
Global and European Issues in Genetic Test Evaluation and Regulation

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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

Genetics as DNA

“The terms “**genetic disease**” and “**genetic condition**” are used to denote a disease or condition that develops as a result of **alterations in the genetic make-up** of an individual. “ (Supplement to the 1993 Report on Genetic Screening. Nuffield Council on Bioethics 2006)

“We consider personal genetic information to be information about the **genetic makeup** of an identifiable person” (Inside Information. HGC 2002)

Defined in terms of physical alteration to the genome with the implication that the disease is to be characterised by data (direct) about DNA sequence or by data from which DNA sequence may be deduced (indirect)

Genetics as Inheritance

“What makes a test or screening programme genetic? A genetic test has been described as a test to detect the presence or absence of, or change in, a particular gene or chromosome.....In our view **the critical aspect to consider is the information....that a test reveals, rather than whether or not it analyses genetic material.** We have therefore **included tests that use non-genetic technology for a disorder that is clearly heritable or genetic, such as lipid analysis to test for familial hypercholesterolaemia, as well as tests that use DNA.** However, we have **excluded the use of tests that analyse genetic material for disorders that are not heritable, such as DNA analysis for bacterial pathogens or the analysis of tumours”**

Supplement to the 1993 Report on Genetic Screening. Nuffield Council 2006

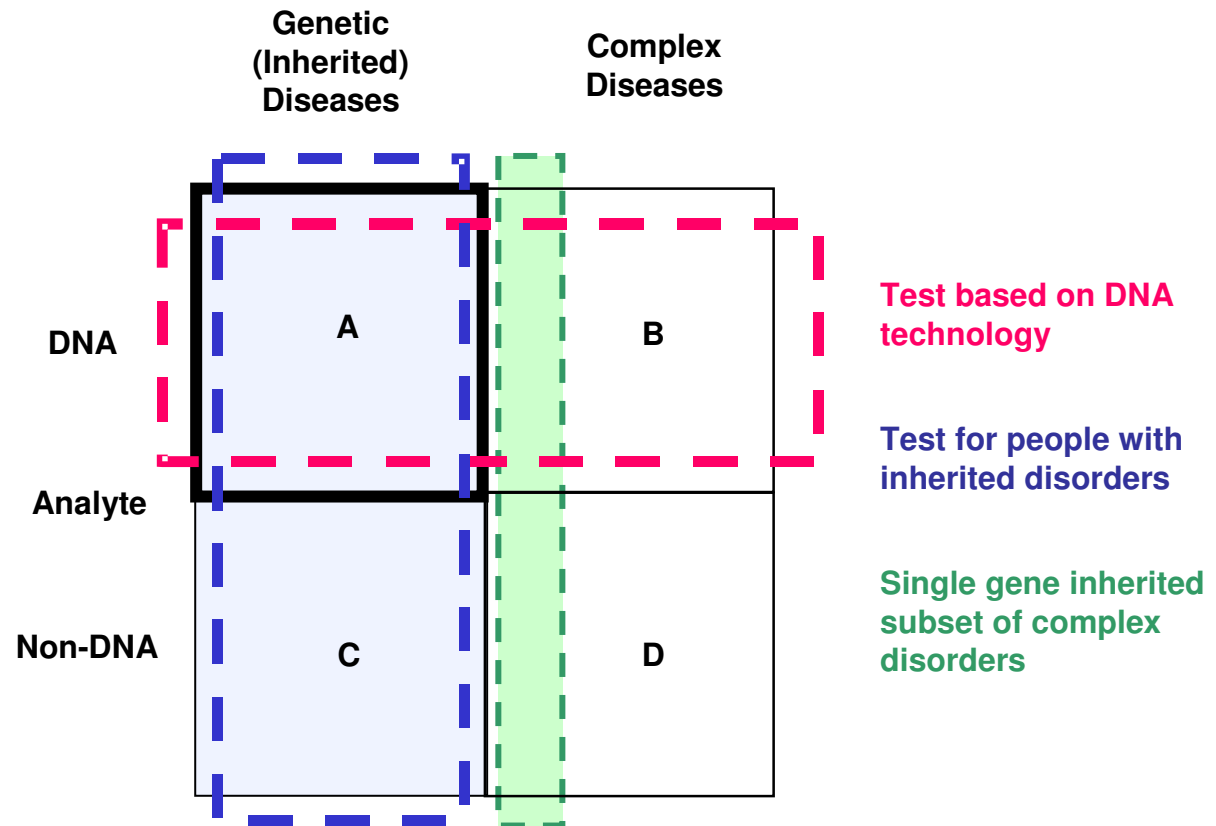
Defined in terms of the heritability of the disorder. Note that the concept of heritability applies to the disorder not the individual genes or nucleotides which are, unless de-novo mutations in somatic cells, all inherited

