



Evaluation and Regulation of Tests

A Conceptual Approach

Dr Caroline Wright
Head of Science, PHG Foundation

Royal Academy of Engineers
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Outline

1. PHG Foundation and context
2. Conceptual issues
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4. Expanding ACCE
5. Regulatory issues
6. Regulatory frameworks
7. ELSI
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...with thanks to

Dr Ron Zimmern

Alison Hall

1. PHG Foundation

The **Foundation for Genomics and Population Health** is an independent international non-profit organisation working to achieve the responsible and evidence-based application of biomedical science for health

- Policy development
- Consultancy projects
- Research



UK Genetic Testing Network

ORGANISATION
FOR ECONOMIC
CO-OPERATION
AND DEVELOPMENT



1. PHG Foundation: Context

Recognition that problems and issues concerning the evaluation and regulation of **genetic tests are **generic**, applicable to all forms of diagnostics and biomarkers, and that the failure to address these matters are of major public health concern**

2. Conceptual issues: assays and tests

Assay

A method for determining the presence or quantity of a component

Test

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

2. Conceptual issues: assays and tests

The term **test** is used as a shorthand for referring to an **assay** used in the **context** of:

1. a particular disease
2. in a particular population
3. for a particular purpose

CONTEXT MATTERS IN DECIDING THE EFFECTIVENESS OF A TEST

Population

Prior prevalence

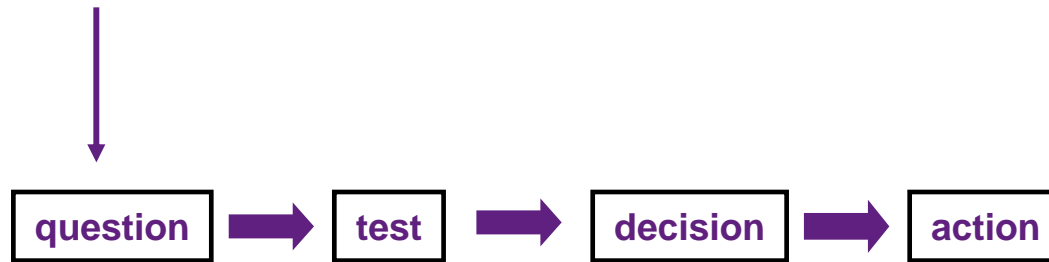
Purpose

Diagnosis, risk prediction, prognosis, guide to treatment, monitoring

The practical implication of the distinction is that whereas the evaluation of an **assay** is reasonably straightforward and allows broadly applicable standards to be established, the evaluation of a **test** is more complex and inherently less susceptible to standardisation. Each **test** is likely to need evaluation on a case by case basis – depending on purpose and population

2. Conceptual issues: why do a test?

Purpose and context are all important



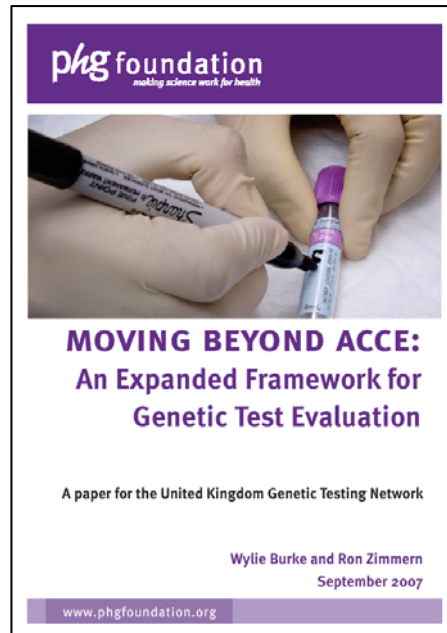
Patient



Outcome

The effectiveness of an intervention is the extent to which it achieves the objective (purpose) for which it was designed

3. The ACCE Framework



Analytical validity of a test defines its ability to measure accurately and reliably the component of interest

