Regulation and Evaluation of Genetic Tests

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Outline of Talk

1. Preliminary issues
2. Regulation
3. Evaluation and the ACCE framework
4. Novel mechanisms

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Preliminary Issues

Two Concepts of Genetics

1. **Genetics as inheritance**
    - **single gene disorders inherited in a mendelian fashion**
    - **genetic services**
    - **familial association**

2. **Genetics as cell and molecular biology**
    - **the genetic component of all human traits and diseases**
    - **the basis of development**
    - **the science of DNA**
    - **modern biology**

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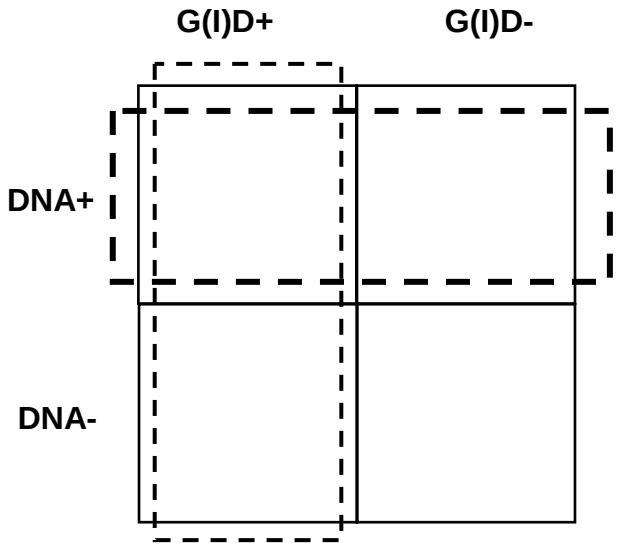
Genetic Tests and Genetic Diseases

Genetic diseases are conventionally regarded as those inherited according to known and accepted patterns of inheritance and for which the risk to family members is high. They are often referred to as inherited diseases.



Test for people with inherited disorders

Test based on DNA technology

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Definitions

The term genetic test is often used as a shorthand for describing a test to detect:

1. **a particular genetic variant (the ‘genotype of interest’)**
2. **for a particular disease**
3. **in a particular population**
4. **for a particular purpose**

Conceptual Issues (1)

CONTEXT MATTERS IN DECIDING THE EFFECTIVENESS OF A TEST

Population

Prior prevalence

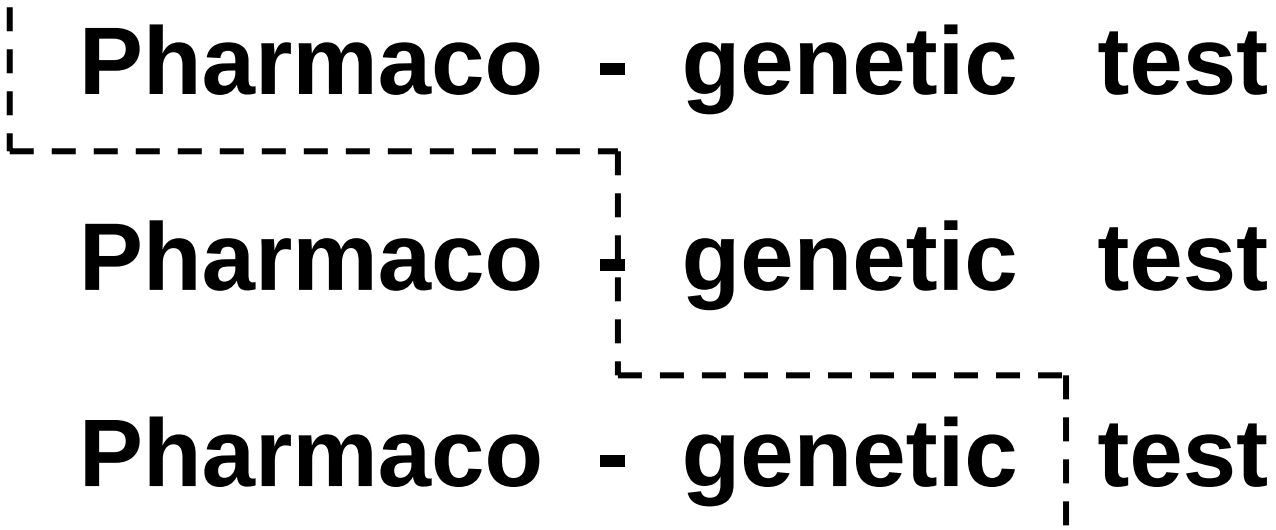
Purpose

Diagnosis, prediction, susceptibility, carrier

Testing, screening and profiling

The importance of the distinction

Conceptual Issues (2)