Definitions of Genetic Testing - The Disorder and The Analyte

ACGT Sep 97	Tests Supplied Directly to the Public	...the presence or absence of, or change in, a particular gene or chromosome
NIH Sep 97	US Task Force on Genetic Testing	... the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable-disease related genotypes, mutations, phenotypes or karyotypes for clinical purposes
HGAC Dec 97	Genetic Testing and Insurance	...based on DNA research , that can be used for diagnostic or pre-symptomatic testing
ACGT Sep 98	Late Onset Genetic Disorder	...the presence of, or alteration in, a particular gene, protein or a gene product in relation to a genetic disorder
HGAC Jul 99	Genetic Testing and Employment	...based on analysis of DNA or chromosomes , or on biochemical or haematological screening
GAIC Jun 00	Guidance	...the presence or absence of, or change in, a particular gene or chromosome

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**.



Assays and Tests

Assay

A method for determining the presence or quantity of a component

A method to analyze or quantify a substance in a sample

Test

A procedure that makes use of an **assay for a particular purpose**

Assays – Closed and Open Ended

Closed Assays

An assay in which the spectrum of mutations or abnormalities the assay is designed to test is specified in advance

Open Ended Assays

An assay in which the abnormality which is sought is not pre-defined – such as karyotype, ultrasound in pregnancy, mutation scanning across a gene, whole genome profiling

The Importance of Context

The term **genetic test** is often used as a shorthand for referring to an **assay to detect**:

1. a particular genetic variant
2. for a particular disease
3. in a particular population
4. for a particular purpose