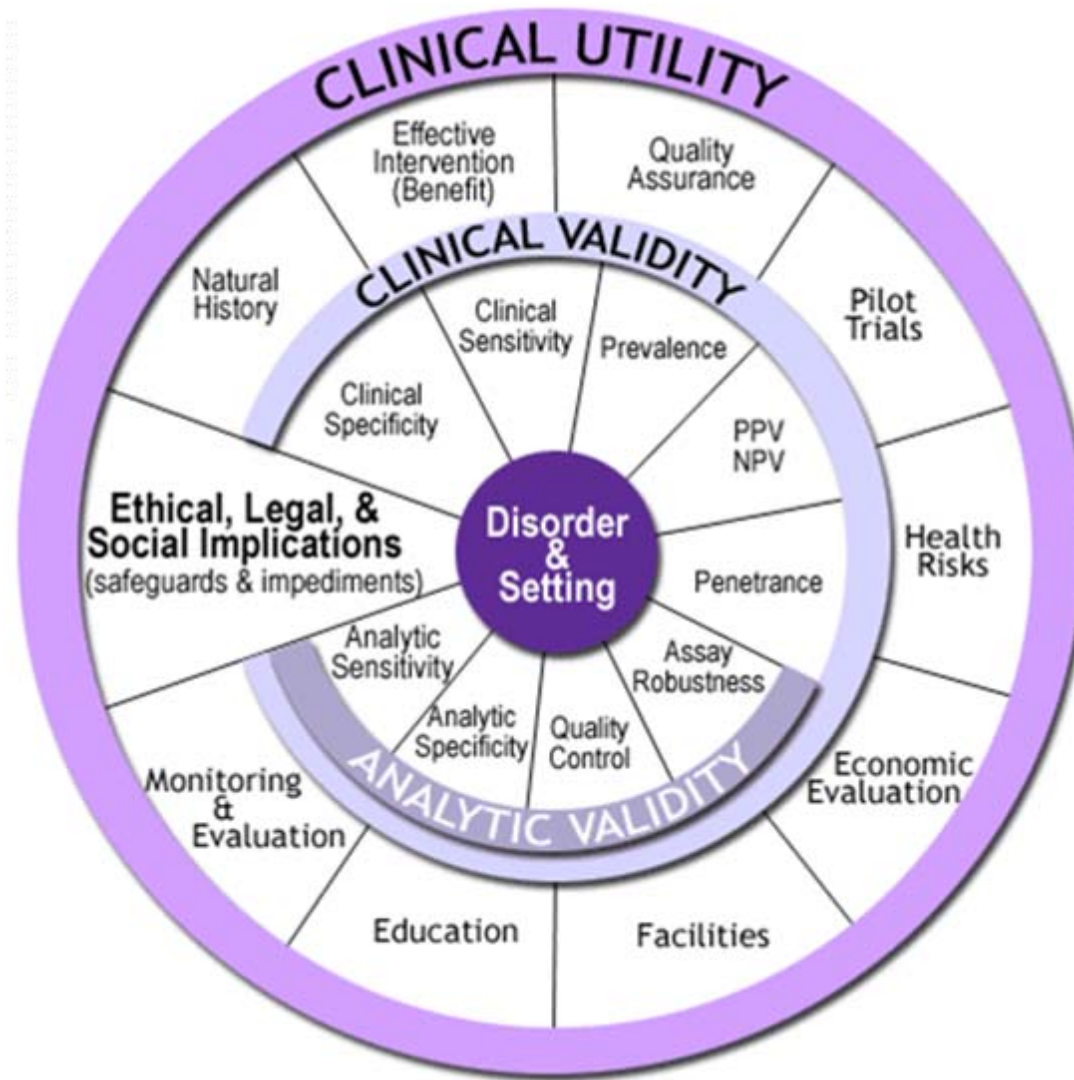
Clinical validity of a test defines its ability to detect or predict the presence or absence of clinical disease

