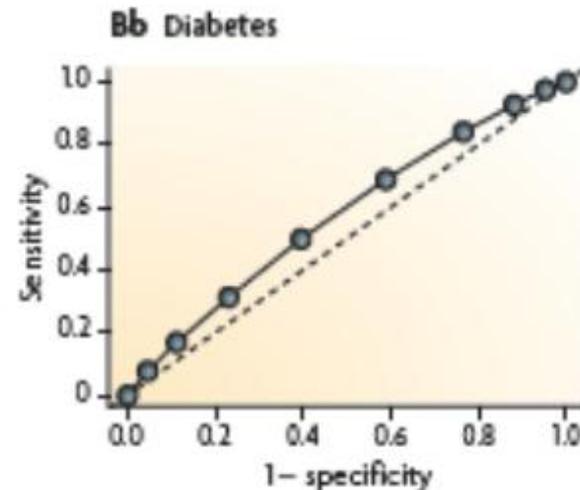
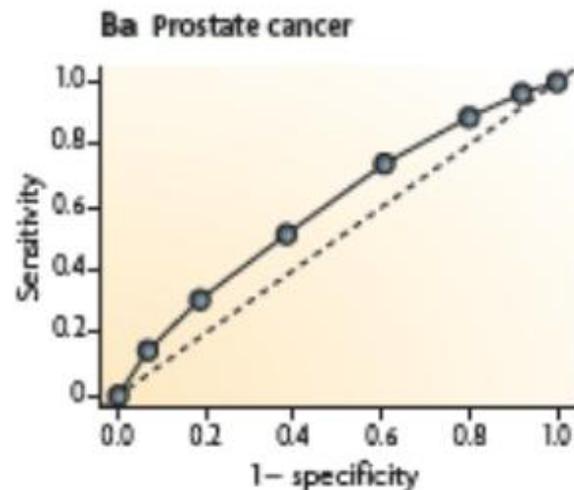
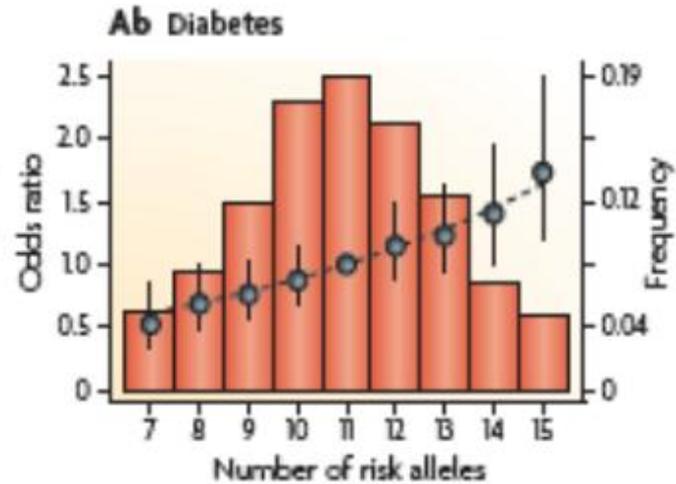
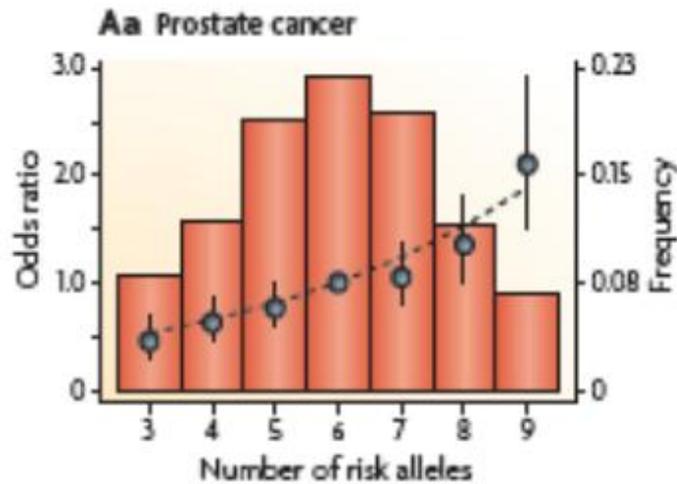
Steps in Clinical Validity

- Establishing credible genetic associations
- The importance of what we do not know
- Evaluating the clinical relevance of associations
 - Measures of sensitivity, specificity and predictive values
 - Added clinical value compared to other risk factors