CONTEXT MATTERS IN DECIDING THE EFFECTIVENESS OF A TEST

Population

Prior prevalence

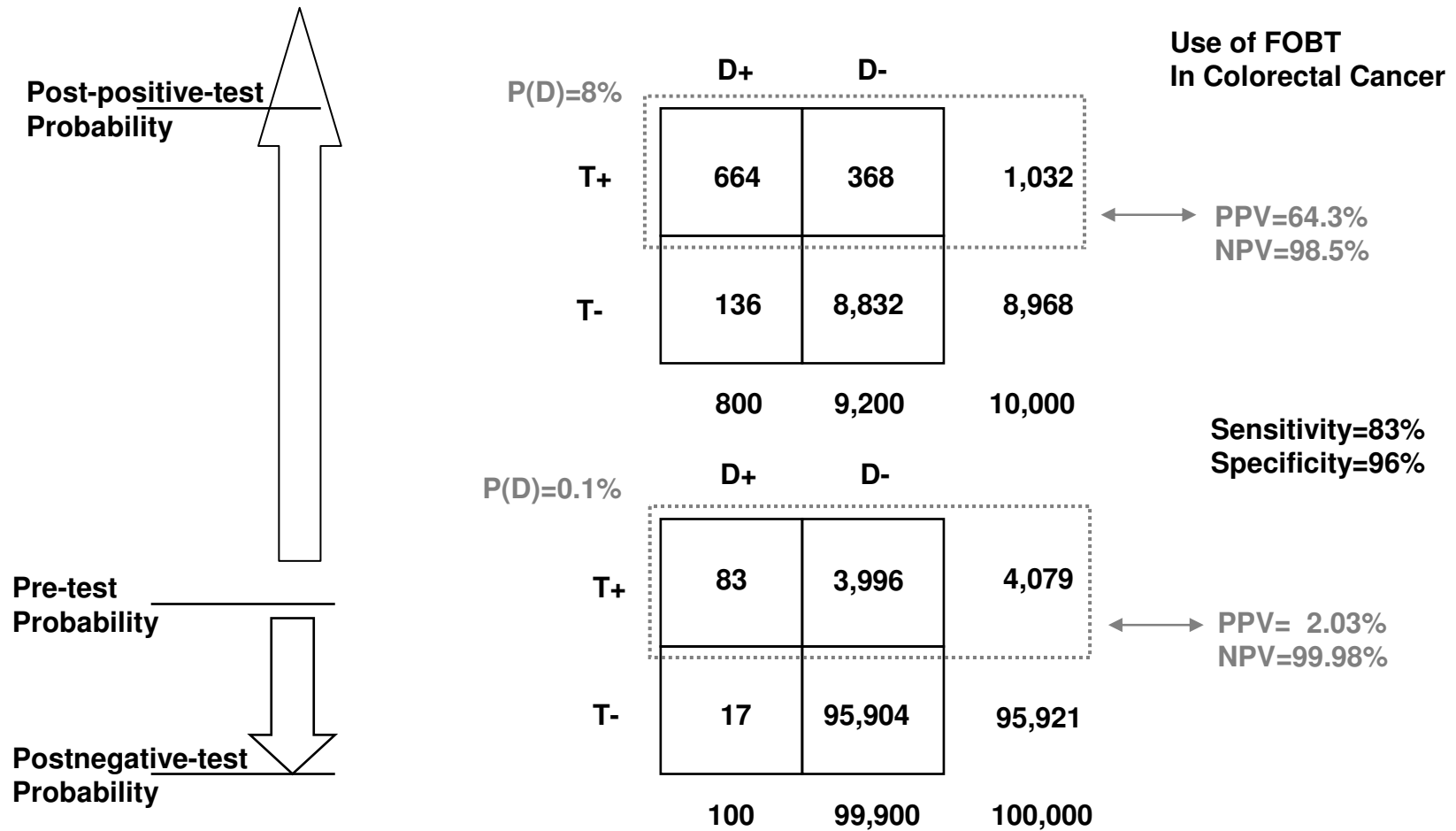
Purpose

Diagnosis, prediction, susceptibility, carrier

Testing and screening

The importance of the distinction

Importance of Pre-Test Probability



From Hunink & Glasziou: Decision Making in Health & Medicine

Biomarkers

Biomarker

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

None of the definitions for genetic testing refer to biomarkers other than DNA, RNA, chromosomes, proteins and gene products. There is no mention of either the use of clinical features or of radiological, electrophysiological or other forms of biomarker from which the presence of inherited disorders or of gene sequence might be inferred.

The ACCE Framework

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

The ACCE framework is equally applicable to other forms of molecular diagnostics or biomarkers