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

→ test purpose, feasibility of delivery, cost- and risk-benefit ratios

Ethical, legal and social implications of the test

3. The ACCE Framework



4. Expanding ACCE: clinical validity

1. Scientific validity

Evaluation of the association between biomarker and disease

2. Test performance

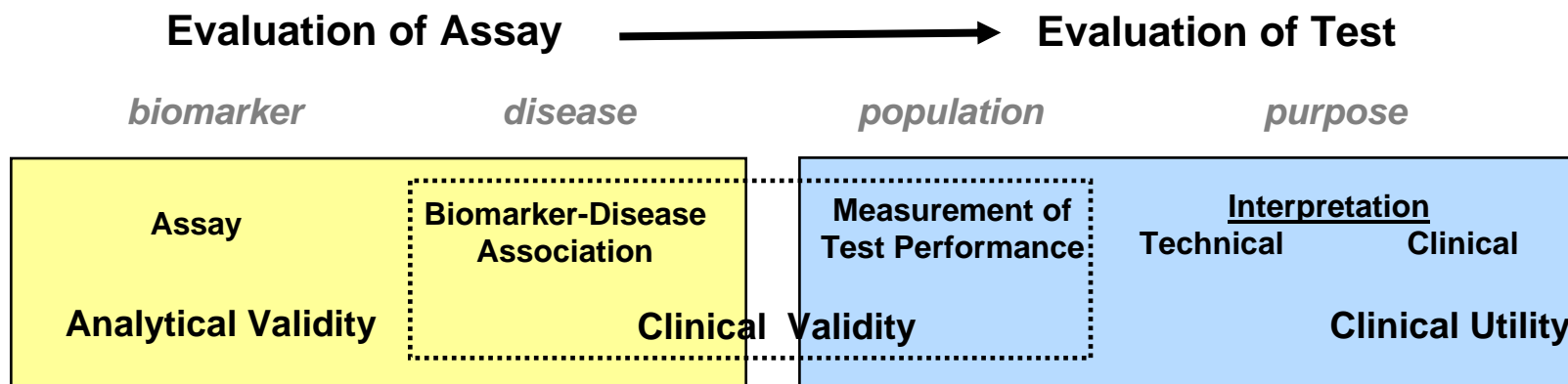
Evaluation of the test performance in the clinical situation

→ sensitivity, specificity, PPV, NPV, AUROCC...

	Disease	No disease
+	TP	FP
-	FN	TN

Evidence of biomarker-disease association is necessary, but by no means sufficient, as an indicator of effective and useful test performance

4. Expanding ACCE



5. Regulatory Issues

Key purposes of regulation: to ensure (a) safety and (b) effectiveness

Clinical evaluation and clinical performance are both terms used by device regulators:

Clinical evaluation is the assessment and analysis of clinical data pertaining to a medical device in order to verify the clinical safety and performance of the device

From Global Harmonisation Task Force: Study Group 5. Clinical Evaluation. May 2007

5. Regulatory issues

		<u>SAFETY</u>	
		Safe	Unsafe
<u>EFFECTIVENESS</u>	Effective	Allow	?
	Ineffective	?	Not Allow

Fundamental issue for statutory regulators:

1) how should the idea of 'safety' be interpreted in the context of tests?

2) what evidence is needed to show the test is effective?

5. Regulatory issues: safety

1. **Direct harm** – caused directly by the test itself
2. **Indirect harm** – caused by knowledge of the result of the test

Does safety only apply to harms **directly caused by the device** or is it relevant also to **consequential harms** that come about as a result of reliance on **information** obtained through the use of a device?

5. Regulatory Issues: performance

- **No systematic processes and platforms for generating data (akin to Phase III studies) to inform test evaluation**
- **There is no agreement about whose responsibility it should be to provide the resources for, or to carry out, such studies**
- **There is no consensus internationally or nationally about the standards required or validation trials needed**
- **There are no organisations that have a specific responsibility for systematically analysing and documenting results from studies of diagnostics and biomarkers**

6. Regulatory Frameworks

1. **Statutory**
 - **legislation**
 - **formal instruments**
2. **Codes of Practice**
3. **Formal Guidelines**
 - **insurers**
 - **commissioners**
4. **Professional governance**
 - **clinical governance**
 - **Royal Academies**

