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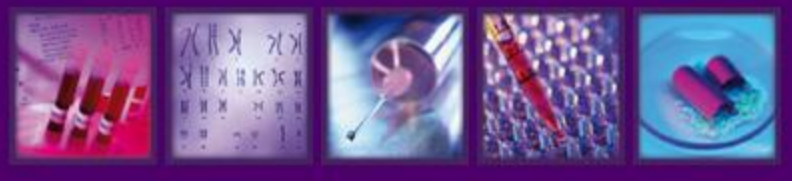

Evaluation and Regulation of Biomarkers
A Public Health Perspective

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OECD Workshop on Policy Issues for the Development and Use of Biomarkers in Health

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Introduction

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Purpose

To promote the responsible and effective use of biomedical science to benefit the health of individuals and society

Values

- **Pro-science and pro-health**
- **Responsible and balanced**
- **Collaborative and multidisciplinary**
- **Inclusive but independent**

Objectives

- **To identify the potential of biomedical science to benefit health and to disseminate that knowledge for public benefit**
- **To contribute to the integration of biomedical science into mainstream clinical and public health services**
- **To foster a social and regulatory environment receptive to the application of biomedical science for health**
- **To promote the development of systems and policies for the evaluation of technologies that derive from biomedical science**
- **To work with partners to provide education and training to support the responsible application of biomedical science for health**

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The Context

1. The completion of the Human Genome Project, new technology and advances in cell and molecular biology have together led to the development of new tests and biomarkers at an unprecedented rate
2. These tests are now more complex than ever before, both in terms of the technologies used and in their interpretation
3. They are being made more generally available – to non specialists and direct to the public
4. 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

5 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 the assessment of analytical validity

6. Commissioners, funders or reimbursers of health services are all under extreme financial pressure and require evidence of effectiveness before they will consider investment in the test

Definition of 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

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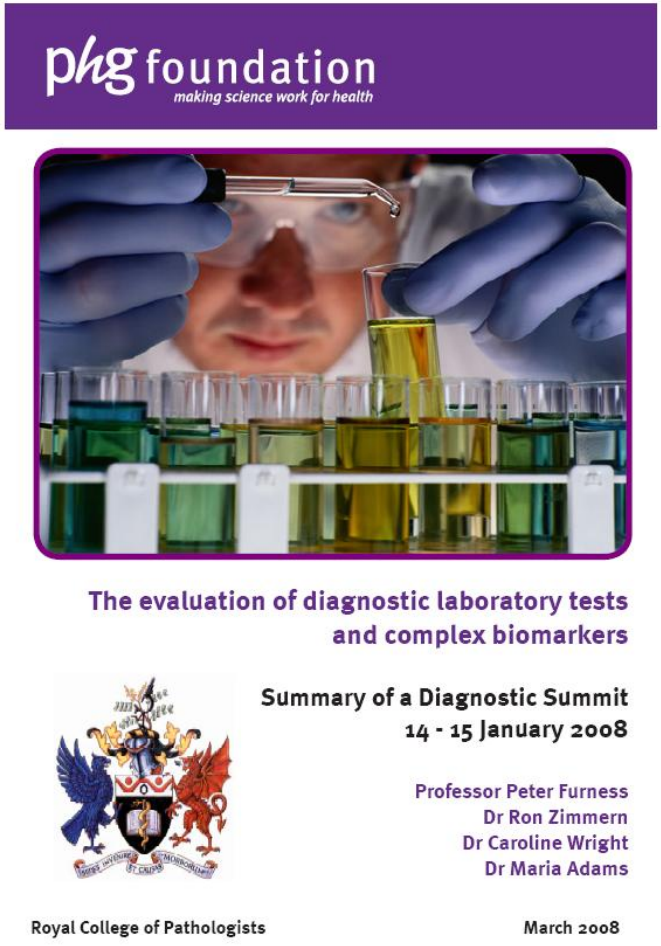
Diagnostic Summit