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Regulation

Evaluation and Regulation

1. **Evaluation and regulation are two distinct conceptual notions**
2. **Evaluation is a technical or methodological exercise**
3. **Regulation is a policy issue**
4. **Regulation may occur at several levels**

Levels of Regulation

Levels of Regulation

1. **Statutory**
   - legislation
   - regulation
   - codes of practice
2. **Resource allocation**
   - insurers
   - commissioners
   - health maintenance organisations
3. **Clinical**
   - clinical governance
   - physician and patient education

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Regulatory Issues

1. **Regulation of laboratories, regulation of technologies and regulation of tests**

2. **Regulation of products and regulation of services**

3. **Regulation of over the counter tests and regulation of professionally ordered tests**

Statutory Regulation

Regulation has been widely defined as any government measure or intervention that seeks to change the behaviour of individuals or groups. It can both give people rights (equal opportunities) or restrict their behaviour (compulsory use of seat belts)

However, there is now greater emphasis on (a) plurality in policy making (b) decentralisation of controls (c) use of non-statutory mechanisms

Prime Mininister's Speech – 26 May 2005

"In my view, we are in danger of having a wholly disproportionate attitude to the risks we should expect to run as a normal part of life. This is putting pressure on policy-making, not just in Government but in regulatory bodies, on local government, public services, in Europe and across parts of the private sector - to act to eliminate risk in a way that is out of all proportion to the potential damage. The result is a plethora of rules, guidelines, responses to 'scandals' of one nature or another that ends up having utterly perverse consequences."

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Principles of Better Regulation

- **Proportionate: Regulators should only intervene when necessary. Remedies should be appropriate to the risk posed, and costs identified and minimised.**
- **Accountable: Regulators must be able to justify decisions, and be subject to public scrutiny.**
- **Consistent: Government rules and standards must be joined up and implemented fairly.**
- **Transparent: Regulators should be open, and keep regulations simple and user friendly.**
- **Targeted: Regulation should be focused on the problem, and minimise side effects.**

