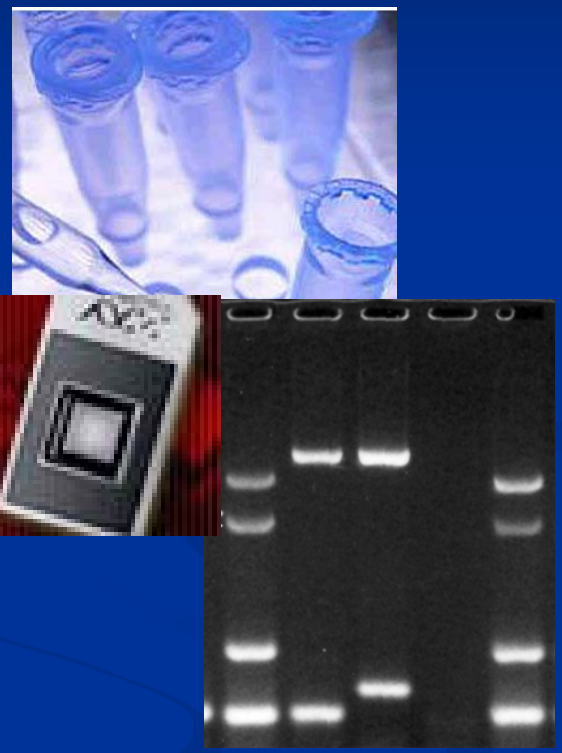
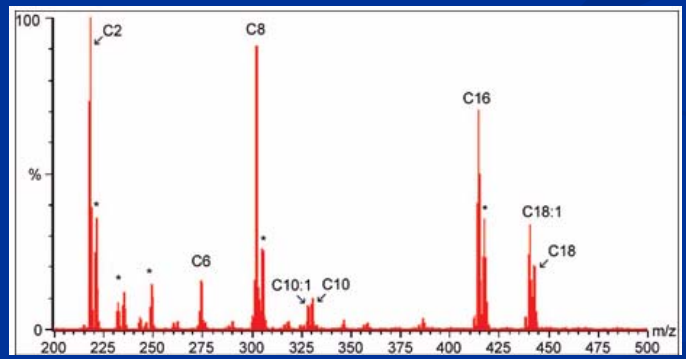
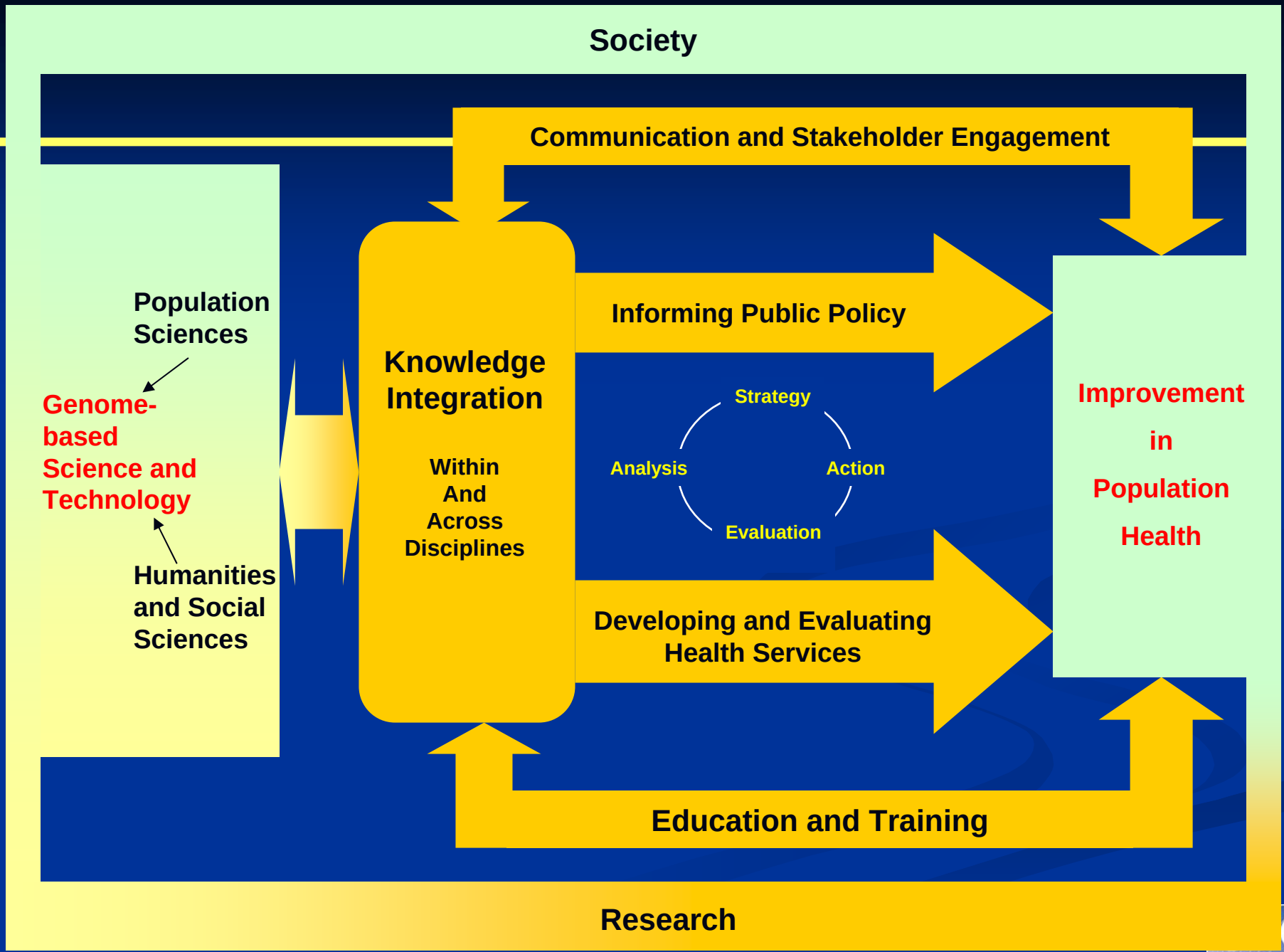
Knowledge Integration in Public Health

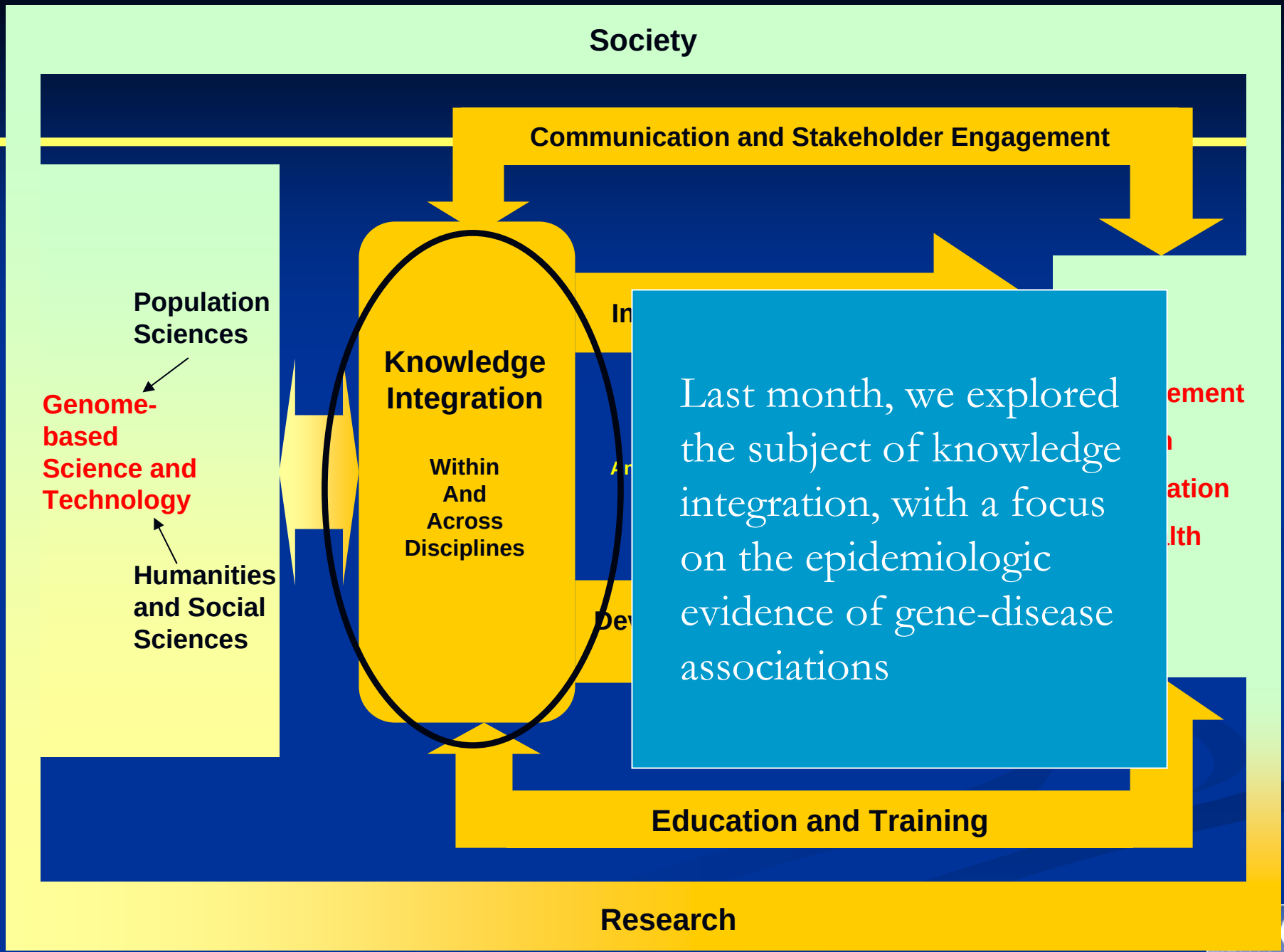
Genomics: Evaluation of Genetic Tests

Muin J. Khoury MD, PhD
National Office of Public Health Genomics
CDC





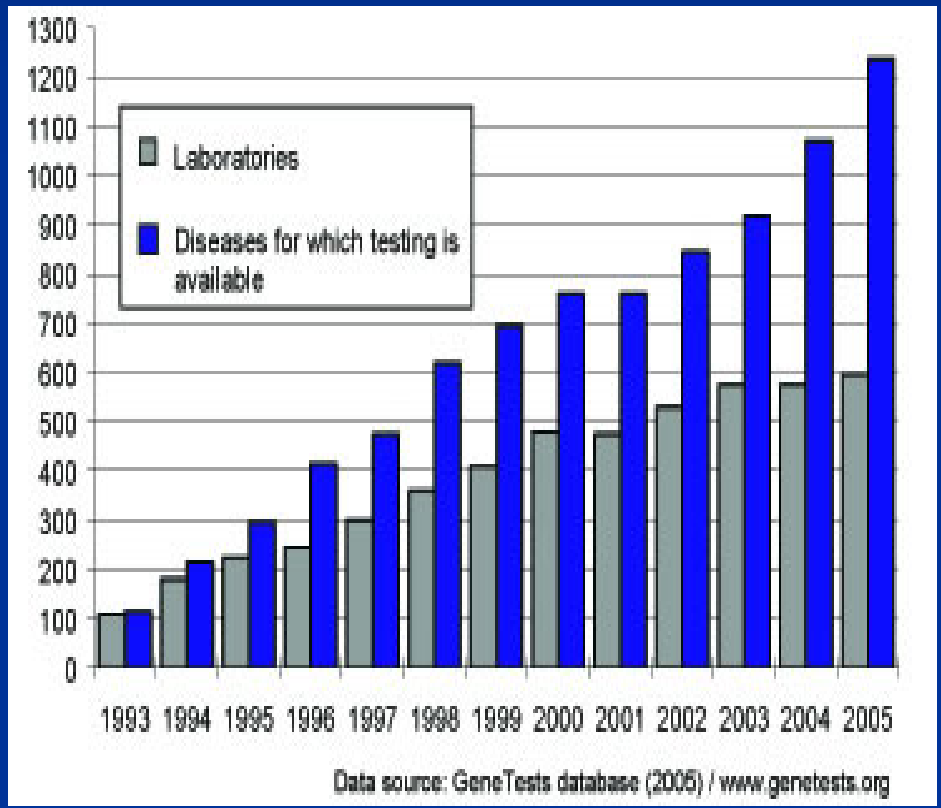

Society
Communication and Stakeholder Engagement
Population Sciences
Genome-based Science and Technology
Humanities and Social Sciences
Knowledge Integration
Within And Across Disciplines
Informing Public Policy
Strategy
Analysis
Action
Evaluation
Developing and Evaluating Health Services
Improvement in Population Health
Education and Training
Research