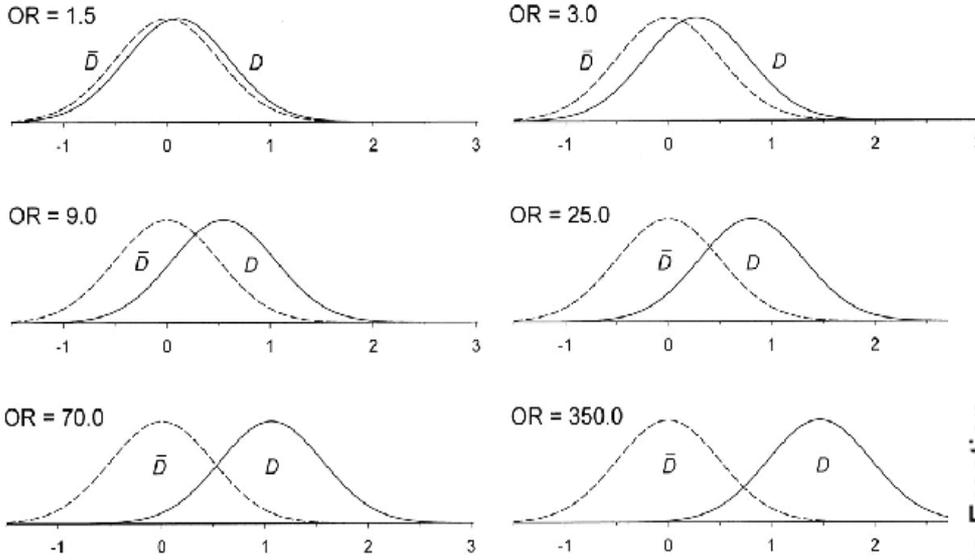
Genetic Associations: Beyond Odds Ratios

Kraft P et al. Nat Rev Genetics 2009

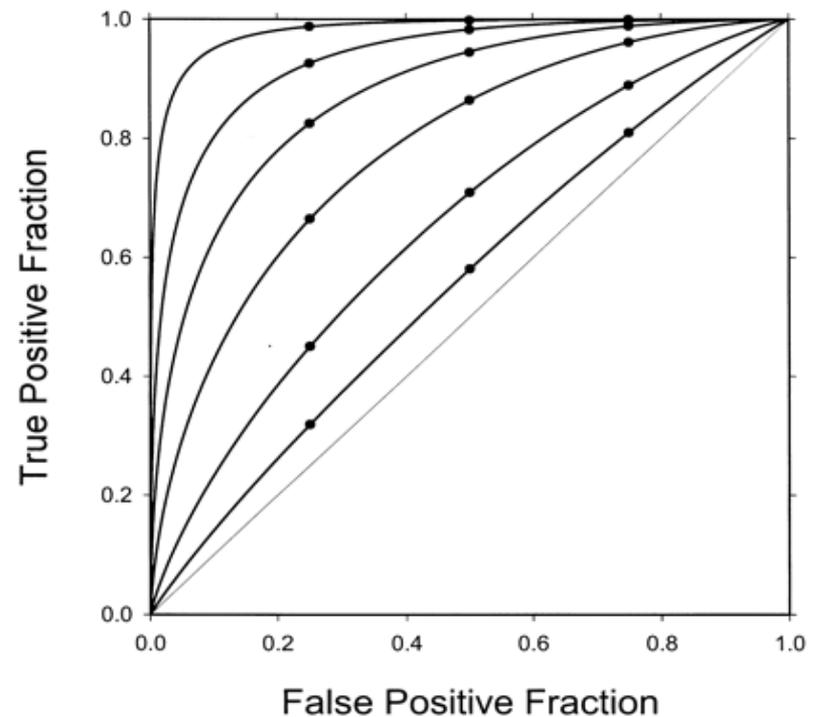
Box 2 | Strong association for disease risk is not indicative of predictive value



Association vs. Classification: Relation Between Genetic Associations and Clinical Validity of Testing for Genetic Risk Factors



AUC Analysis



Pepe et al. Am J Epidemiol
2004;159:882

Genotype Score in Addition to Common Risk Factors for Prediction of Type 2 Diabetes

James B. Meigs, M.D., M.P.H., Peter Shrader, M.S., Lisa M. Sullivan, Ph.D., Jarred B. McAteer, B.A., Caroline S. Fox, M.D., M.P.H., Josée Dupuis, Ph.D., Alisa K. Manning, M.A., Jose C. Florez, M.D., Ph.D., Peter W.F. Wilson, M.D., Ralph B. D'Agostino, Sr., Ph.D., and L. Adrienne Cupples, Ph.D.