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

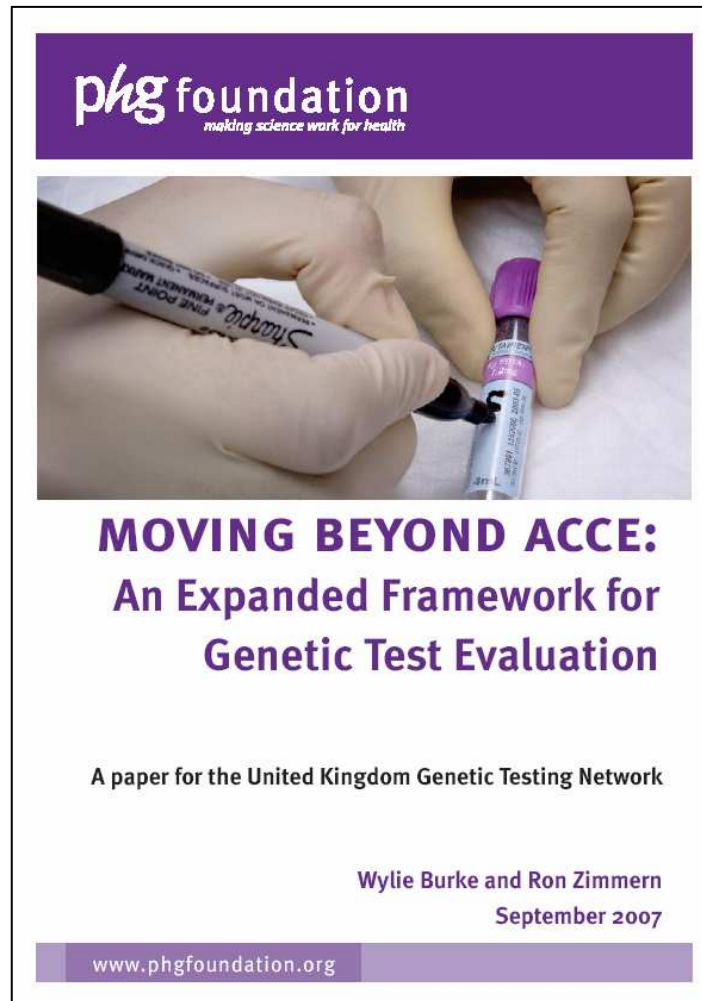
Clinical utility of a genetic test refers to the likelihood that the test will lead to an improved outcome

Ethical, legal and social implications of a genetic test

Clinical Validity

- 1. Evaluation of the relationship between genetic variant and disease**
- 2. Evaluation of the test performance in the clinical situation**

Dimensions of Clinical Utility (1)



This discussion framework was produced for, and has now been endorsed by the UK Genetic Testing Network