Society
Communication and Stakeholder Engagement
Population Sciences
Genome-based Science and Technology
Humanities and Social Sciences
Knowledge Integration
Within And Across Disciplines
Last month, we explored the subject of knowledge integration, with a focus on the epidemiologic evidence of gene-disease associations
Education and Training
Research

Outline

- Introduction: Why are genetic tests a public health issue?
- Definition and Types of Genetic tests
- A Multidisciplinary Framework for the Evaluation of Genetic tests
- Examples and Applications

Genetic Tests as a Public Health Issue



- Translating research to testing in clinical practice
- Providing information on appropriate use to providers, policy makers and the public
- Monitoring use and ensuring appropriate access
- Addressing complex social issues
- Very few tests will be used for population screening

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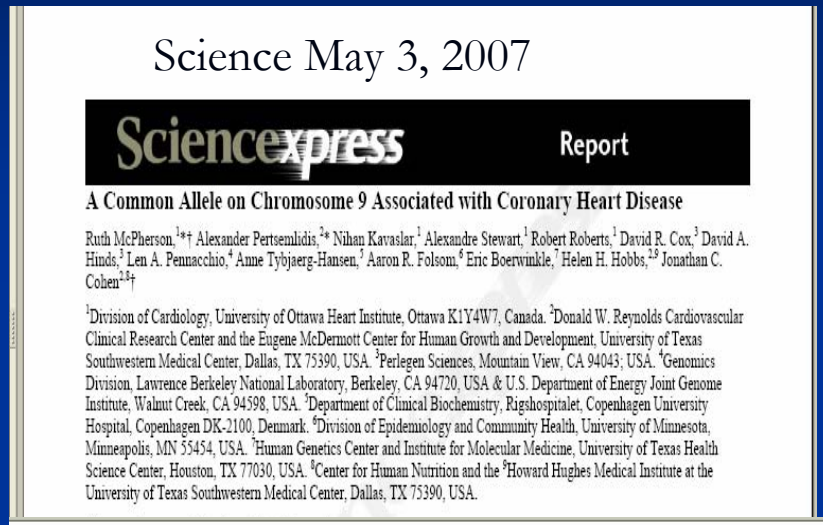
"DNA Mutation Raises Heart Disease Risk in Whites"



Science May 3, 2007

Sciencexpress Report

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

Ruth McPherson,[1*†] Alexander Pertsemlidis,[2*] Nihan Kavaslar,[1] Alexandre Stewart,[1] Robert Roberts,[1] David R. Cox,[3] David A. Hinds,[3] Len A. Pennacchio,[4] Anne Tybjaerg-Hansen,[5] Aaron R. Folsom,[6] Eric Boerwinkle,[7] Helen H. Hobbs,[2,8] Jonathan C. Cohen[2,8†]

[1]Division of Cardiology, University of Ottawa Heart Institute, Ottawa K1Y4W7, Canada. [2]Donald W. Reynolds Cardiovascular Clinical Research Center and the Eugene McDermott Center for Human Growth and Development, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA. [3]Perlegen Sciences, Mountain View, CA 94043; USA. [4]Genomics Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA & U.S. Department of Energy Joint Genome Institute, Walnut Creek, CA 94598, USA. [5]Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Copenhagen DK-2100, Denmark. [6]Division of Epidemiology and Community Health, University of Minnesota, Minneapolis, MN 55454, USA. [7]Human Genetics Center and Institute for Molecular Medicine, University of Texas Health Science Center, Houston, TX 77030, USA. [8]Center for Human Nutrition and the [9]Howard Hughes Medical Institute at the University of Texas Southwestern Medical Center, Dallas, TX 75390, USA.

Science May 3, 2007

Sciencexpress Report

A Common Variant on Chromosome 9p21 Affects the Risk of Myocardial Infarction

Anna Helgadottir,[1*] Gudmar Thorleifsson,[1*] Andrei Manolescu,[1*] Solveig Gretarsdottir,[1] Thorarinn Blondal,[1] Aslaug Jonasdottir,[1] Adalbjorg Jonasdottir,[1] Asgeir Sigurdsson,[1] Adam Baker,[1] Arnar Palsson,[1] Gisli Masson,[1] Daniel Gudbjartsson,[1] Kristinn P. Magnusson,[1] Karl Andersen,[2] Allan I. Levey,[3] Valgerdur M. Backman,[1] Sigurborg Matthiasdottir,[1] Thorbjorg Jonsdottir,[1] Stefan Palsson,[1] Helga Einarsdottir,[1] Steinunn Gunnarsdottir,[1] Arnaldur Gylfason,[1] Viola Vaccarino,[3] W. Craig Hooper,[3] Muredach P. Reilly,[4] Christopher B. Granger,[5] Harland Austin,[3] Daniel J Rader,[4] Svati H. Shah,[5] Arshed A. Quyyumi,[3] Jeffrey R. Gulcher,[1] Gudmundur Thorgeirsson,[3] Unnur Thorsteinsdottir,[1] Augustine Kong,[1†] Kari Stefansson[1†]

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*These authors contributed equally to this work.

†To whom correspondence should be addressed. E-mail: augustine.kong@decode.is (A.K.); kstefans@decode.is (K.S.)

The global endemic of cardiovascular diseases calls for

chance (fig. S1). Hence, we further explored the SNPs that

- 'A hunt for genes has found that up to three quarters of people of Northern European descent have DNA that raises their risk for heart disease. "DECODE plans to bundle this discovery with other genetic variants into a DNA-based test for gauging inherited risk of heart attacks". The company said in a statement'
  - Reuters, May 3, 2007

Outline

- Introduction: Why are genetic tests a public health issue?
- Definition and Types of Genetic tests
- A Multidisciplinary Framework for the Evaluation of Genetic tests
- Examples and Applications

Secretary's Advisory Committee on Genetic Testing

Definition of a 'genetic test'

"... an analysis performed on human DNA, RNA, genes, and/or chromosomes to detect heritable or acquired genotypes, mutations, phenotypes, or karyotypes that cause or are likely to cause a specific disease or condition. A genetic test also is the analysis of human proteins and certain metabolites, which are predominantly used to detect heritable or acquired genotypes, mutations, or phenotypes."

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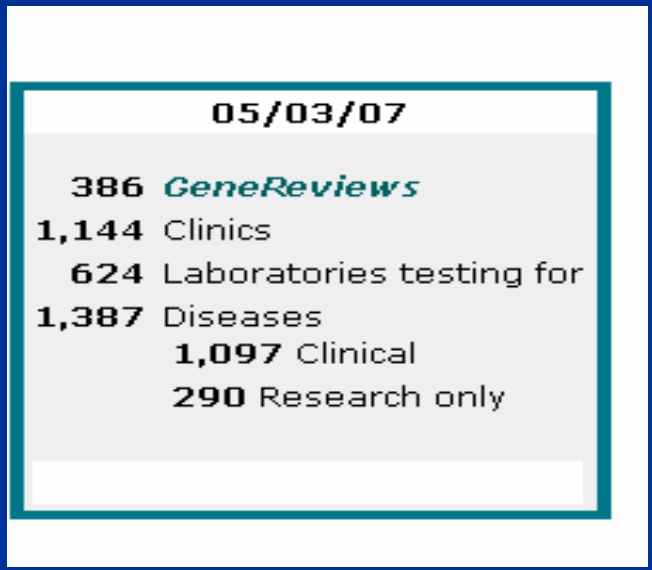
What is a Genetic Test?

GeneTests



- Diagnosis
  - Mainly rare, single-gene disorders
  - Chromosome abnormalities
  - Newborn screening
- Population-based applications
  - Carrier detection
  - Predictive testing
  - Pharmacogenomics
  - Susceptibility testing
- Potential for broad public health impact

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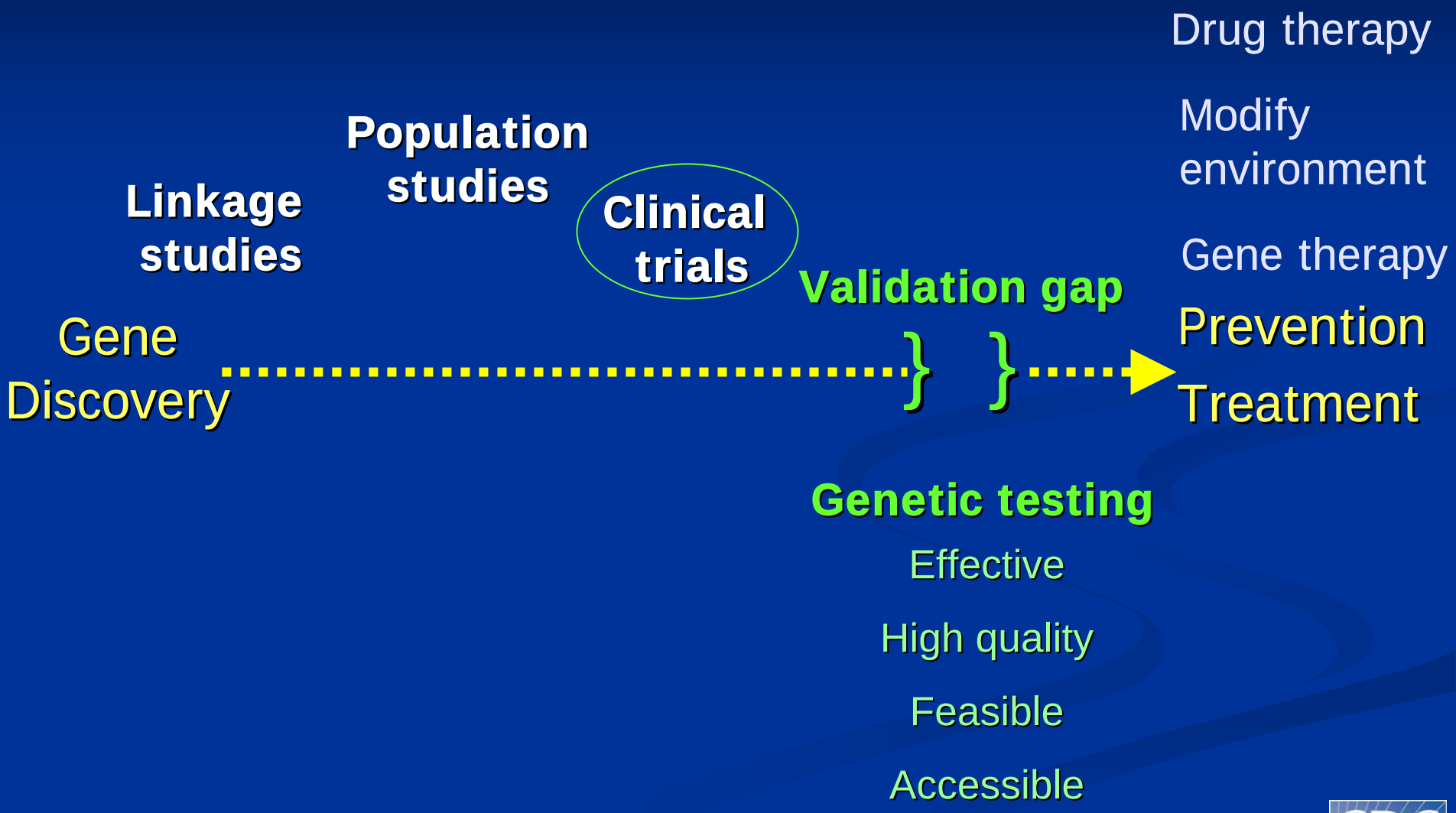
Translation Continuum for Population Health



Population level Questions for Use of Genetic Information in Clinical Practice and Disease Prevention

- How many people have this genetic variant?
- Is prevalence different in subgroups of the population?
- How much of the population burden of heart disease does it explain?
- Does the variant interact with modifiable risk factors?