CONCLUSIONS

A genotype score based on 18 risk alleles predicted new cases of diabetes in the community but provided only a slightly better prediction of risk than knowledge of common risk factors alone.

AUC sex	= 0.534
AUC sex + 18 polymorphisms	= 0.581
AUC clinical risk factors	= 0.900
AUC clinical risk factors + 18 polymorphisms	= 0.901

Multiple Genetic Variants and Testing for Susceptibility to Various Diseases

Added Value to Traditional Risk Factors?

Year	Researchers	Disease	Genetic variant	AUC	Δ AUC
2005	Lyssenko et al.	Type 2 diabetes	3 establ. variants	0.68	+0.00
2006	Podgoreanu et al.	MI after surgery	3 (out of 48)	0.70	+0.06
2007	Humphries et al.	CHD	4 (out of 12)	0.66	+0.04
2007	Morisson et al.	CHD	11 (out of 116)	0.76	+0.01
2008	Vaxillaire et al.	Type 2 diabetes	3 (out of 19)	0.82	+0.00
2008	Zheng et al	Prostate cancer	5 (out of 16)	0.61	+0.02
2008	Kathiresan et al.	CVD	9 (out of 11)	0.80	+0.00
2008	Lango et al.	Type 2 diabetes	18 establ. variants	0.78	+0.02
2008	Van Hoek et al.	Type 2 diabetes	18 establ. variants	0.66	+0.02
2008	Meigs et al.	Type 2 diabetes	18 establ. variants	0.90	+0.00
2008	Lyssenko et al	Type 2 diabetes	11 establ. variants	0.74	+0.01

Practice of Epidemiology

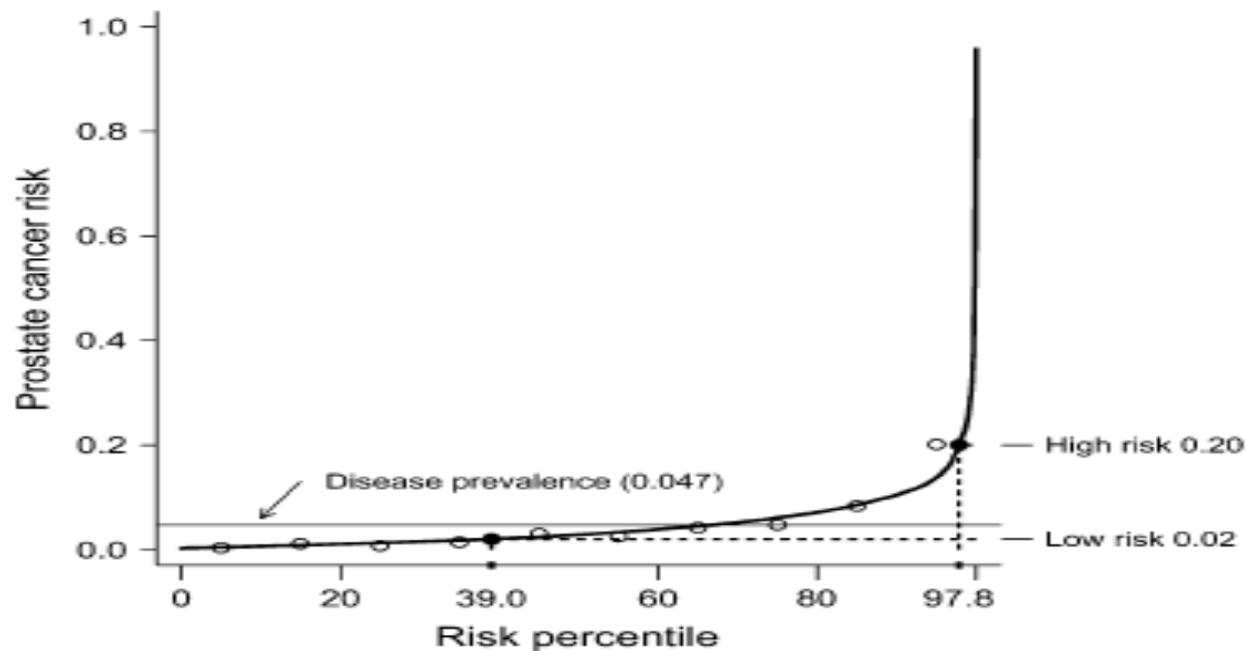
Integrating the Predictiveness of a Marker with Its Performance as a Classifier