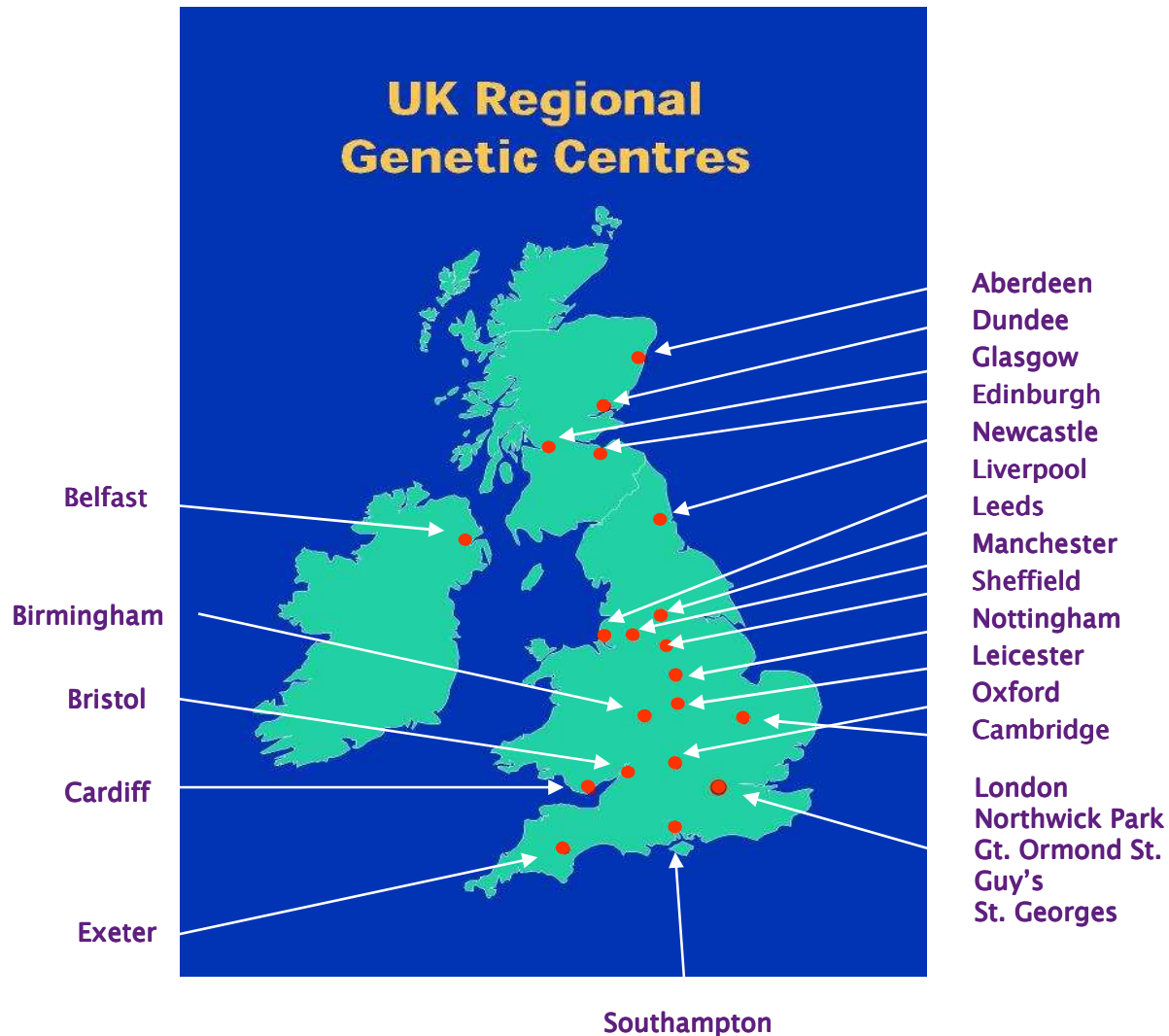
Dimensions of Clinical Utility (2)

Domain	Specific Element	Focus of evaluation
Pre-evaluation definition	<i>Test Definition</i>	Precise definition of: Genetic variants to be assayed Disorder Population Purpose
Assay		
	<i>Analytic validity</i>	Sensitivity Specificity PPV, NPV
	<i>Reliability and Reproducibility</i>	Kappa
Clinical Validity		
	<i>Gene-Disease Association</i>	Primary research Systematic review Meta-analysis
	<i>Clinical Test Performance</i>	Sensitivity, Specificity PPV, NPV, LR+, LR-, ROC

Dimensions of Clinical Utility (3)

Clinical Utility		
Test Purpose	<i>Legitimacy</i>	Conformity to the social preferences expressed in ethical principles, values, norms, mores, laws and regulations
	<i>Efficacy</i>	Potential of test and associated services to deliver health benefit
	<i>Effectiveness</i>	Actual delivery of health benefit in routine clinical setting
	<i>Appropriateness</i>	Expected health benefit exceeds expected negative consequences by a sufficiently wide margin that the test is worth doing
Feasibility of Test Delivery	<i>Acceptability</i>	Conformity to the wishes, desires, and expectations of patients and their families
	Economic <i>Efficiency</i>	Ability to lower the costs of care without diminishing benefits
	<i>Optimality</i>	Balancing improvements in health against costs of improvements
	<i>Equity</i>	Just and fair distribution of health care and its benefits among members of the population.