Population level Questions for Use of Genetic Information in Clinical Practice and Disease Prevention

- How many people have this genetic variant?
- Is prevalence different in subgroups of the population?
- How much of the population burden of heart disease does it explain?
- Does the variant interact with modifiable risk factors?
- How good is the genetic test?
- What are the benefits? What are the harms?
- What are the economic implications of testing?
- How can we ensure quality testing and access?
- How can we educate providers and consumers?
- How can we measure health impact?

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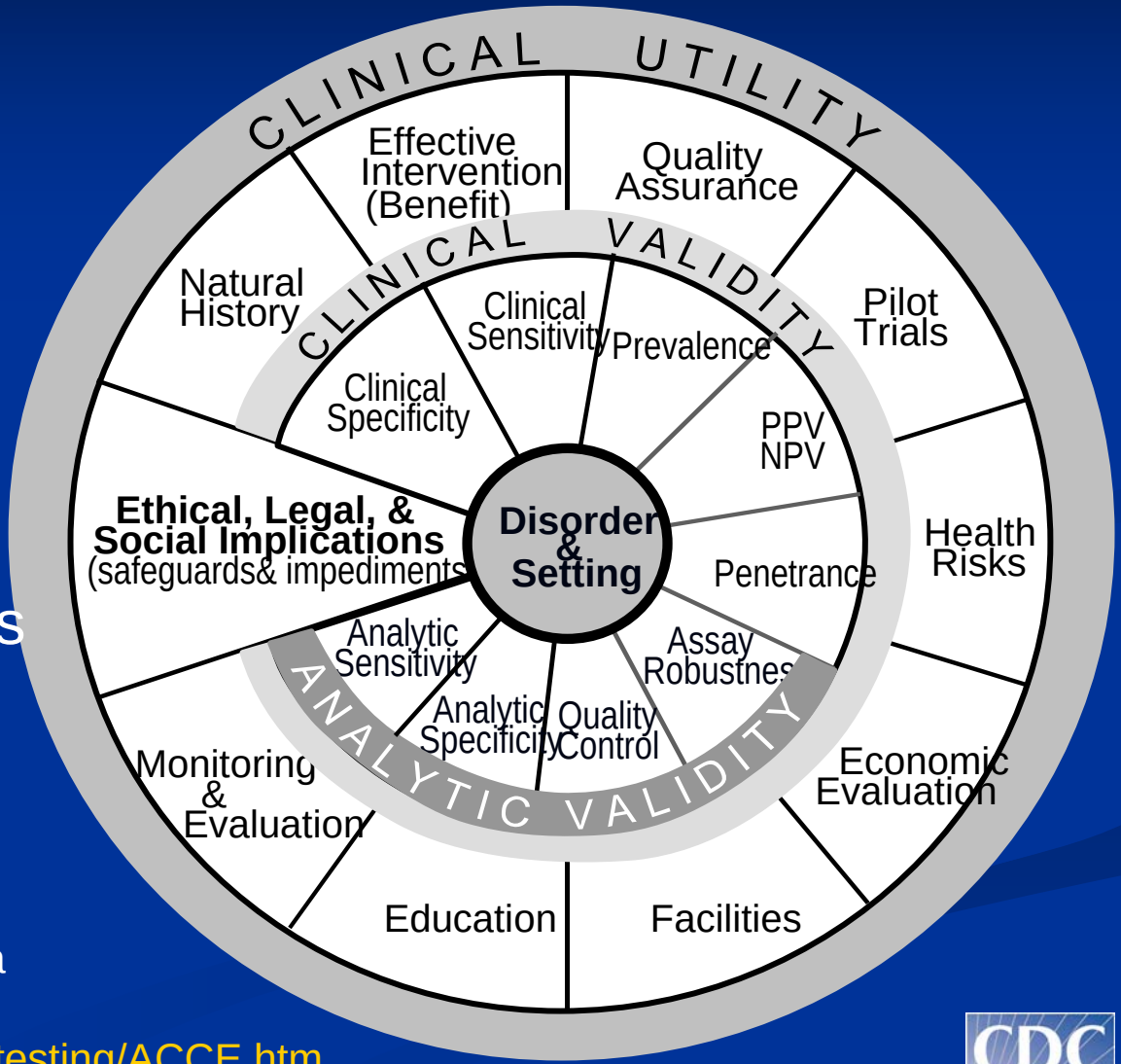
Knowledge Integration on Genetic Tests

- Collect, analyze and synthesize data
  - Establish test performance & value added
  - Identify ethical, legal & social issues
- Disseminate findings
  - Guide policy development
  - Educate health care providers & public
  - Identify public health and clinical research priorities

ACCE

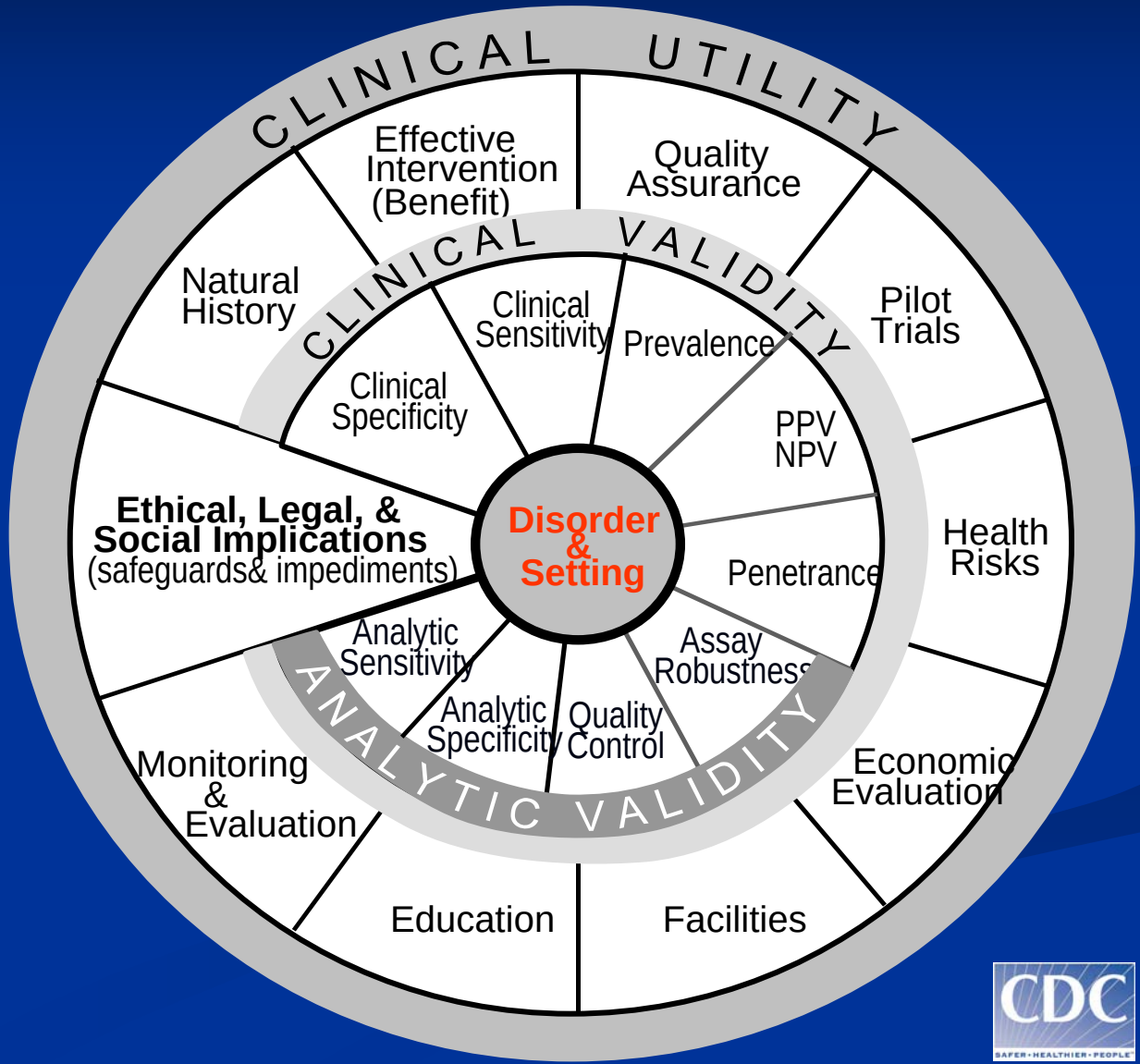
- Name reflects four components of evaluation
- Define test, disorder, and setting
- Analytic framework – 40+ targeted questions



Haddow JE, Palomaki GE: ACCE: A Model Process for Evaluating Data on Emerging Genetic Tests, 2003. http://www.cdc.gov/genomics/gtesting/ACCE.htm.

ACCE - Five Steps

- **Disorder**
  Problems can arise when the "disorder" is described in terms of the test
- **Setting**
  Validity & utility can vary by setting