Margaret S. Pepe^{1,2}, Ziding Feng¹, Ying Huang², Gary Longton¹, Ross Prentice¹, Ian M. Thompson³, and Yingye Zheng¹

¹ Fred Hutchinson Cancer Research Center, Seattle, WA.

² University of Washington, Seattle, WA.

³ University of Texas Health Sciences Center, San Antonio, TX.



Risk Reclassification for Clinical Action

- Risk assessment models should assess
 - Discrimination: correctly classifying those w/wo disease (or state of disease)
 - Calibration: correctly predicting the risk of disease within groups
 - Reclassification: risk levels crossing threshold for clinical action

NCEP III Guidelines (to be updated in 2010)

Category	10 Yr 'hard'¹ CHD risk	Target	LDL-C (mg/dL) TLC Drug Therapy	
High	>20%	<100	≥100	≥100
Int High	10-20%	<130	≥130	≥130
Intermediate	<10%	<130	≥130	≥160
Low	0-1 TRF	<160	≥160	≥190

Addition of 9p21 variant to ARIC prospective cohort can lead to MI risk reclassification

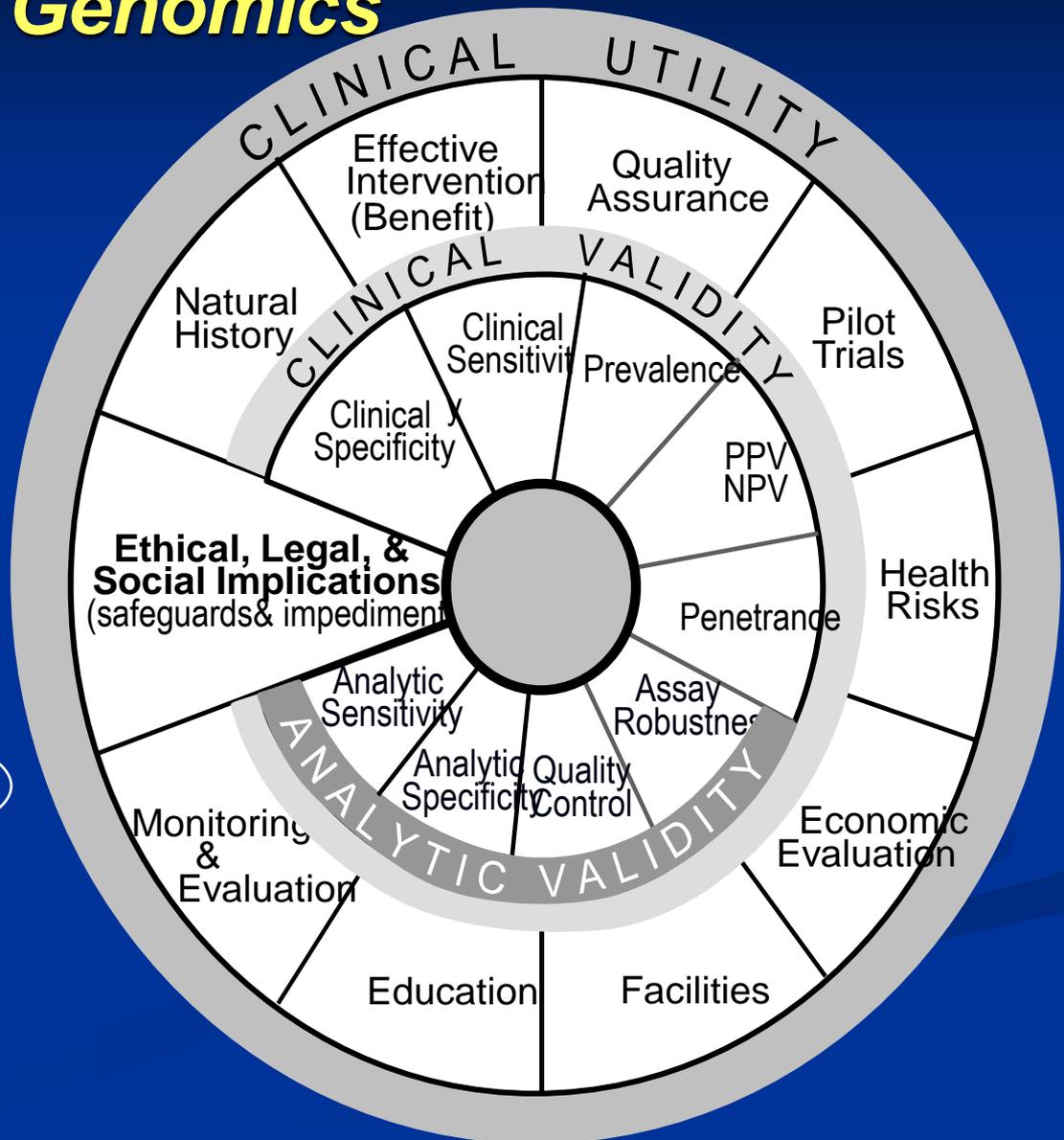
Ariel Brautbar; Christie Ballantyne; Kim Lawson; Vijay Nambi; Lloyd Chambless; Aaron Folsom; James Willerson; Eric Boerwinkle