1. **A new body should be established to ensure the evaluation of diagnostic tests.**
2. **A publically available database be created of new and existing laboratory tests – a 'diagnostics formulary' – containing evidence for clinical performance, and explicitly stating where any evidence is lacking.**
3. **Policy makers and industry should be encouraged to address issues around gathering the necessary evidence for clinical evaluation.**
4. **An independent expert body should be responsible for evaluating the evidence for test performance and for making recommendations about appropriate clinical use.**
5. **Commissioners and health care professionals should be encouraged to use only those tests where appropriate evidence of clinical performance exists.**
6. **Statutory regulators should be empowered to require transparency relating to evidence of test performance, and ensure responsive and proportionate risk assessment to ensure patient safety.**

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Some Conceptual Issues

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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

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Tests -The Importance of Context

CONTEXT MATTERS IN DECIDING THE EFFECTIVENESS OF A TEST

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**

An allternative conceptualisation is to treat the *assay* as the measurement and the *test* as the interpretation of that measurement

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Implications of the Assay-Test Distinction

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 in its individual context, depending on disease, purpose and population

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Diagnosis

What is diagnosis?

> **The crucial process that labels patients and classifies their illnesses, that identifies (and sometimes seals) their likely fates or prognoses, and that propels us toward specific treatments in the confidence (often unfounded) that they will do more good than harm.**
>
> **David Sackett (1991) Clinical Epidemiology: A Basic Science for Clinical Medicine**

The label - the diagnosis - is not an end in itself but an intermediary, a means to an end

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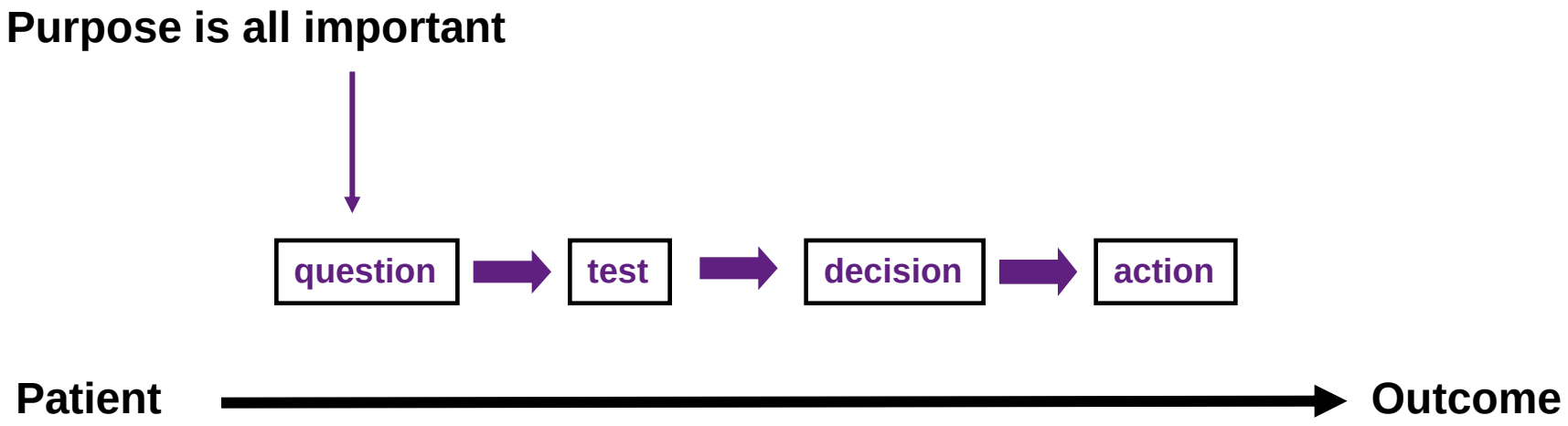
Why Do A Test?



After Price CP & Christenson RH (2007) The Clinical Question: A System for Formulating Answerable Questions in Laboratory Medicine. In Evidence Based Laboratory Medicine. Ed: Price CP and Christenson RH.