Disorder & Setting: CFTR example

- Newborn screening
- Diagnosis
- Pre-symptomatic testing
- Clinical workups

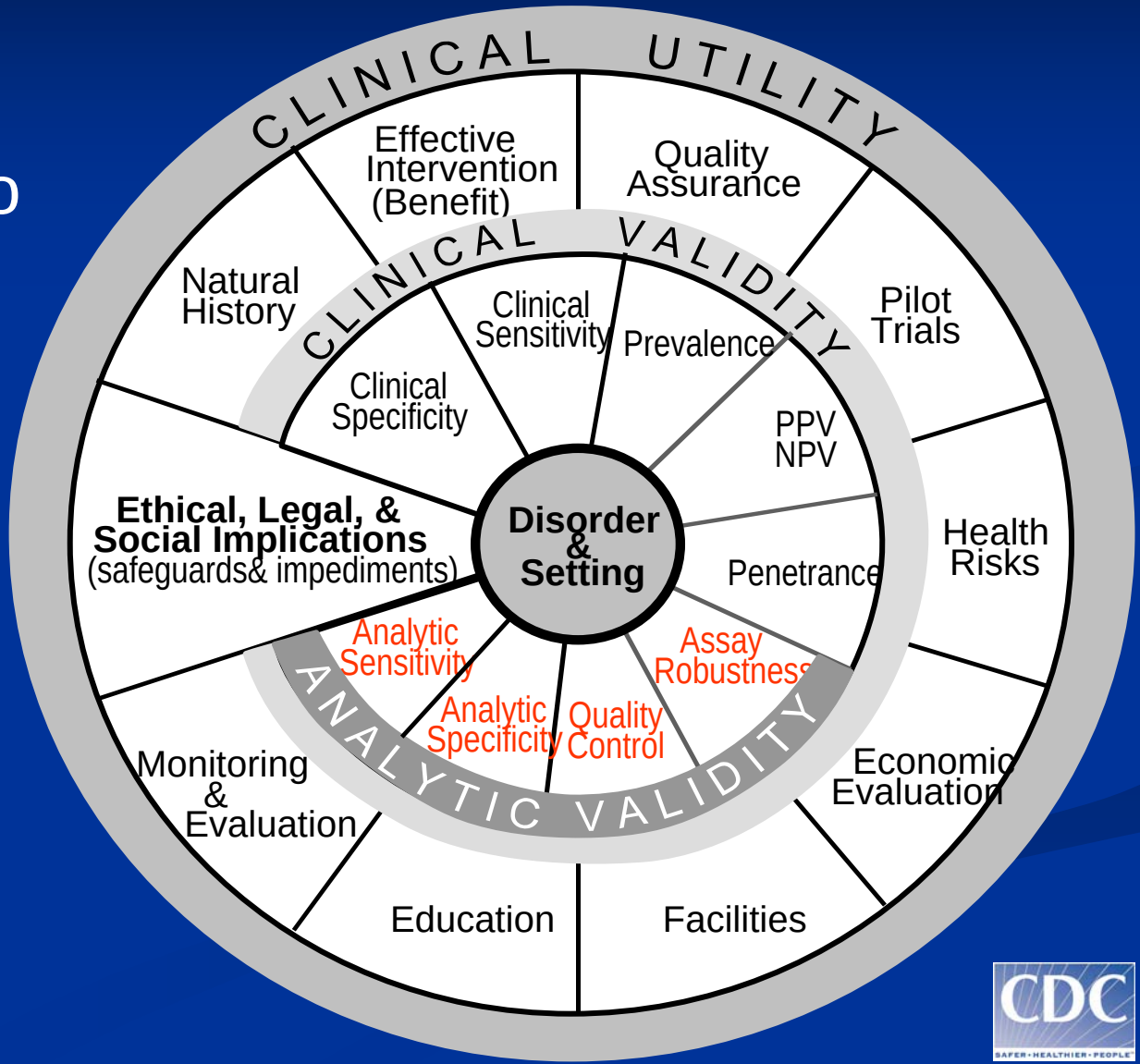
- Carrier testing
- Prenatal diagnosis

- Public health program
- Child w/ classical CF
- Testing before symptoms (usually 6-12 months)
- Chronic or recurrent sinus infections

- Before pregnancy
- Pregnant couples & fetal diagnosis

Analytic Validity

- Defines the ability of a test to accurately and reliably identify or measure the analyte or mutation of interest



Analytic Sensitivity & Specificity

Sensitivity: Proportion of positive results when variant/analyte is present

Specificity: Proportion of negative results when variant/analyte is absent

- Measures intrinsic performance of assay technology
- Part of laboratory validation before use
- Established using positive and negative control samples characterized using “gold standard” or by consensus
- Need to establish assay robustness and quality control

Issues in Evaluating AV

- Published data are limited
  - Control materials with confirmed genotypes
- Gaps in knowledge
  - Method-specific data
  - Some mutations never tested
- Reliability assessed in “real world” settings
- Comparability of methods & protocols between studies
- Consideration of pre- and post-analytic variables
  - Sample mix-ups
  - Data entry errors

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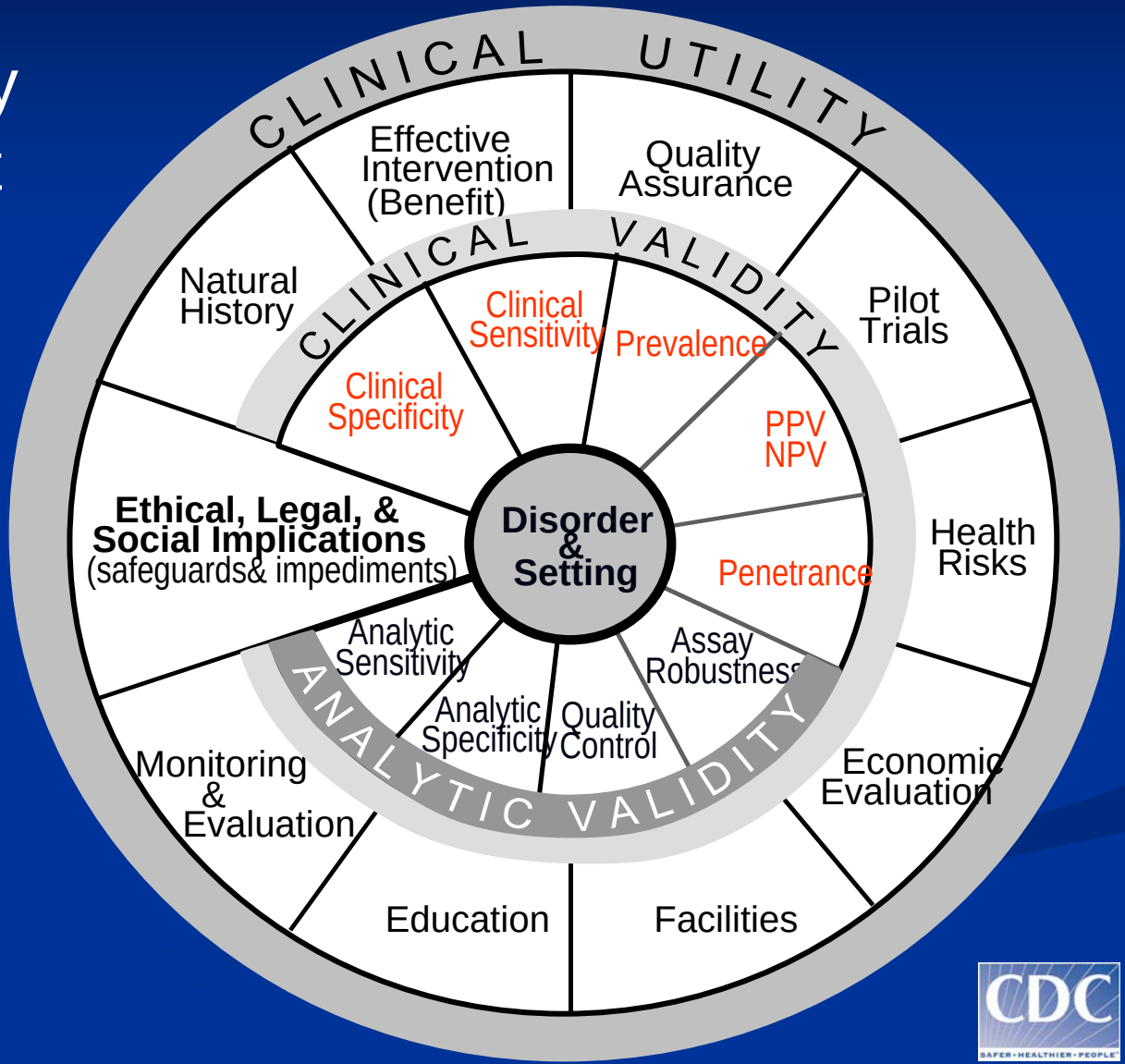
Clinical Validity

- Defines the ability of a test to detect or predict the phenotype or particular clinical outcome
- Elements build upon analysis of analytic validity



Clinical Sensitivity & Specificity: The Epi 2 by 2 Table Revisited

Test Result	Disease Phenotype: Yes	Disease Phenotype: No
Pos	A	B
Neg	C	D

Sensitivity: Proportion of positive test results in individuals who have the phenotype = A / (A+C)

Specificity: Proportion of negative test results in individuals who do not have the phenotype = D / (B+D)

Positive & Negative Predictive Values

		Disease Phenotype	
		Yes	No
Test Result	Pos	A	B
	Neg	C	D

Positive predictive value = A / (A+B)

Probability that person with positive test will have the phenotype

Negative predictive value = D / (C+D)

Probability that person with negative test will not have the phenotype

Positive & Negative Predictive Values

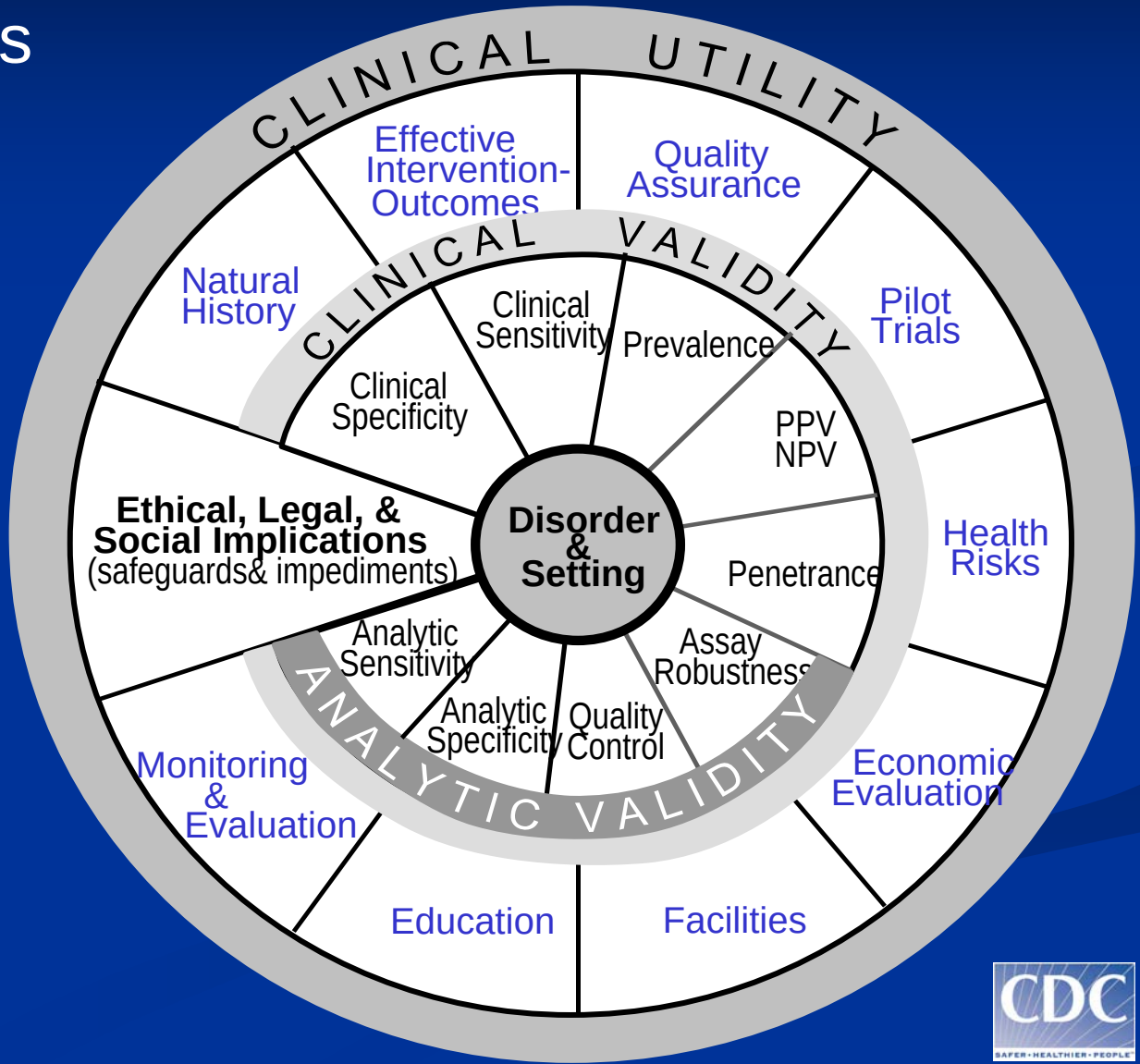
- Depend on
  - Definition of phenotype
  - Prevalence
  - Characteristics of tested population
  - Penetrance
    - Not every woman with a *BRCA1/2* mutation will develop breast cancer
  - Genetic heterogeneity
    - Absence of an identifiable *BRCA1/2* mutation does not eliminate the risk of breast cancer

Issues in Evaluating CV

- Case definitions may vary
- Small numbers or potentially biased populations
- Populations may not be stratified by variables such as gender, age, race/ethnicity
- Protocols may not be comparable (e.g., AV, confirmatory testing, clinical follow-up)
- Comparability of case and control populations
- Need for long-term follow-up for predictive tests
- Unknown impact of genetic and environmental modifiers