		Classification using ACRS + 9p21 allele				
		Classification using ACRS alone (percent of total cohort)				
Category		0-5%(%)	5-10%(%)	10-20%(%)	>20%(%)	
Total number reclassified for category (%)						
10-year risk 0-5%	Low	3,428	3,237	191 (5.6)	0	191 (5.6)
Observed event rate [†]		2.3	3.9	0	0	2.4
10-year risk 5-10%	Intermediate	2,328	165 (7.1)	1,878	285 (12.2)	450 (19.3)
Observed event rate		4.98	6.1	10.6	0	6.7
10-year risk 10-20%	Intermediate-high	2,641	0	184 (7)	2,194	263 (10)
Observed event rate		0	9.3	12.6	16.2	12.76
10-year risk >20%	High	1,607	0	0	135 (8.4)	1,472
Observed event rate				13.7	22.61	21.86
TOTAL		10,004	3,402	2,253	2,614	1,735
Observed event rate		13.49	2.5	6.2	12.5	22

* Percentage of individuals reclassified from ACRS based risk model after adding 9p21 allele to risk calculation. † Observed event rate have been extrapolated to 10-year rate (number of events per 100 people per 10 years of observation) from a follow up time of 14.6 years. **Conclusion:** The addition of the 9p21 allele to traditional risk factors, in the white population of the ARIC study, improved CHD risk prediction and reclassified a number of subjects, especially in the intermediate and intermediate-high risk categories. For the majority of the reclassified individuals, target LDL-C levels would be changed, thus altering therapy

Multidisciplinary Evaluation of Personal Genomics

- Each intended use
- ACCE Framework
- Four components
 - Analytic Validity
 - Clinical Validity
 - **Clinical Utility**
 - ELSI



Case Study 1: Prostate Cancer Susceptibility Testing

- 48 year old white male in good health,
 - father diagnosed with localized prostate cancer at age 68
- Concerned, he got tested using deCODE Prostate Cancer Genetic Test:
 - Relative risk = 1.88
- High risk prompted early PSA test by primary care
 - PSA – high normal at 2.0ng/ml
- High risk prompted urologist to perform TRUS-guided biopsy
 - Positive -Gleason score of 6
 - Radical prostatectomy with nerve sparing

Case Study 2: Dr Oz

- “Dr. Oz found out he's 30 percent less likely than the average man is of developing prostate cancer. Which means, he can be a little less diligent about scheduling regular prostate examinations. "Think of the trade-off," he says. "Thanks to this test, I don't have to have rectal exams



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Prostate Cancer Health Center

Prostate Cancer Gene Test Coming Soon

FONT SIZE

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 samples are analyzed, the test takes about a week.

"The genetic findings in our paper can be used to identify men who may benefit from available in the next few months," says Jianfeng Xu, director of the Center for Human Genomics, in a statement for WebMD.

Xu's team describes the test in today's advance online edition of *Journal of Medicine*.