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Purpose or Uses of a Biomarker

1. Diagnosis
2. Risk stratification
3. Disease prognosis
4. Treatment stratification
5. Treatment monitoring
6. Population screening

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Effectiveness

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

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Evaluation and The ACCE Framework

(Diagnostic and Predictive Tests)

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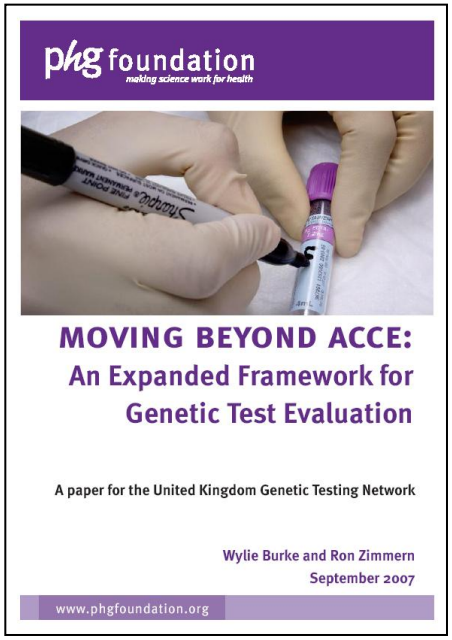
The ACCE Framework



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

Analytical validity of a 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 or predisposition to disease

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

Ethical, legal and social implications of a test

The ACCE framework is applicable to all forms of molecular diagnostics and biomarkers

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Dimensions of Clinical Utility

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

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Two Components of Clinical Validity

Scientific validity

Evaluation of the relationship between biomarker and disease

Test performance

Evaluation of the test performance in the clinical situation

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

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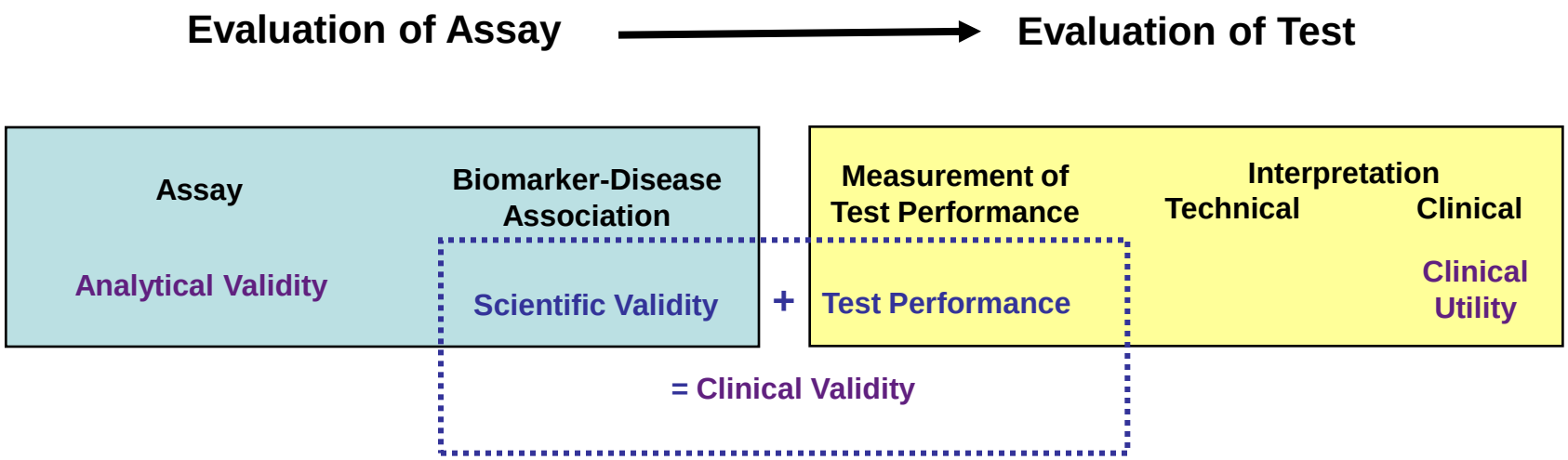
Expanding ACCE - An Alternative Conceptualisation