Clinical Utility

- Defining the risks and benefits associated with introduction into routine clinical practice
- Likelihood of improved health outcome

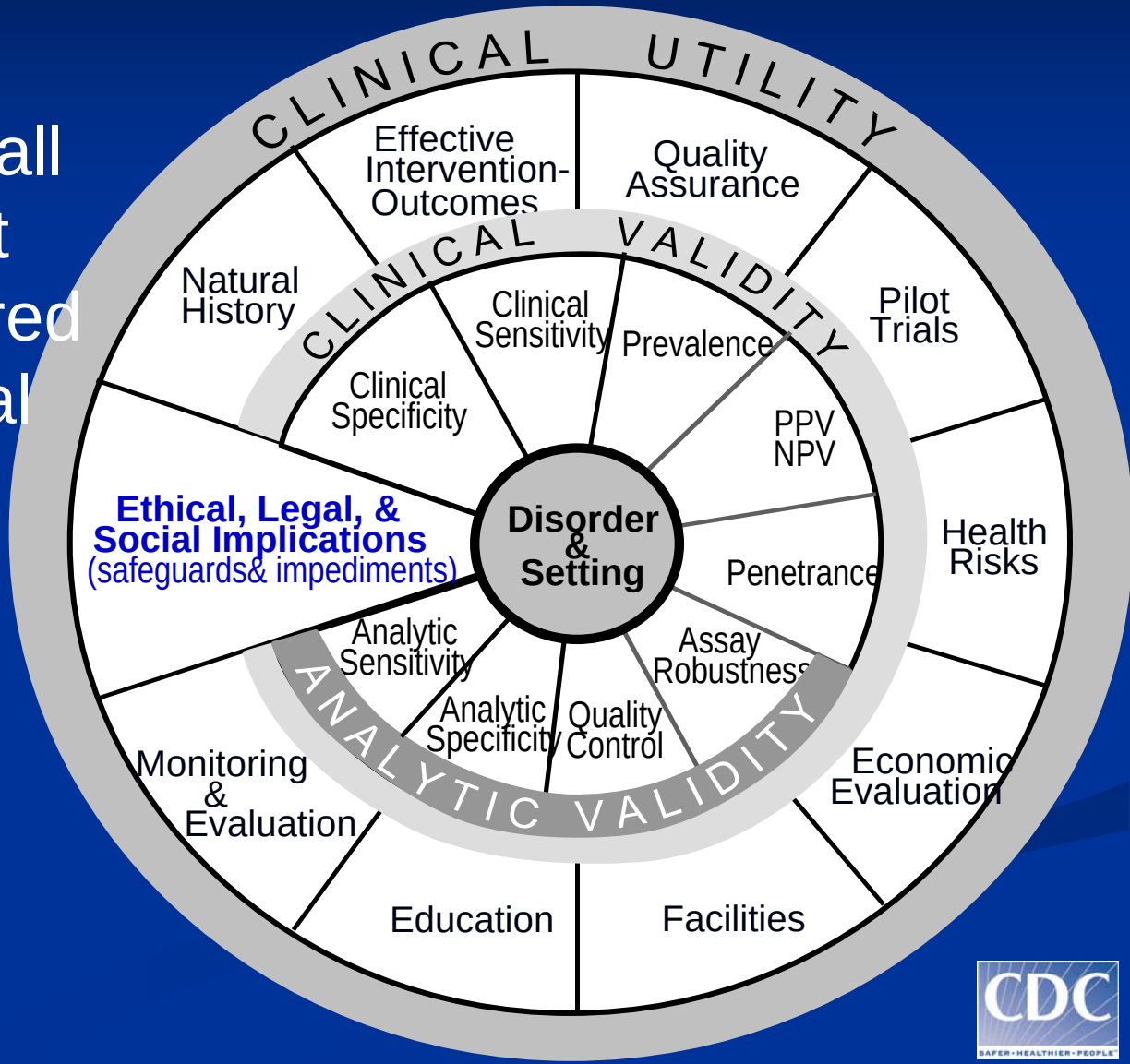


Clinical Utility

- Task Force on Genetic Testing, 1997
  - "Before …generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results."
- ACCE Project, 2000
  - Broader view - range of elements considered when evaluating risks and benefits in routine practice
- Grosse and Khoury (Genet Med 2006)
  - "What is the clinical utility of genetic testing?"

Ethical, Legal and Social Issues

- Penetrating pie slice-applies to all components but can be considered as part of clinical utility



Ethical, Legal & Social implications

- What is the occurrence of negative consequences?
  - Stigmatization or discrimination
  - Health disparities
  - Privacy/confidentiality
  - Personal/family/societal issues
- What safeguards have been described or are in place and effective?
- Legal issues to be considered
  - Consent, ownership and storage of data and samples
  - Patents & licensing or proprietary testing
  - Obligation to disclose

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Case Studies of Genetic Test Evaluation with a Focus on Clinical Utility

- Should we screen the general population for hereditary hemochromatosis?
- Should we screen women for Factor V Leiden before prescribing oral contraceptives?
- Should we screen children for TPMT deficiency before ALL rx with 6MP?
- What about type 2 diabetes susceptibility testing?

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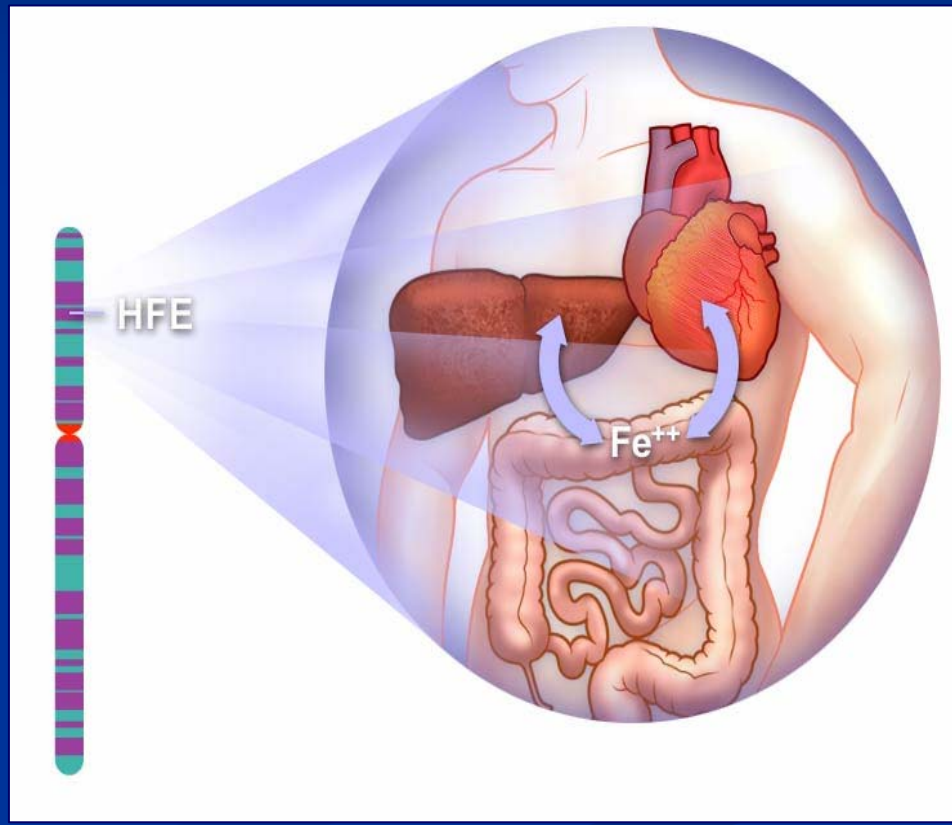
Case Study 1: Hereditary Hemochromatosis

- "The Genetic Disorder of the 21st Century"
- Iron Overload
- Multiple organ system
- Intervention: simple
- Gene on Chromosome 6
- CDC-NIH 1997 Expert Panel on Population Screening
- Developed & implemented a public health research Agenda



Prevalence of Hereditary Hemochromatosis Mutations in the USA

NHANES III

Genotype Prevalence (%)

Genotype/Group	White	Black	Hisp
C282Y/C282Y	0.3	.06	.03
H63D/H63D	2.2	0.3	1.1
C282Y/H63D	2.4	.06	0.2