-  **PROSTATE CANCER GUIDE**
- 1 Overview & Facts
 - 2 Symptoms & Types
 - 3 Diagnosis & Tests
 - 4 Treatment & Care

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.

Loci Associated with Prostate Cancer, 2008

Region	p-value	Risk Allele	Odds ratios	
		Freq.	Heterozygotes	Homozygotes
8q24 (loc1)	6.7×10^{-16}	0.1	1.49 (1.34-1.64)	1.83 (1.32-2.53)
10q11	8.7×10^{-14}	0.38	1.20 (1.10-1.31)	1.61 (1.42-1.81)
8q24 (loc2)	4.7×10^{-13}	0.50	1.13 (1.02-1.26)	1.46 (1.30-1.64)
17q21	1.5×10^{-10}	0.52	1.25 (1.13-1.34)	1.47 (1.31-1.65)
11q13	4.1×10^{-10}	0.50	1.18 (1.08-1.28)	1.48 (1.27-1.74)
10q26	1.7×10^{-7}	0.25	1.14 (0.94-1.38)	1.40 (1.16-1.69)
7p15	3.2×10^{-7}	0.76	1.18 (1.07-1.31)	1.54 (1.37-1.73)

NCI CGEMS data, courtesy N Chatterjee, November 2008

So What is Going on Here?

- What do these odds ratios mean? Are they reliable?(clinical validity)
- Are these numbers actionable? What do you do with this information? (clinical utility)
- What would you tell individuals contemplating such testing?
- And what would you tell those already tested?
- Imagine this scenario repeated over multiple diseases in clinical practice? What is the net balance of benefits and harms on a population basis?

The Debate About Prostate Cancer Screening

ORIGINAL ARTICLE

Published at www.nejm.org March 18, 2009
(10.1056/NEJMoa0810696)

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., Robert L. Grubb, III, M.D., Sandra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D., Mona N. Fouad, M.D., Edward P. Gelmann, M.D., Paul A. Kvale, M.D., Douglas J. Reding, M.D., Joel L. Weissfeld, M.D., Lance A. Yokochi, M.D., E. David Crawford, M.D., Barbara O'Brien, M.P.H., Jonathan D. Clapp, B.S., Joshua M. Rathmell, M.S., Thomas L. Riley, B.S., Richard B. Hayes, Ph.D., Barnett S. Kramer, M.D., Grant Izmirlian, Ph.D., Anthony B. Miller, M.B., Paul F. Pinsky, Ph.D., Philip C. Prorok, Ph.D., John K. Gohagan.

ORIGINAL ARTICLE

Published at www.nejm.org March 18, 2009
(10.1056/NEJMoa0810084)

Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Roeske, M.D., Antonio Rovenger, M.D., Liisa Mänttinen, Ph.D., Chris H. Bangma, Bert G.

EDITORIAL

Published at www.nejm.org March 18, 2009
(10.1056/NEJMe0901166)

Screening for Prostate Cancer — The Controversy That Refuses to Die

Michael J. Barry, M.D.

Editor's note: Do the benefits of PSA screening outweigh the risks? Watch video of a roundtable discussion, participate in a poll, and contribute your comments in our Clinical Directions feature — [Screening for Prostate Cancer](#). Commenting closes April 1, 2009.

THIS ARTICLE

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What is the Evidence of Clinical Utility of Personal Genomics?

- Are there genotype specific interventions?
- Is risk reclassification enough to show clinical utility?
- If not, does genetic information change behavior?
- When do we need RCTs?
- What about “personal utility” in the absence of interventions?