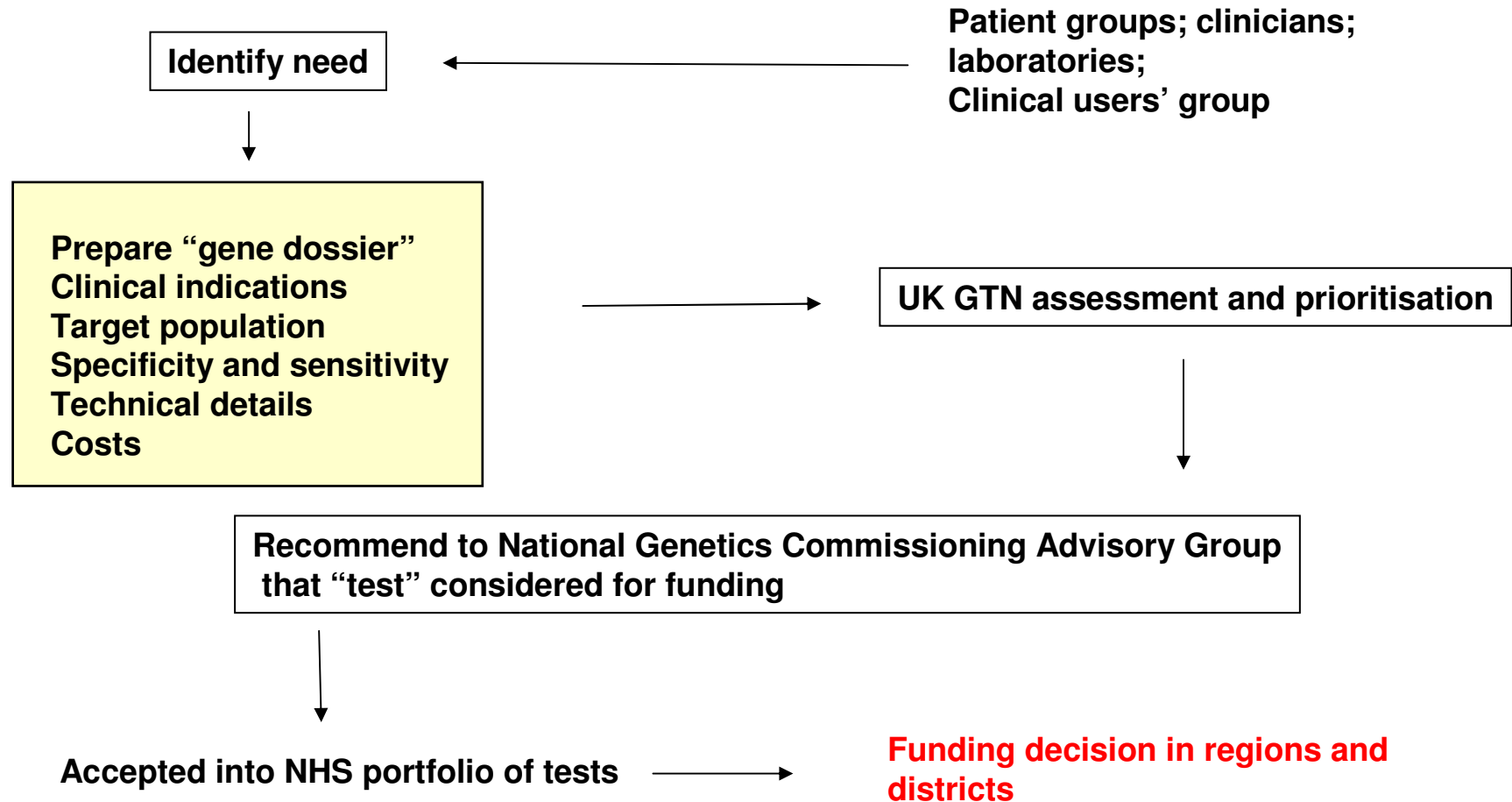
UK Regional Genetic Centres



The network was originally built on the integrated clinical and laboratory services of the regional genetic centres and the collaborative work in particular of the Clinical Molecular Genetics Society

Most serve 2 to 3 million people (range 0.5 to 5)

UKGTN Process



Gene Dossier Mechanism

NHS
UK Genetic Testing Network

UK Genetic Testing Network Steering Group
Procedures and Criteria for the Evaluation of genetic tests for NHS Service

1. Introduction

The UK Genetic Testing Network (UK) equips laboratory services for patient advice, diagnosis and management. The introduction or reviewing genetic tests (we call them 'disorders where Nucleic Acid' considered for adoption as mainstream NHS).