Steinberg KK et al., JAMA 2001;285:2216

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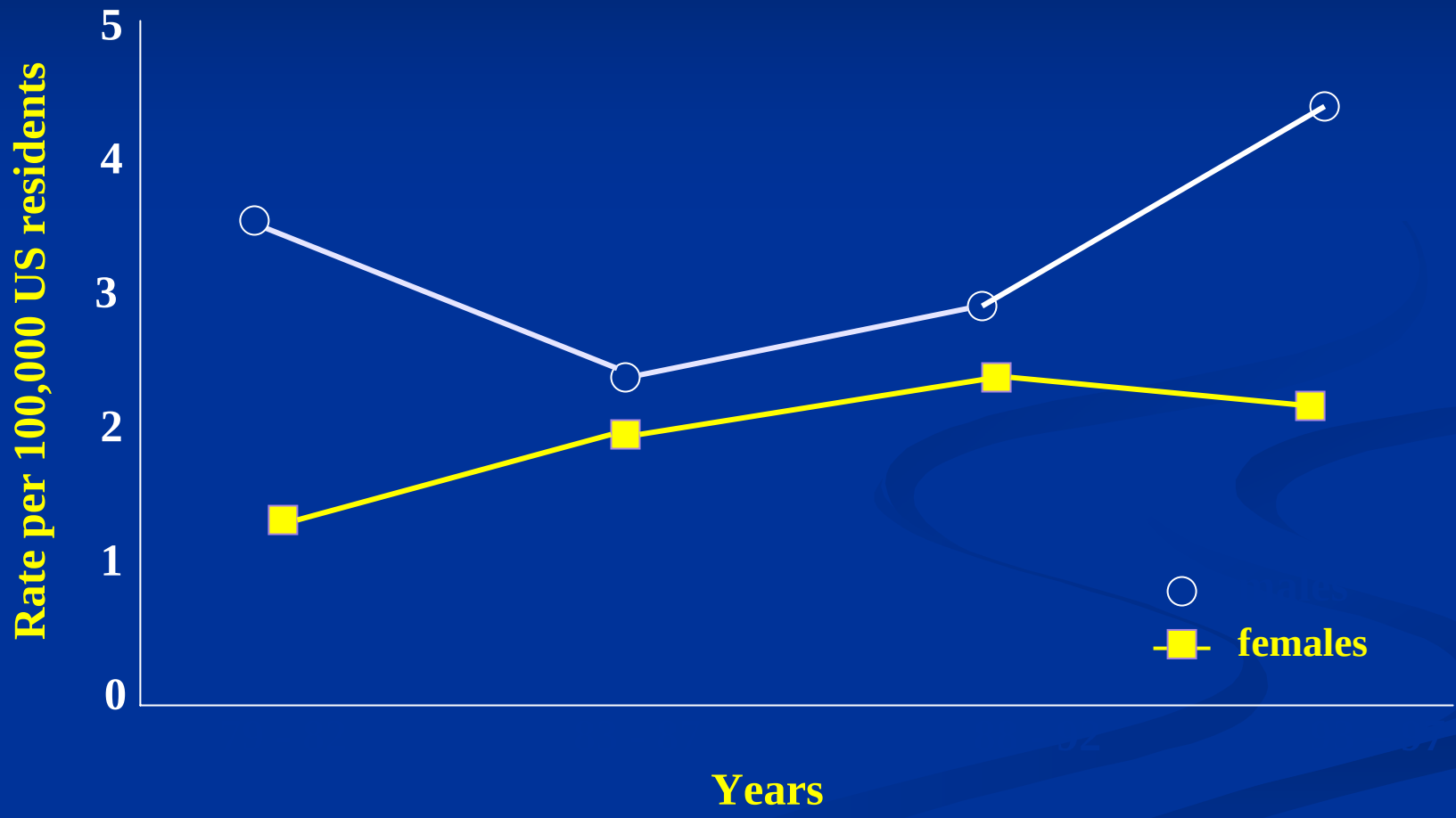
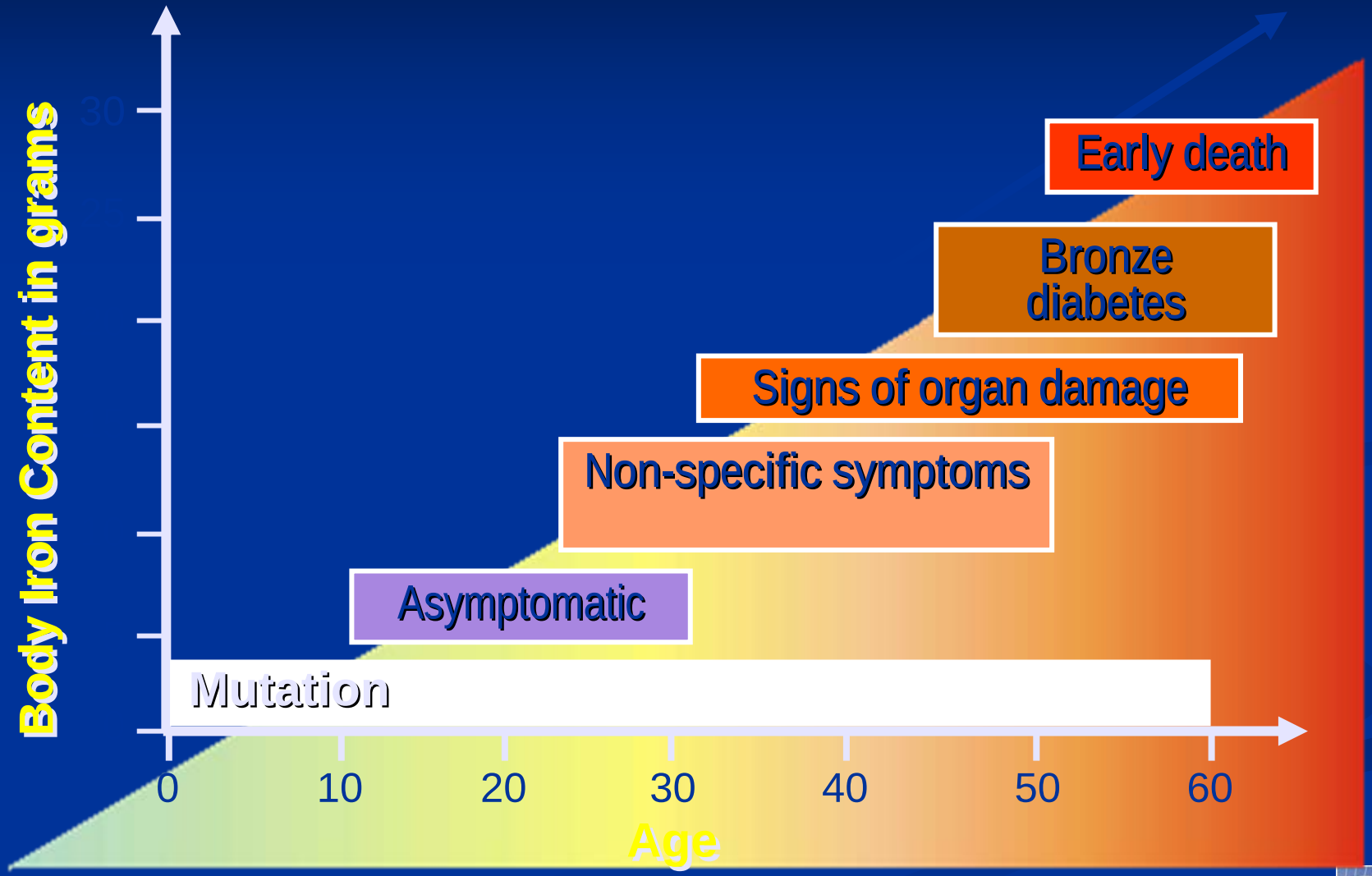
Hemochromatosis-Associated Hospitalizations, National Hospital Discharge Survey 1979-1997

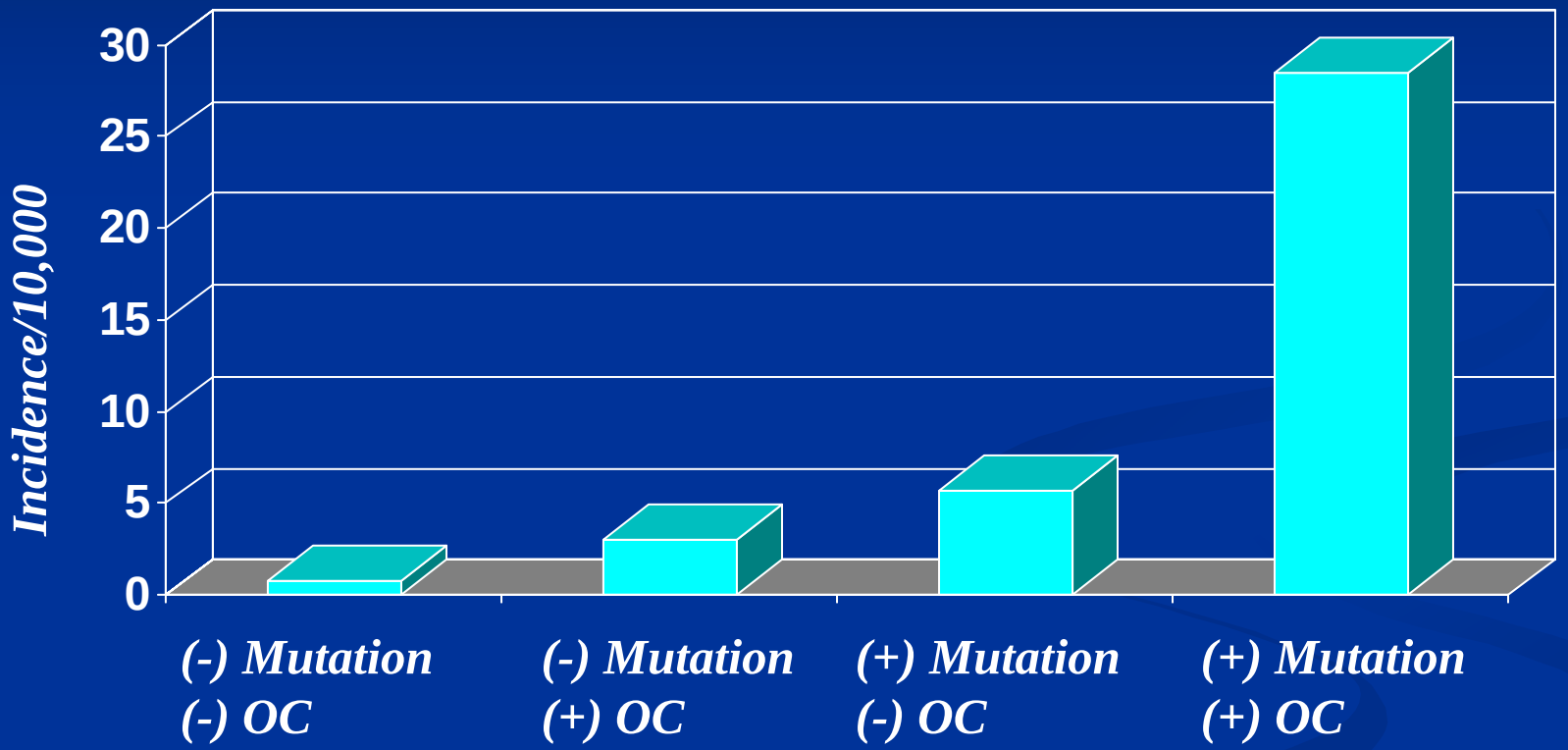


Brown al et al. Genet Med 2001;3:109-111

Natural History of Hereditary Hemochromatosis



Case Study 2:
Incidence of Venous Thrombosis Among Women by Factor V Leiden and Oral Contraceptive Use



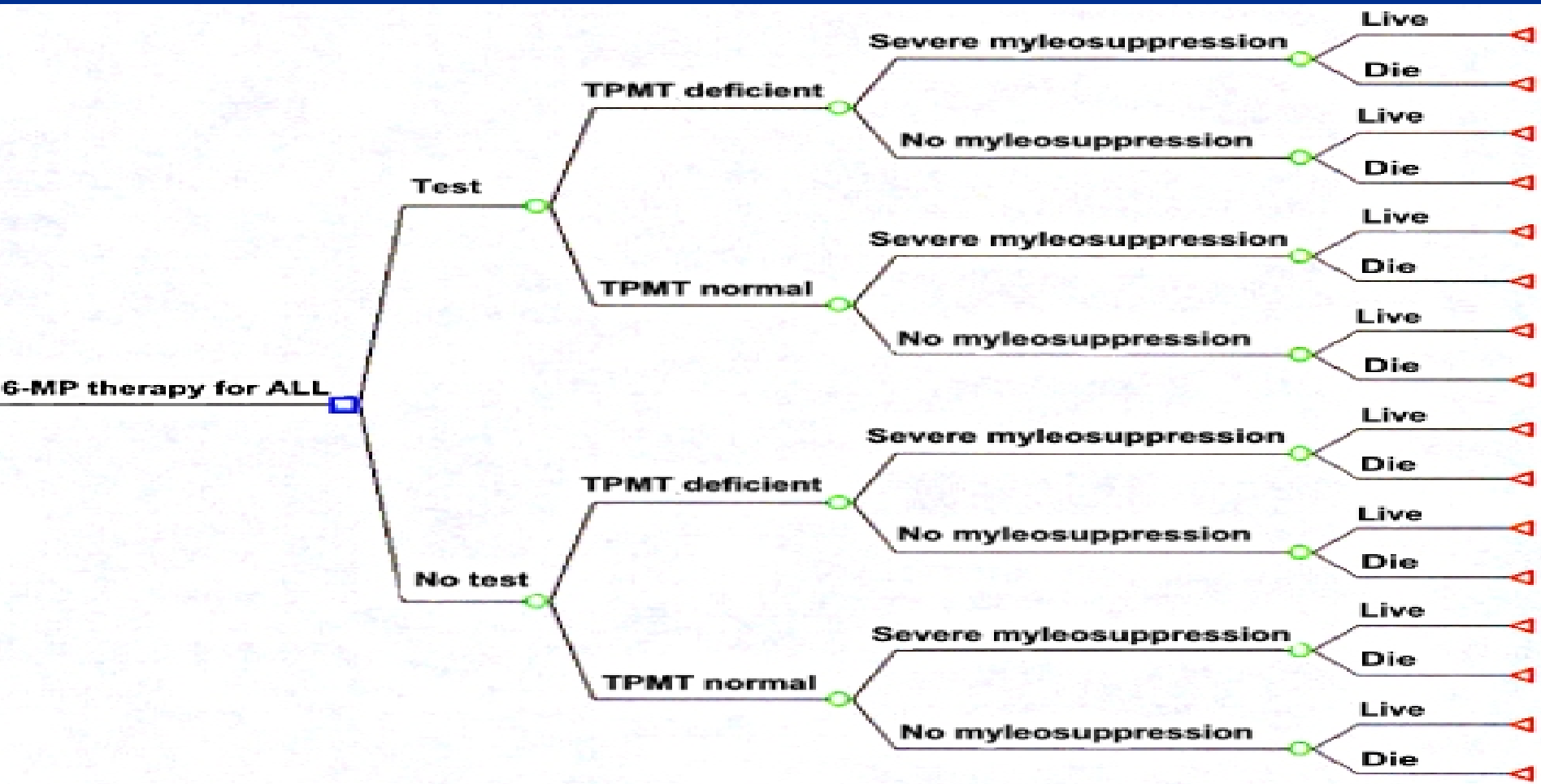
Mutation = Factor V Leiden; OC = Oral Contraceptives

Source: Adapted from Vandenbroucke JP, et al. BMJ 1996; 313: 1127-1130

"Screening for Factor V Leiden Mutation Before Prescribing Oral Contraceptives?"