Better Regulation Task Force

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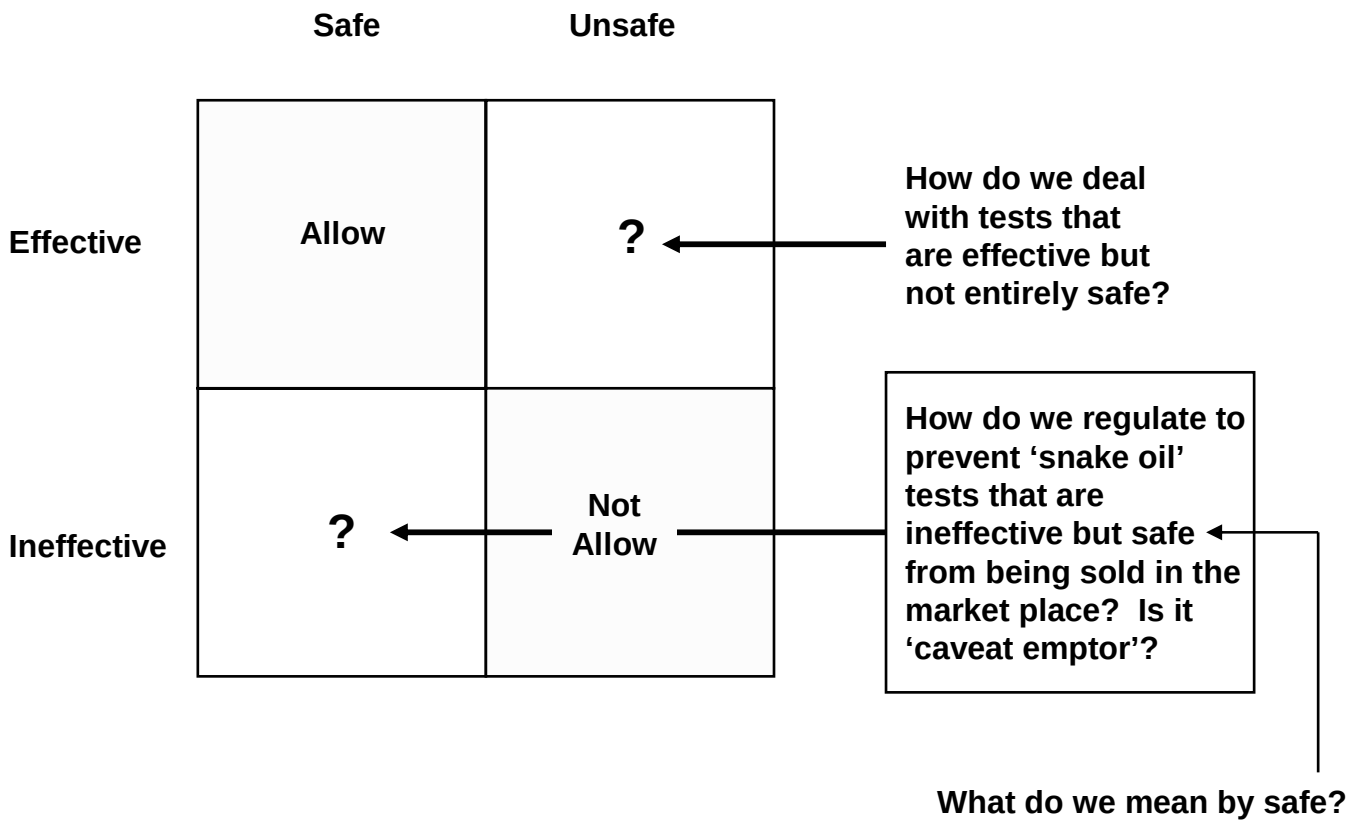
Evaluation and the ACCE Framework

The Fundamental Issue: Safety, Efficacy and Snake Oil



The ACCE Framework

1. A nalytical validity
2. C linical validity
3. C linical utility
4. E thical, legal and social

Analytical validity of a genetic test defines its ability to measure accurately and reliably the genotype of interest.

Clinical validity of a genetic test defines its ability to detect or predict the presence or absence of the phenotype, clinical disease or predisposition to disease

Clinical utility of a genetic test refers to the likelihood that the test will lead to an improved outcome