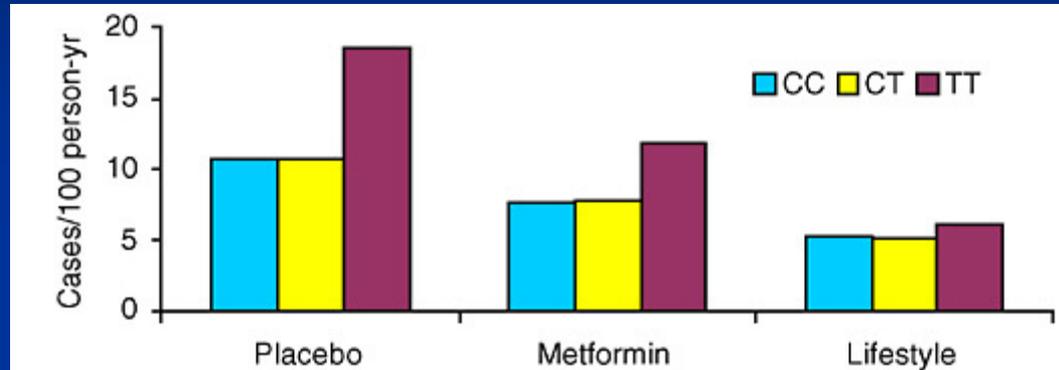


FIGURE 3-4 TCF7L2 and risk of T2D in Diabetes Prevention Program.

SOURCE: Data derived from Florez et al., 2006.

Data from Diabetes Prevention Program (DPP)

RCT results stratified by genotype

“Biomedical Risk Assessment as an Aid for Smoking Cessation?”

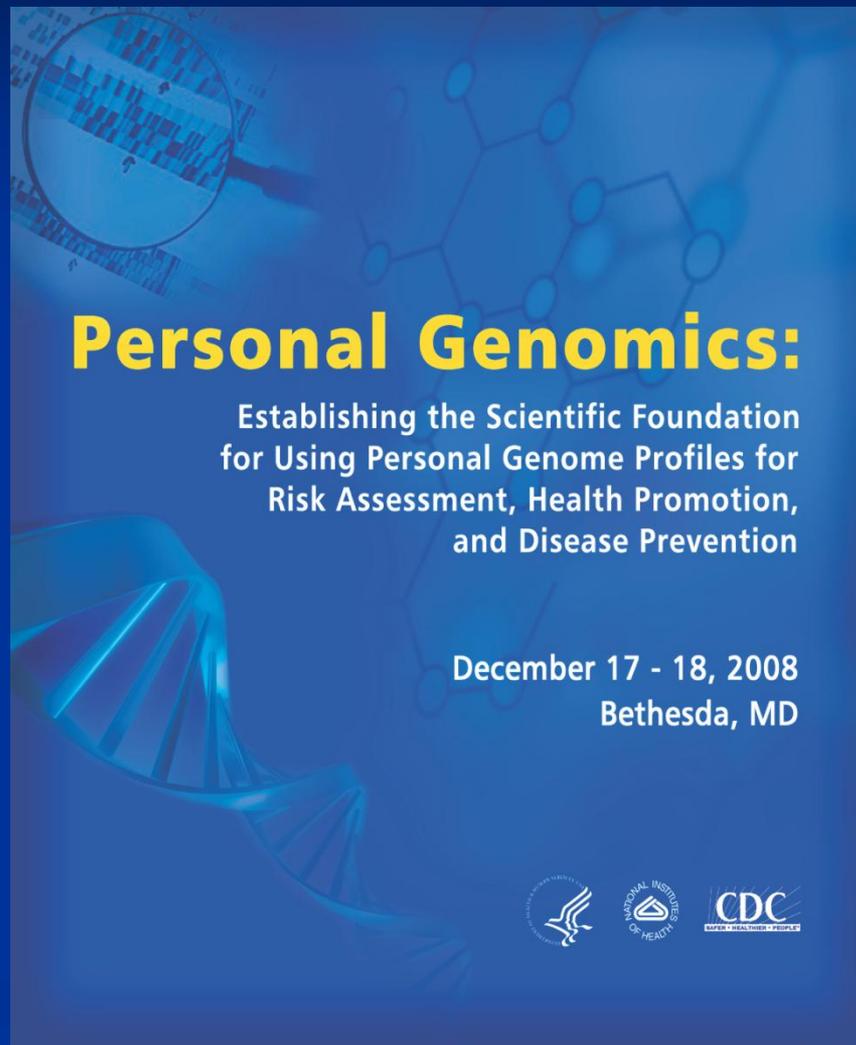
- A strategy for increasing smoking cessation rates could be to provide smokers with feedback on the biomedical or potential future effects of smoking,
 - Risk assessment includes measurement of exhaled carbon monoxide (CO), lung function, and genetic susceptibility to lung cancer.
 - **Review of 8 clinical trials**
- “Due to the scarcity of evidence of sufficient quality, we can make no definitive statements about the effectiveness of biomedical risk assessment as an aid for smoking cessation”
 - Bize et al. Cochrane Review 2008

Outline

- Personal genomics 2009
- A scientific foundation for personal genomics
- Recommendations of NIH-CDC workshop
December 2008

Workshop Recommendations

- 1. Develop and implement industry-wide scientific standards for personal genomics
- 2. Develop and implement a multidisciplinary research agenda



The poster features a blue background with a DNA double helix on the left, a magnifying glass over a microarray chip in the upper left, and a molecular structure on the right. The text is centered and right-aligned.