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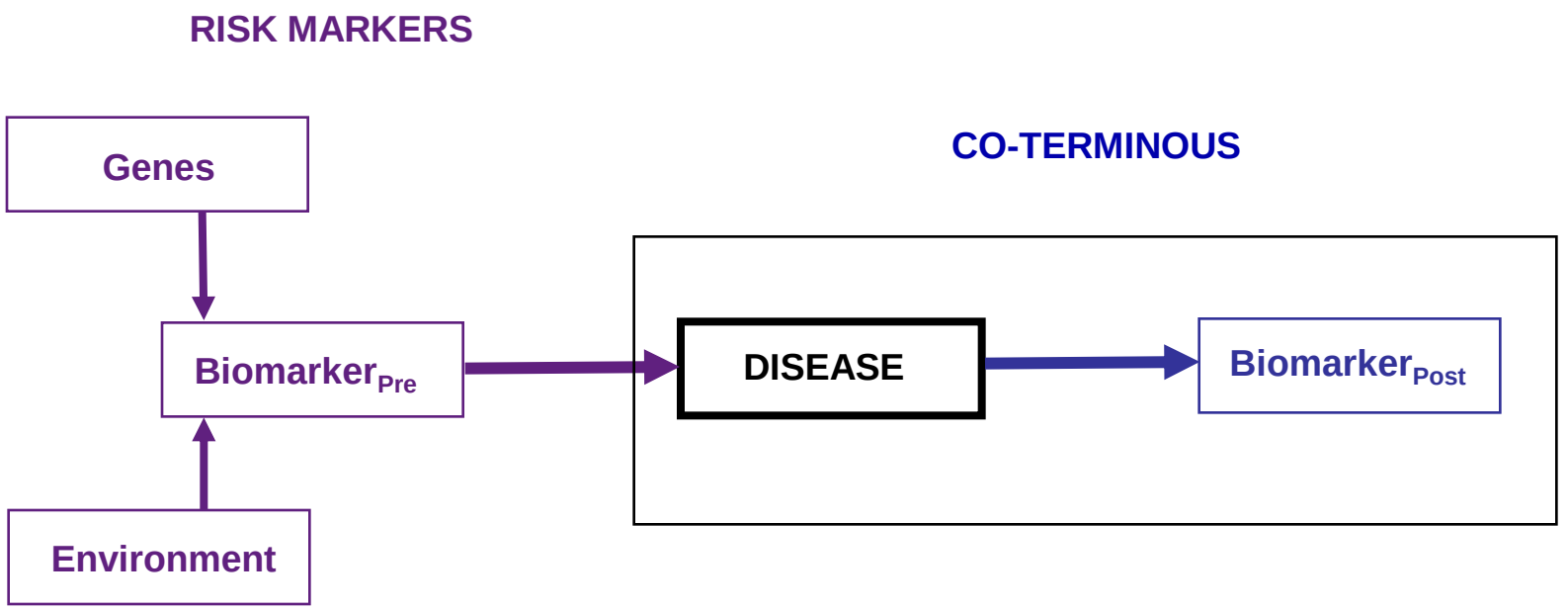
Diagnostic and Predictive Tests