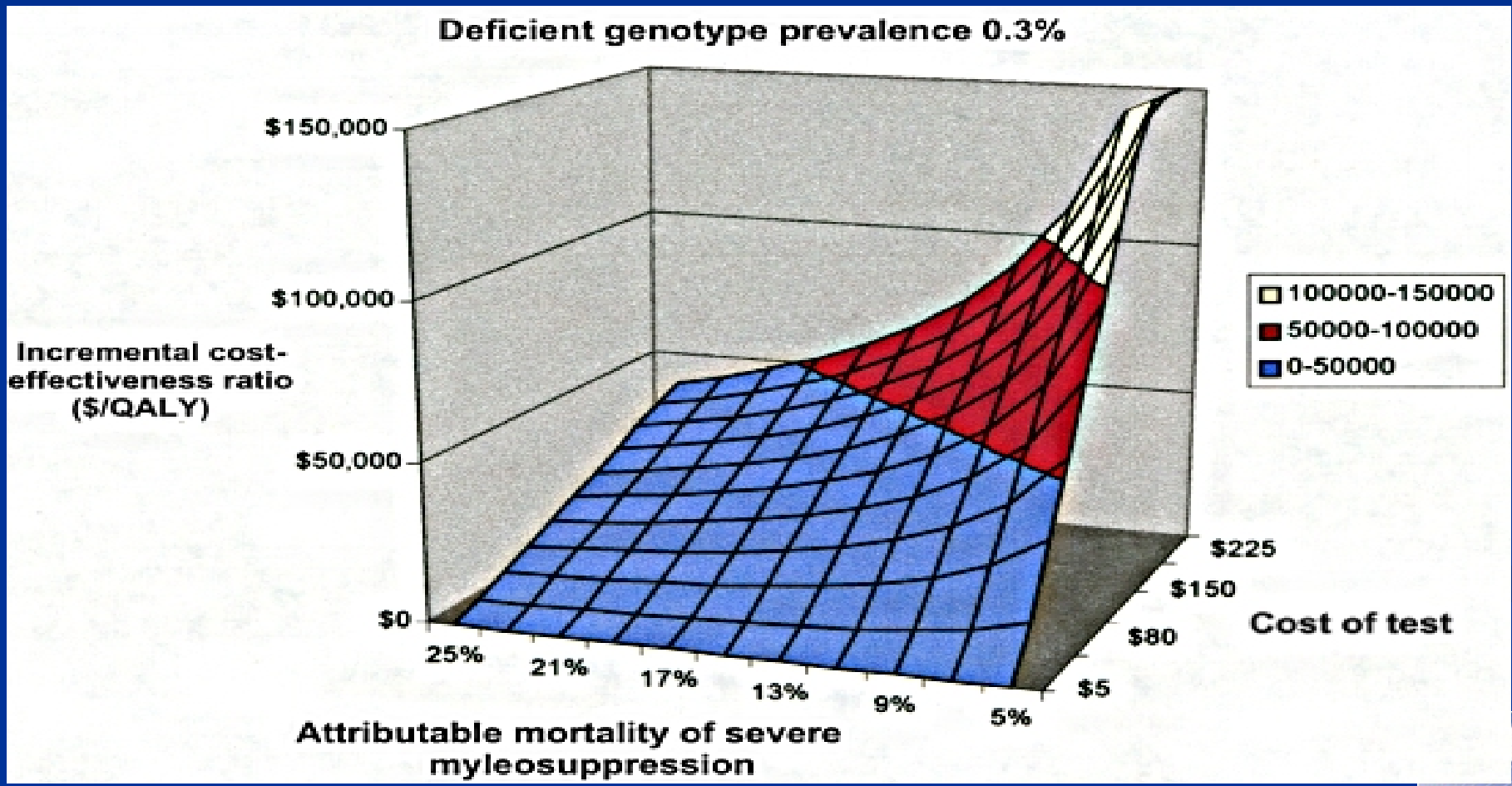
- Cost-effectiveness of screening for factor V Leiden mutation in women in the United States
- To prevent one venous thromboembolic death attributable to oral contraceptives in women with factor V Leiden mutation, >92,000 carriers need to be identified and stopped from using these pills
- Estimated charge to prevent this one death exceeds $300 million
  - Creinin MD et al. Fertil Steril 1999;72(4):646-51

Case Study 3:
Genetic Testing (TPMT) Decision Analysis Tree for 6-MP Therapy for ALL (Veenstra et al. AAPS Pharmasci 2000;2)



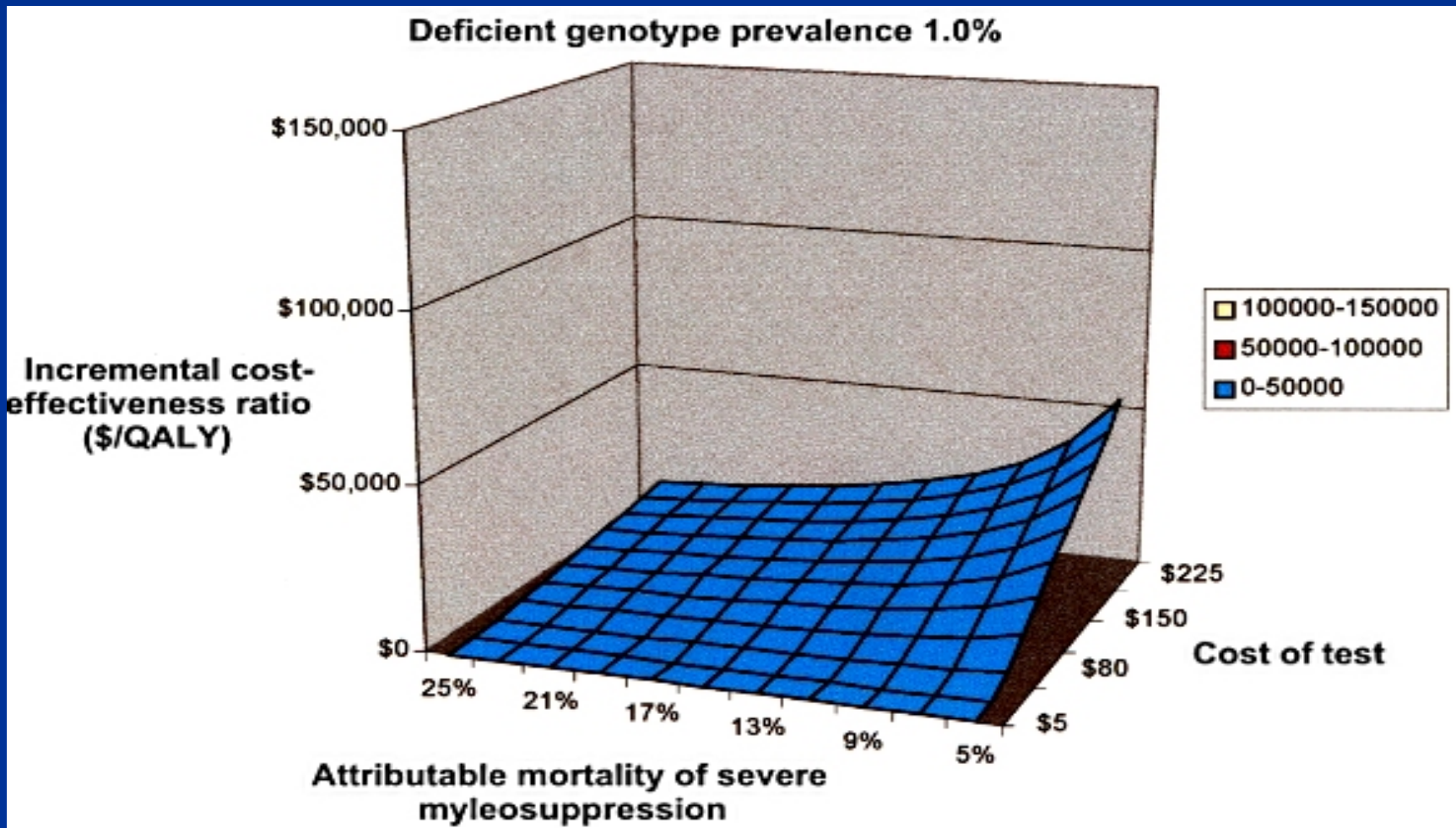
Influence of Cost of Genetic Test and Outcome Severity on Hypothetical Cost-Effectiveness of Genotyping

Genotype Prevalence=0.3%



Influence of Cost of Genetic Test and Outcome Severity on Hypothetical Cost-Effectiveness of Genotyping

Genotype Prevalence=1%



Framework for Evaluating the Potential Cost-Effectiveness of Pharmacogenomics

FACTORS	FACTORS for COST-EFFECTIVENESS
Outcome severity	+++
Drug monitoring	NA/difficult
Geno-Pheno Corr	+++
Assay	Rapid, inexpensive
Polymorphism	High allele frequency

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Genetic Prediction of Future Type 2 Diabetes

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1 Department of Clinical Sciences, Diabetes and Endocrinology, Lund University, University Hospital Malmö, Malmö, Sweden, **2** School of Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden, **3** Department of Medicine, Division of Diabetology, Helsinki University Hospital, Helsinki, Finland, **4** Folkhälsan Research Center, Institute of Genetics, Helsinki, Finland

Competing Interests: LG is a member of the editorial board of *PLoS Medicine*.

Author Contributions: VL extracted, genotyped, and analyzed the data, and drafted the report. PA and DA were responsible for the statistical analyses, MOM and MS for genotyping, and CS and TT for the phenotype data. LG designed the study and supervised all parts of the work including drafting the final report. All researchers took part in the revision of the report and approved the final version.

Academic Editor: Andrew Hattersley, Peninsular Medical School, Exeter, United Kingdom

Citation: Lyssenko V, Almgren P, Anevski D, Orho-Melander M, Sjögren M, et al. (2005) Genetic prediction of future type 2 diabetes. PLoS Med 2(12): e345.

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DOI:
10.1371/journal.pmed.0020345

ABSTRACT

Background

Type 2 diabetes (T2D) is a multifactorial disease in which environmental triggers interact with genetic variants in the predisposition to the disease. A number of common variants have been associated with T2D but our knowledge of their ability to predict T2D prospectively is limited.

Methods and Findings

By using a Cox proportional hazard model, common variants in the *PPARG* (P12A), *CAPN10* (SNP43 and 44), *KCNJ11* (E23K), *UCP2* (−866G>A), and *IRS1* (G972R) genes were studied for their ability to predict T2D in 2,293 individuals participating in the Botnia study in Finland. After a median follow-up of 6 y, 132 (6%) persons developed T2D. The hazard ratio for risk of developing T2D was 1.7 (95% confidence interval [CI] 1.1–2.7) for the *PPARG* PP genotype, 1.5 (95% CI 1.0–2.2) for the *CAPN10* SNP44 TT genotype, and 2.6 (95% CI 1.5–4.5) for the combination of *PPARG* and *CAPN10* risk genotypes. In individuals with fasting plasma glucose $\geq$ 5.6 mmol/l and body mass index $\geq$ 30 kg/m^2, the hazard ratio increased to 21.2 (95% CI 8.7–51.4) for the combination of the *PPARG* PP and *CAPN10* SNP43/44 GG/TT genotypes as compared to those with the low-risk genotypes with normal fasting plasma glucose and body mass index $<$ 30 kg/m^2.

Conclusion

We demonstrate in a large prospective study that variants in the *PPARG* and *CAPN10* genes predict future T2D. Genetic testing might become a future approach to identify individuals at risk of developing T2D.