Ethical, legal and social implications of a genetic test

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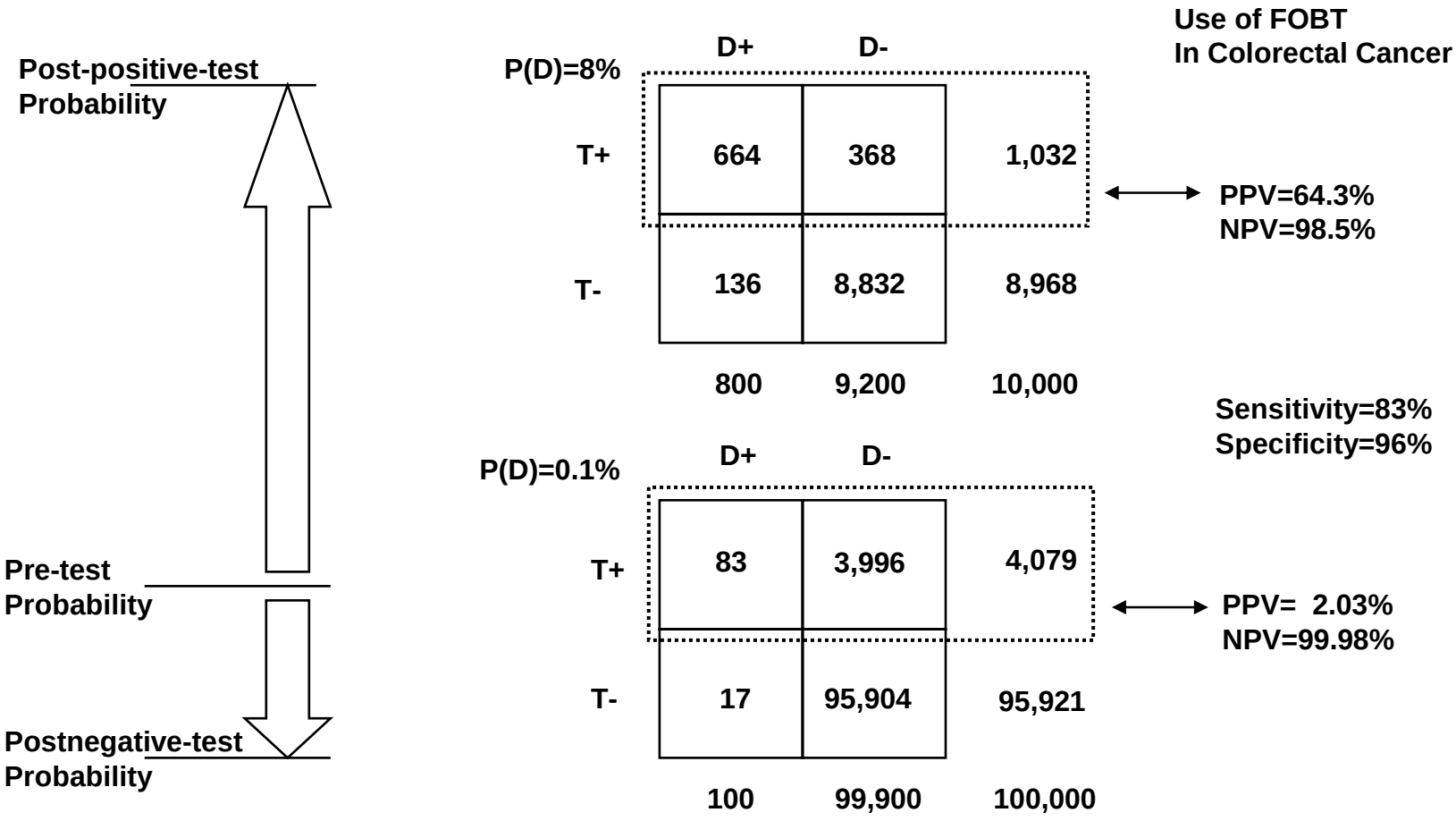
Importance of Pre-Test Probability



From Hunink & Glasziou: Decision Making in Health & Medicine

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Issues in Analytic and Clinical Validity

1. Disease definition – by genotype or phenotype
2. Genotype of interest - locus and allelic heterogeneity
3. Predictive and susceptibility testing
4. Penetrance – gene-gene and gene-environment effects
5. Two stage tests – mutation scanning followed by direct gene tests
6. Reference standards
7. Controls and small numbers

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Causes of False +ves and -ves

False Positive	False Negative
Sample mix-up	Sample mix-up
Technical errors	Technical errors
Imperfect analytic specificity	Imperfect analytic sensitivity
Reduced penetrance	Genetic heterogeneity
Clinical misclassification	Clinical misclassification

Clinical Utility

1. **Risks and benefits – safety and effectiveness**
2. **Clinical impact - likelihood of test result changing management or improving outcomes**
3. **Economic evaluation – cost-benefit**

Novel Mechanisms

Problems

1. **Existing regulatory and evaluative mechanisms carried out under the European Directive on In Vitro Devices are weak and by and large confined to the assessment of analytical validity**
2. **Manufacturers and service providers produce little convincing evidence for the clinical validity or utility of their tests**
3. **Special considerations apply to the assessment of predictive or susceptibility tests – it is not entirely practical or feasible to wait many years before outcome is definitively known**
4. **Commissioners, funders or reimbursers of health services are all under extreme financial pressure and will require evidence of effectiveness before they will consider investment in the test**
5. **No agreement exists on the processes and platforms for generating data (akin to Phase III studies) to inform test evaluation nor on the standards required**
6. **Huge amount of resources are spent on research studies to determine the scientific relationship between genetic variant and disease, but hardly any on the evaluation of novel tests and biomarkers for clinical use**

Solutions

1. **Establish platforms and processes for generating data and evidence to support the evaluation of tests**
2. **Establish mechanisms to set and agree standards for the clinical validity and utility of tests**
3. **Establish methodologies and facilities for the epidemiological evaluation of their clinical validity and utitlity**

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