Predict future risk of disease
Monitor risk
Intervene to prevent disease

Diagnose disease
Follow course of disease
Monitor treatment

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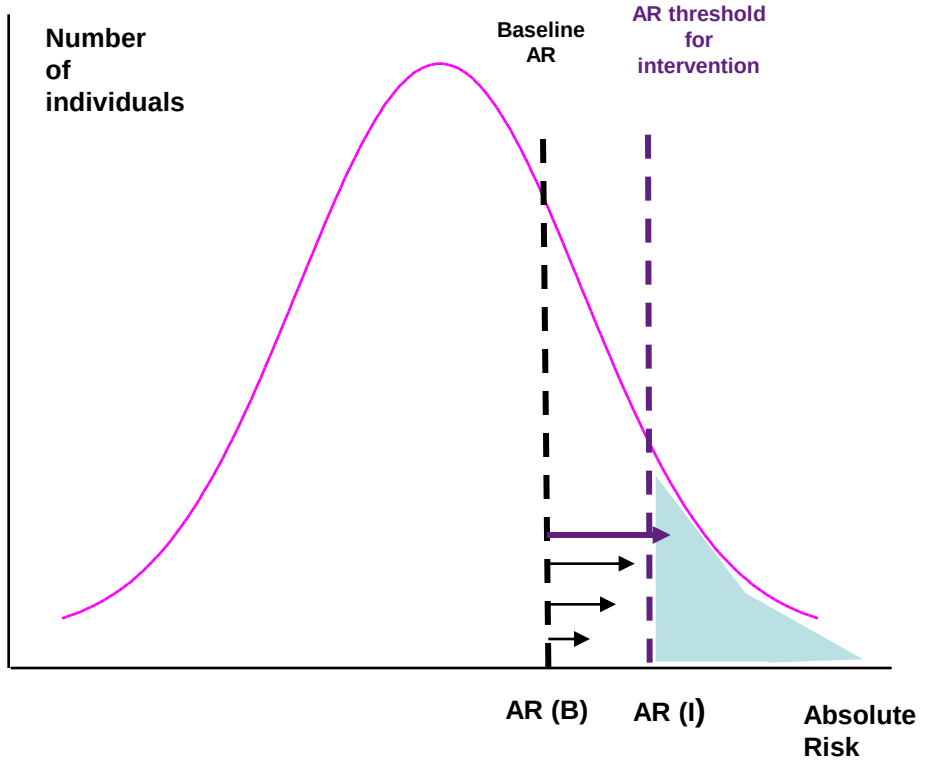
Predictive Tests – The Use of Absolute Risk

1. Standard method of diagnostic test assessment using 2 X 2 table for sensitivity and specificity is not appropriate
2. Need for risk prediction algorithms
3. Algorithms to include both biomarkers and environmental factors
4. Base data provided by age-sex specific risk
5. Absolute risk is key
6. Utility demands the existence of a validated preventive intervention
7. Risk threshold for intervention required



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Prediction and Susceptibility

Variable	Case Subjects	Control Subjects	Regression Coefficient	Odds Ratio (95% CI)	P Value†	P Value for Trend‡
Age			0.01	1.01 (1.00–1.02)	0.02	
Geographic region			–0.75	0.47 (0.40–0.55)	<0.001	
No. of associated factors**						
0	144 (5.0)	174 (10.1)	NA	1.00		
1	778 (26.9)	581 (33.6)	0.48	1.62 (1.27–2.08)	1.27×10^{-4}	
2	1053 (36.4)	622 (36.0)	0.73	2.07 (1.62–2.64)	5.86×10^{-9}	
3	642 (22.2)	286 (16.6)	0.99	2.71 (2.08–3.53)	9.54×10^{-14}	
4	236 (8.2)	60 (3.5)	1.56	4.76 (3.31–6.84)	9.17×10^{-19}	
≥5	40 (1.4)	5 (0.3)	2.24	9.46 (3.62–24.72)	1.29×10^{-8}	4.78×10^{-28}

Cumulative Effect: Risk of Prostate Cancer-Genotype & Family History
From Zheng et al (2008) NEJM Feb 13

We agree with Zheng et al. (Feb. 28 issue) that additional research is needed to assess the value of their finding of genetic variants associated with the risk of prostate cancer. Unfortunately, the planned marketing of a test based on this study is premature and may cause more harm than good. Finding a genetic association is only the first step in the continuum of translating research into practice. The results have not been independently confirmed, and adding the genetic test results to age, region, and family history only marginally improved risk prediction (the area under the curve [AUC] increased from 0.61 to 0.63). The clinical utility of the test is questionable because it cannot be used to reduce risk, since there are no known modifiable risk factors; to encourage screening, since the balance of benefits and harms is unknown; or to predict the clinical course of the disease, since the variants were associated equally with aggressive and nonaggressive cancers. In the absence of evidence of improved outcomes, this test may lead to unnecessary or potentially harmful procedures.