Personal Genomics:

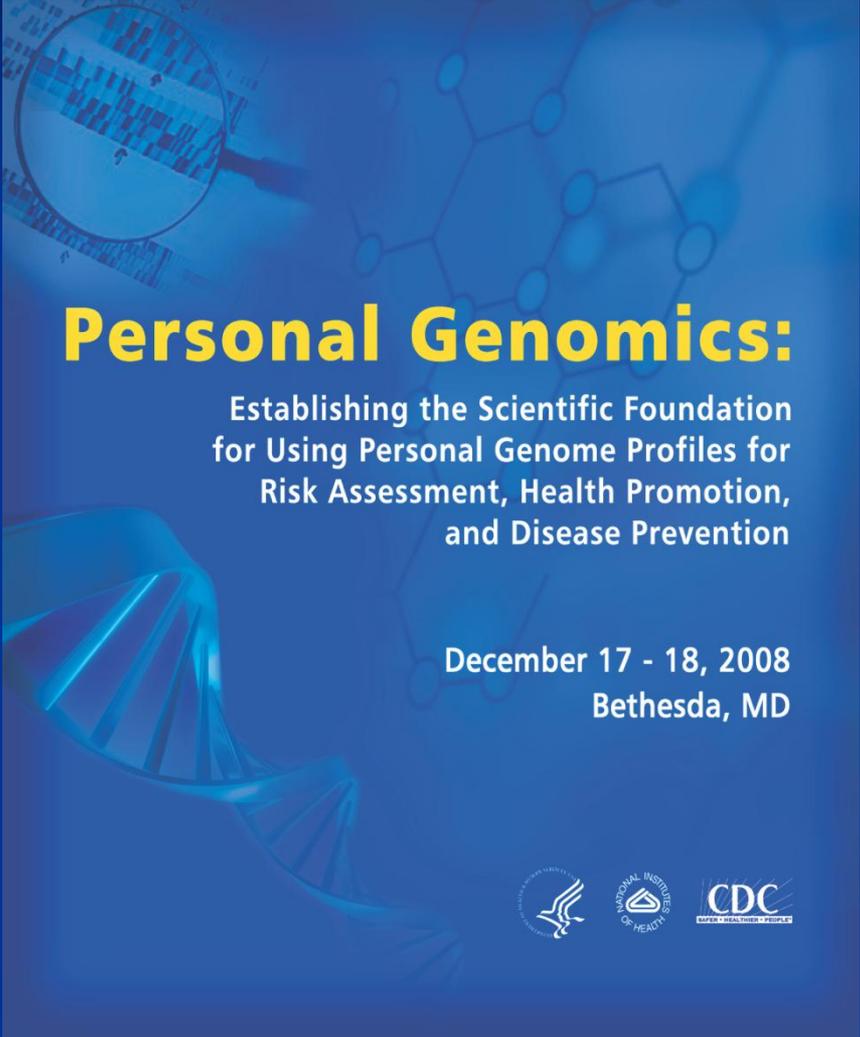
Establishing the Scientific Foundation
for Using Personal Genome Profiles for
Risk Assessment, Health Promotion,
and Disease Prevention

December 17 - 18, 2008
Bethesda, MD

Workshop Recommendations

- 3. Enhance credible knowledge synthesis and dissemination of information to providers and consumers
- 4. Link scientific research on validity and utility to evidence-based recommendations for use of personal genomic tests
- 5. Consider the value of personal utility and develop metrics of evaluation



The poster features a blue background with a glowing DNA double helix on the left and a magnifying glass over a DNA microarray in the upper left. The text is centered and right-aligned.

Personal Genomics:

Establishing the Scientific Foundation
for Using Personal Genome Profiles for
Risk Assessment, Health Promotion,
and Disease Prevention

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Logos for the Department of Health and Human Services, National Institutes of Health, and CDC are at the bottom right.