Does Genetic Testing Really Improve the Prediction of Future Type 2 Diabetes?

A. Cecile J. W. Janssens, Marta Gwinn, Subramony Subramonia-Iyer, Muin J. Khoury

From their study on the genetic prediction of future type 2 diabetes (T2D), Lyssenko and colleague
"genetic testing might become a future ap
individuals at risk of developing T2D" [1].
most striking findings is an impressive 21.
risk for T2D in obese carriers of the *PPAR*
SNP43/44 GG/TT genotypes with elevate
glucose (FPG).

0270 February 2006 | Volume 3 | Issue

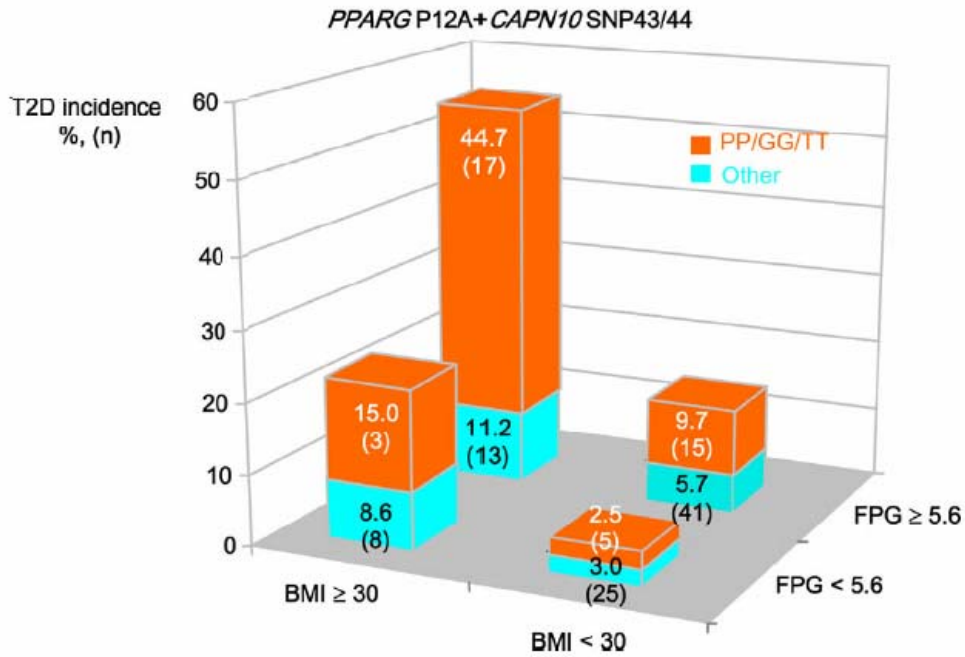
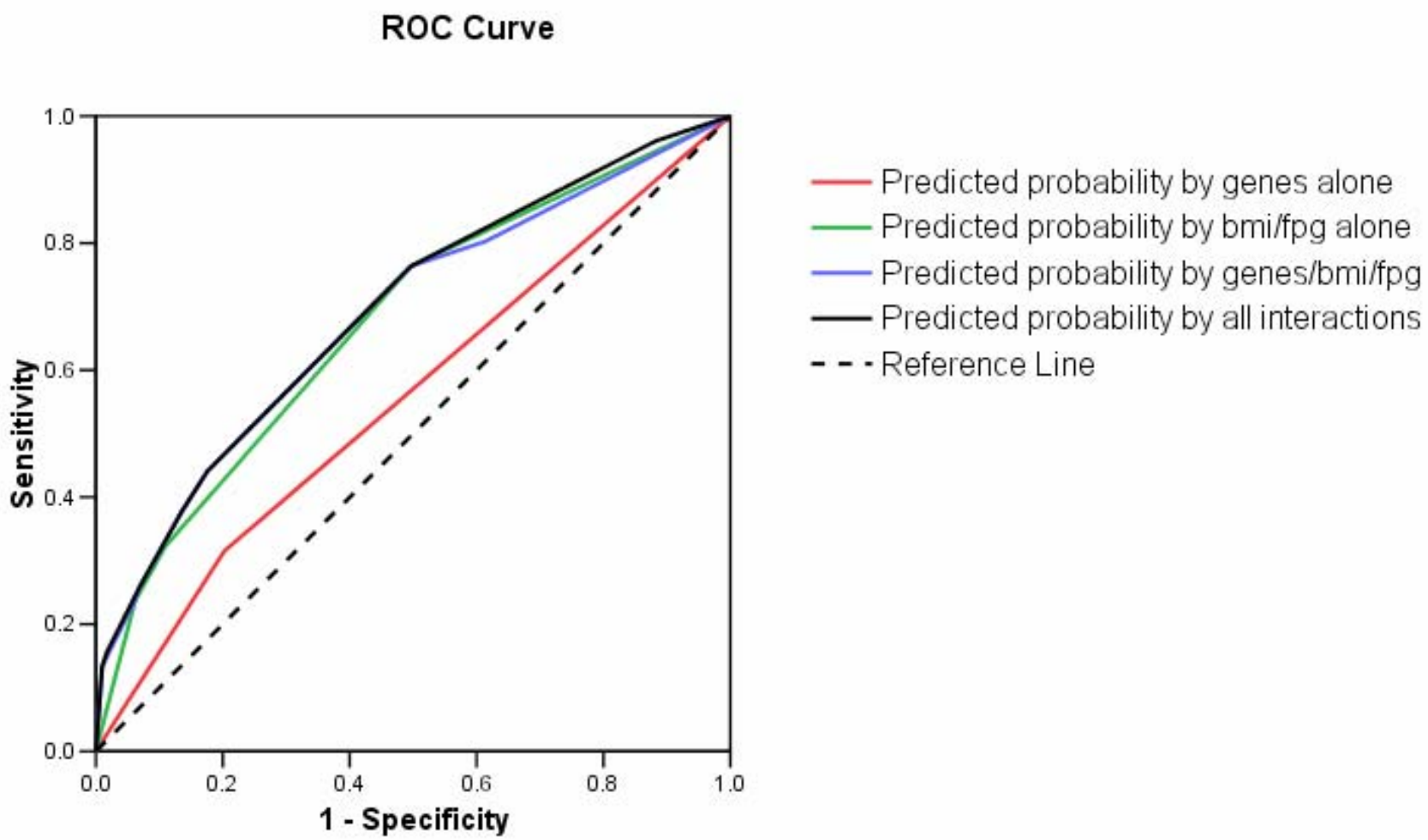
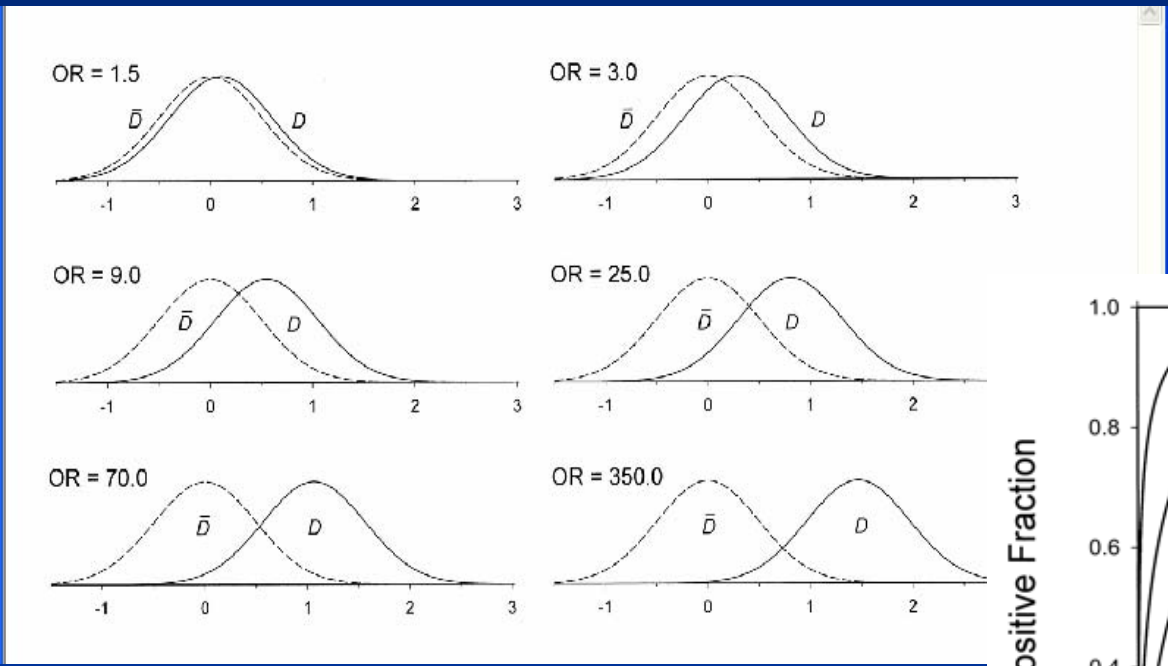


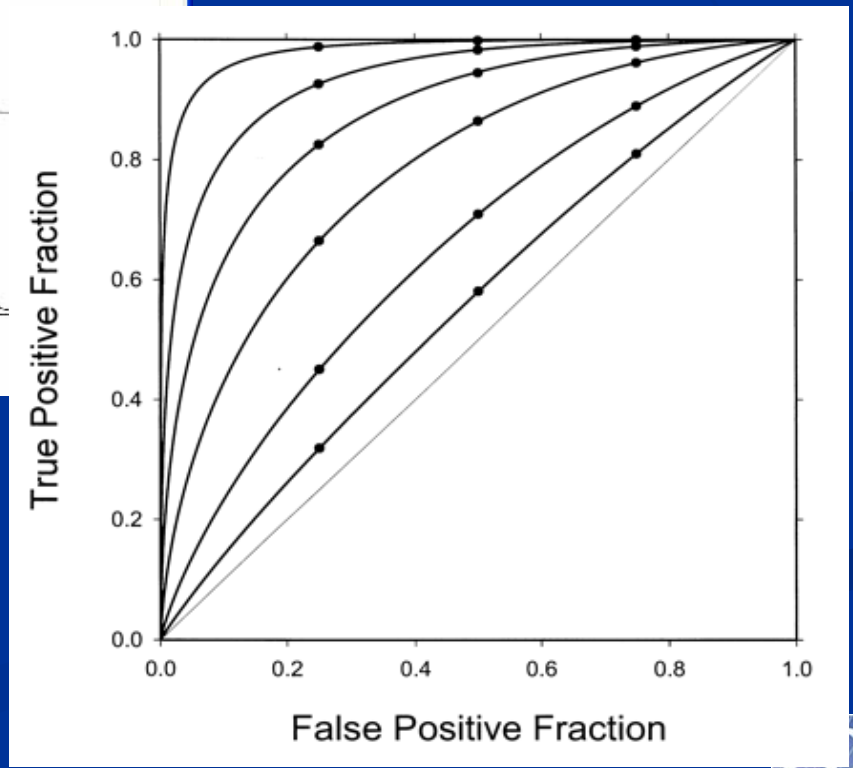
Figure 2. The Effects of Risk Genotypes of the *PPARG* P12A Polymorphism (PP), the Combination of *CAPN10* SNP43/44 (GG/TT), and the Combination of *PPARG* and *CAPN10* SNP43/44 (PP/GG/TT) Together with FPG and BMI for the Risk of Developing T2D

Multiple Genetic Testing by PPARG and CAPN10 SNP 43/44 Does Not Improve the Prediction of Type 2 Diabetes by BMI and FPG



Association vs. Classification: Relation Between Genetic Associations and Clinical Validity





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

Outline

- Introduction: Why are genetic tests a public health issue?
- Definition and Types of Genetic tests
- A Multidisciplinary Framework for the Evaluation of Genetic tests
- Examples and Applications

- Evidence-based Guideline Development