Coates, Khoury & Gwinn. CDC. NEJM June 2008

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Policy Implications

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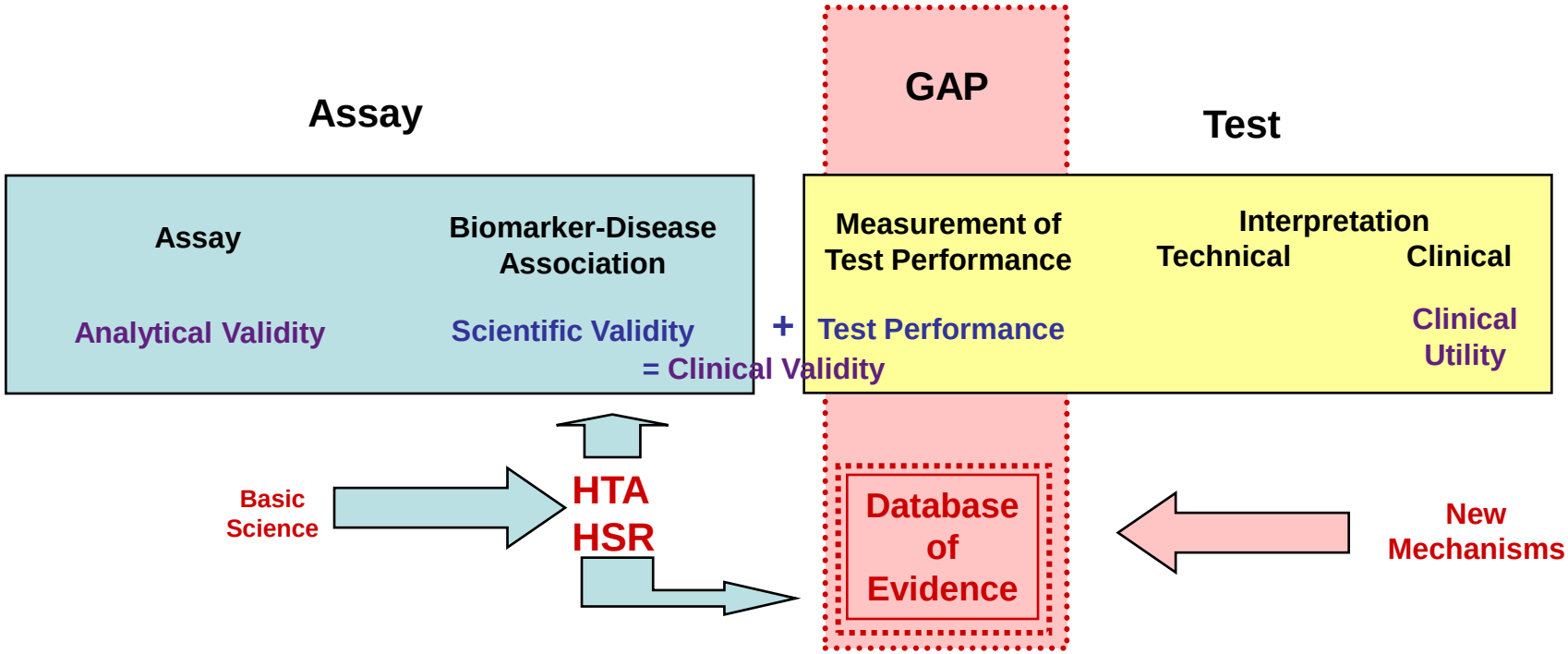
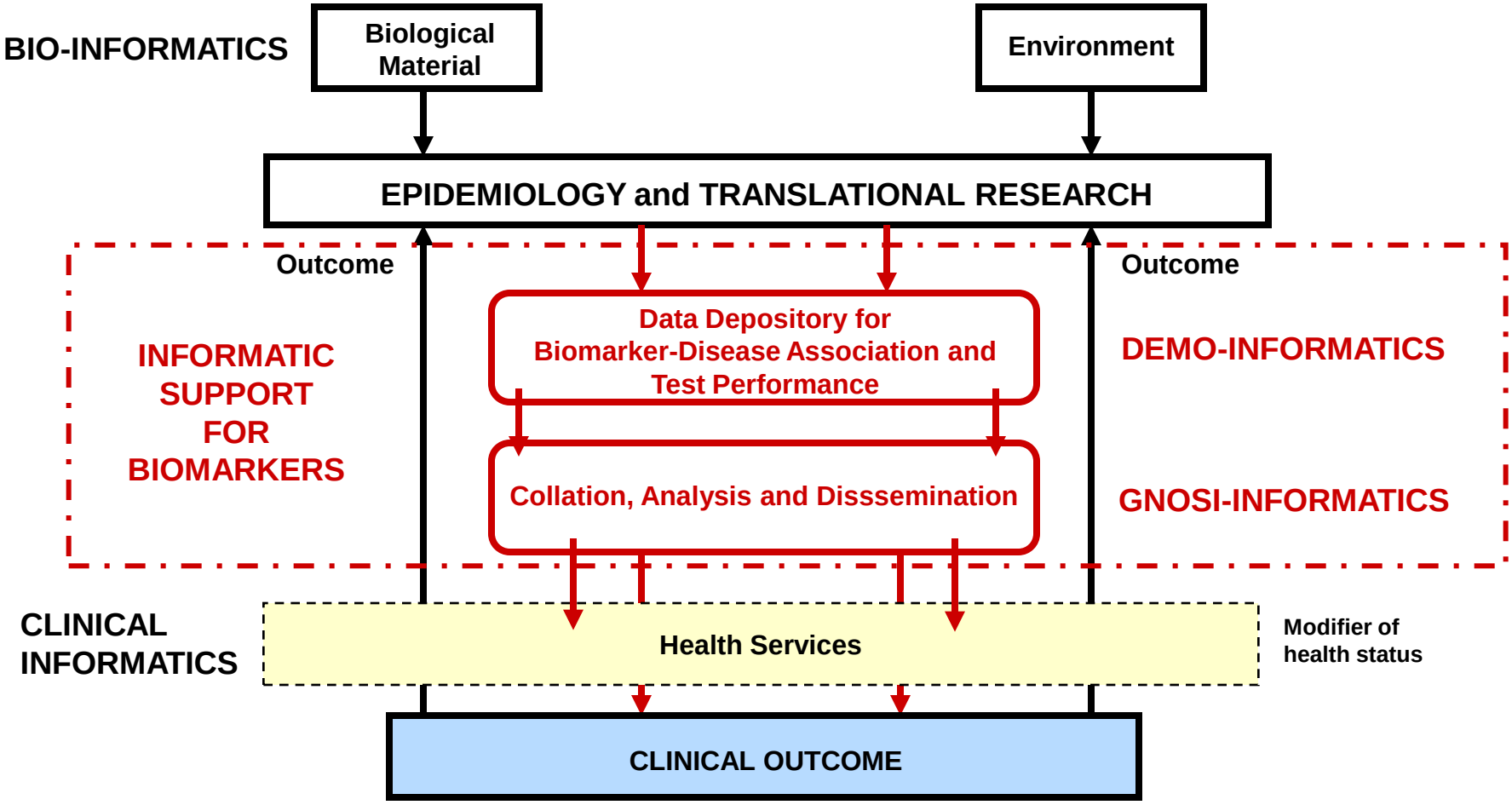
Expanding ACCE - An Alternative Conceptualisation



Biomarker Data and Evidence



Policy Implications

1. **Policies, systems and funding mechanisms exist in most OECD countries that allow data of biomarker-disease association to be generated. Such evidence is usually carried out by the scientific community and are funded through academic research grants**

2. **Policies, systems and funding mechanisms do not exist for the large scale generation of data to inform the assessment of test performance (sensitivity, specificity, positive and negative predictive values and the area under the ROC curve) of diagnostics. This is to be contrasted with therapeutic agents where clinical trials are mandatory. Such evidence is needed to determine the clinical validity of a biomarker.**

3. **Governments should be aware of this gap and the relevant parties (academics, research funders, the commercial sector) need to discuss their relative roles and responsibilites for funding and establishing such mechanisms**

4. **The assessment of predictive or susceptibility (as distinct from diagnostic) tests is in its infancy and will require a reorientation of research effort to focus on (a) the establishment of risk prediction algorithims and (b) determination of the threshold at which preventive interventions should be undertaken**