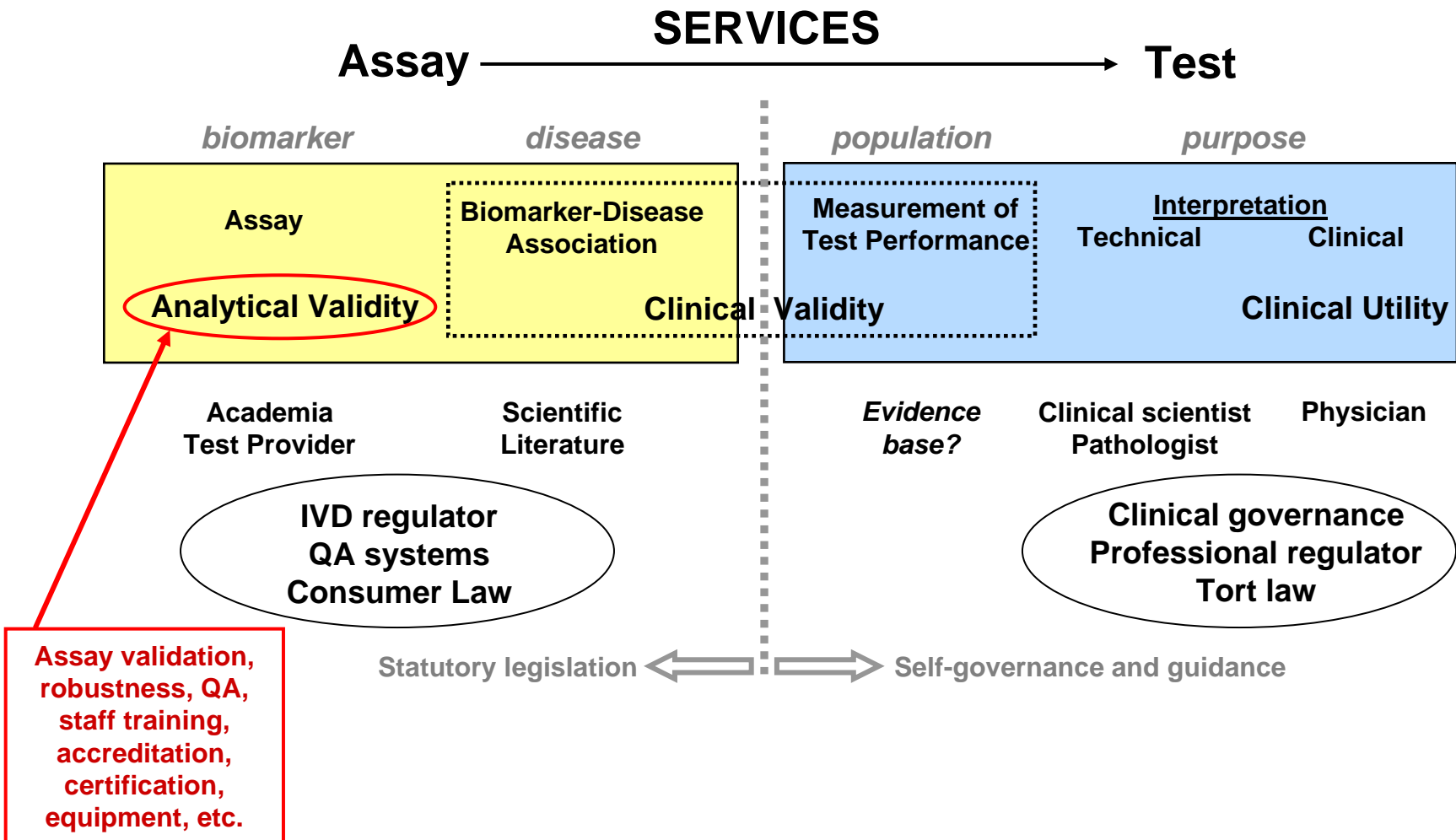
6. Regulatory Frameworks

Regulation of assays, tests AND services...

- | | | |
|-------|-----------------------------|--|
| 1. | Devices and products | Device regulators |
| 2. | Labelling | Device regulators |
| | | |
| 3. | Laboratories | Accreditation and QA |
| 4. | Professional interpretation | Professional bodies |
| 5. | Claims | Advertising standards
Trade descriptions |
| 6. | Services | Regulators of service provision
Consent and confidentiality |


6. Regulatory Frameworks


Boundaries of statutory legislation?



7. ELSI

Ethical, Legal and Social Implications

- Reliability and accuracy versus gold standard test
 - **Benefit/harm trade-offs**
 - Responsibility and accountability
 - **Specification creep**
- 
- Technical

- Informed consent and patient autonomy
 - **Privacy and confidentiality**
 - Access to data
 - **Storage of sample and data**
- 
- Ethico-legal

- Equity of access
 - **Acceptability of test**
 - Potential for stigmatisation or discrimination
 - **Implications for family and/or society**
- 
- Social

8. Conclusions

- Evaluation of a test is substantially more complex than – though equally important as – evaluation of an assay, and less amenable to regulatory control
- Evaluation of a test involves consideration of the analytical validity of the assay, as well as the clinical validity and clinical utility of the test, and a consideration of its ethical, legal and social implications
- Regulation of a clinical test relates both to its effectiveness (and therefore its purpose) and to its safety (and therefore the potential direct and indirect harms associated with testing)