The Genetic Testing Network Steering Committee and the evaluation of genetic tests based on the recommendation of the NHS Service. The Steering group will identify tests recommended for inclusion in the commissioning process in its area.

It has been agreed that the Panel has evaluated every genetic test carried out particularly on how tests or those exist without review.

A Gene Dossier has been developed as a tool to be used by molecular genetic lab research colleagues, to initiate the process of the UK Genetic Testing Network. The evaluation use in a particular disease and in a specific population.

2. Criteria for Evaluation and Prioritisation

2.1 The UK GTN steering group prioritisation of tests for funding professional judgement. It is neither a technique or scoring systems (we compare the importance of, for all consequences with that of a more severe disabling phenotype. The these criteria are implicitly been through discussion and debate, so should be accorded to the tests submitted.

30 Nov 2004

NHS
UK Genetic Testing Network

UK Genetic Testing Network Steering Group
Proposal form for the evaluation of a genetic test for NHS Service:
Gene Dossier

This Gene Dossier has been developed as a tool to evaluate genetic tests and should be submitted to the UK GTN Steering Group.

This dossier is most likely to be used by molecular genetic laboratories, in collaboration with clinical and research colleagues where appropriate, to initiate the process of evaluation of tests to be part of the UK GTN genetic test portfolio. The evaluation of a test will be made in the context of its use in a particular disease and in a specified population.

The guidelines for completion of the proposal form can be found in the document "Procedures and Criteria for the evaluation of genetic tests for NHS Service" <http://www.ukgtntestnetwork.org.uk> or <http://www.ukgtn.org>

Additional written information from interested parties may be submitted in support of this application, but should accompany this form.

Further information on the completion of this form may be obtained from the UK GTN Lead Scientist, Dr Mevian Boxer, Tel: 020 206 6013, email: mevian.boxer@nhs.uk

To propose a test for consideration for possible inclusion in the Network Provision in the Commissioning Cycle 2005-2006, this form must be submitted by 30th July 2004.

Please return the form to: UK Genetic Testing Network
221, Erith Road
Bexleyheath
Kent
DA2 6HZ

August 2004

Assessed by a working group, ratified by whole Steering Group through consensus against published criteria

- Seriousness of condition
- Prevalence
- Purpose of test
- Population group
- Sensitivity, specificity and predictive value
- Utility
- Ethical, legal, social considerations
- Cost

www.ukgtn.nhs.uk

Evaluation and Regulation

Principles

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**
5. Regulating information and regulating its **use**

Levels

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

After Burke & Zimmern (2004). Nature Reviews Genetics 5, 955

Problems (1)

- 1. Tests are becoming more complex, both in terms of the technologies used and in their interpretation**
- 2. Tests are being made more generally available - to non specialists and direct to the public**
- 3. The assessment of predictive or susceptibility tests brings its own challenges – it is not entirely practical or feasible to wait many years before outcome is definitively known**
- 4. Existing regulatory and evaluative mechanisms carried out under the European Directive on In Vitro Devices are primarily concerned with the safety of devices and assays and by and large confined to the assessment of analytical validity**
- 5. Manufacturers and service providers produce little data as evidence for the clinical validity or utility of their tests**

Problems (2)

6. **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**
7. **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**
8. **There is no agreement on the processes and platforms for generating data (akin to Phase III studies) to inform test evaluation nor on the standards required**

Conclusion

- 1. Clarity about definition of genetic test**
- 2. Clinical validity is more than gene disease association**
- 3. Main problem is lack of data**
- 4. There is no policy about responsibility for data generation in test evaluation**