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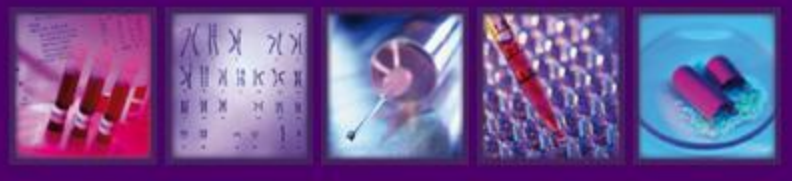

The Regulation of Biomarkers
Some Policy Perspectives

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

Wellcome Trust Conference Centre
Hinxton, 7 October 2008

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Introductory Remarks

Biomarkers, Regulation, Definitions

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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 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

Levels of Regulation

1. **Statutory**
   - legislation
   - formal instruments
2. **Codes of Practice**
3. **Resources**
   - insurers
   - commissioners
   - health maintenance organisations
4. **Clinical**
   - clinical governance
   - physician and patient education

Modified and amplified from Burke & Zimmern (2004) Nature Reviews Genetics 5, 955

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Better Regulation

"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."

PM's Speech 26 May 2005

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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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

The Regulatory Questions

Products and Tests

How do we regulate to ensure that a biomarker is safe and valid for clinical use? What are the standards for its measurement and evaluation?

Services

What mechanisms may be used to ensure that services that provide tests based on biomarkers are properly carried out and interpreted?

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Regulating Products and Tests

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Regulatory Categories

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

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Products

1. Products (test kits)
2. Laboratory developed tests (LDTs)
3. Risk predictive algorithms

Arctic DX Test for Macular Degeneration

Macula-Risk™ (Arctic DX)

Indication for use

Adults with a family history of Age-related Macular Degeneration (AMD) or other risk factors for AMD such as a body mass index (BMI) >30 and/or history of smoking and all patients over the age of 50

Intended Use

Macula Risk™ determines a person's genetic predisposition to AMD and combines these genetic results with environmental risk factors to provide a person's life-time risk of developing AMD. Patients can then be stratified for follow on surveillance (screening), education and disease management programs.

Gene	Polymorphism	Licensor
LOC387715/ARMS-2	rs 10490924	Vanderbilt / Duke
C3	Rs2230199	Cambridge
CFH	rs 1280514	Michigan
CFH	rs 412852	Michigan
CFH	rs 11582939	Michigan
CFH	rs 1048663	Michigan
BF	rs 522162	Public Domain
BF	rs 760070	Public Domain
BF	rs 550513	Public Domain
C2	rs 4151667	Public Domain
C2	rs 4151669	Public Domain
C2	rs 4151572	Public Domain

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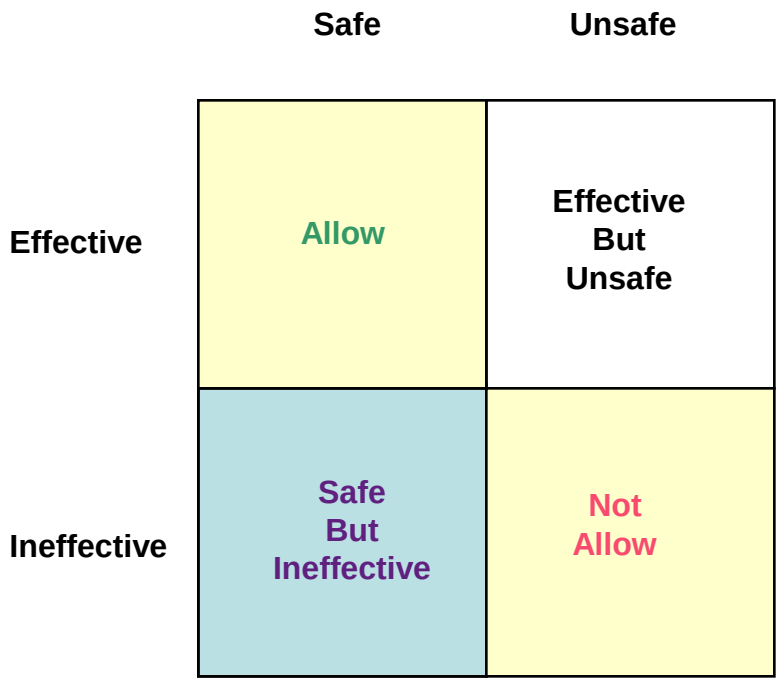
The Fundamental Issues for Statutory Regulators



1. Should statutory regulators concern themselves with tests that are safe but ineffective?

2. 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?

3. How should the idea of 'safety' be interpreted in the context of tests?

Note: An effective test is one that fulfils the objective or purpose for which is was carried out

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Clinical Evaluation in a Regulatory Context (1)

Clincal evaluation and clinical performance are technical 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 perfomance of the device

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

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Clinical Evaluation in a Regulatory Context (2)

1. Based on a comprehensive analysis of available pre- and post- market data
2. Must address any clinical claims made about the device, the adequacy of product labelling and product information
3. Consideration should be given to….design features of the device…. target treatment populations that require specific attention….
4. And whether data from comparable devices can be used to support the safety and/or performance….
5. In which case they should have the same intended use….which relates to the clinical condition being treated ….the severity and stage of disease….the site of application in the body….the patient population

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

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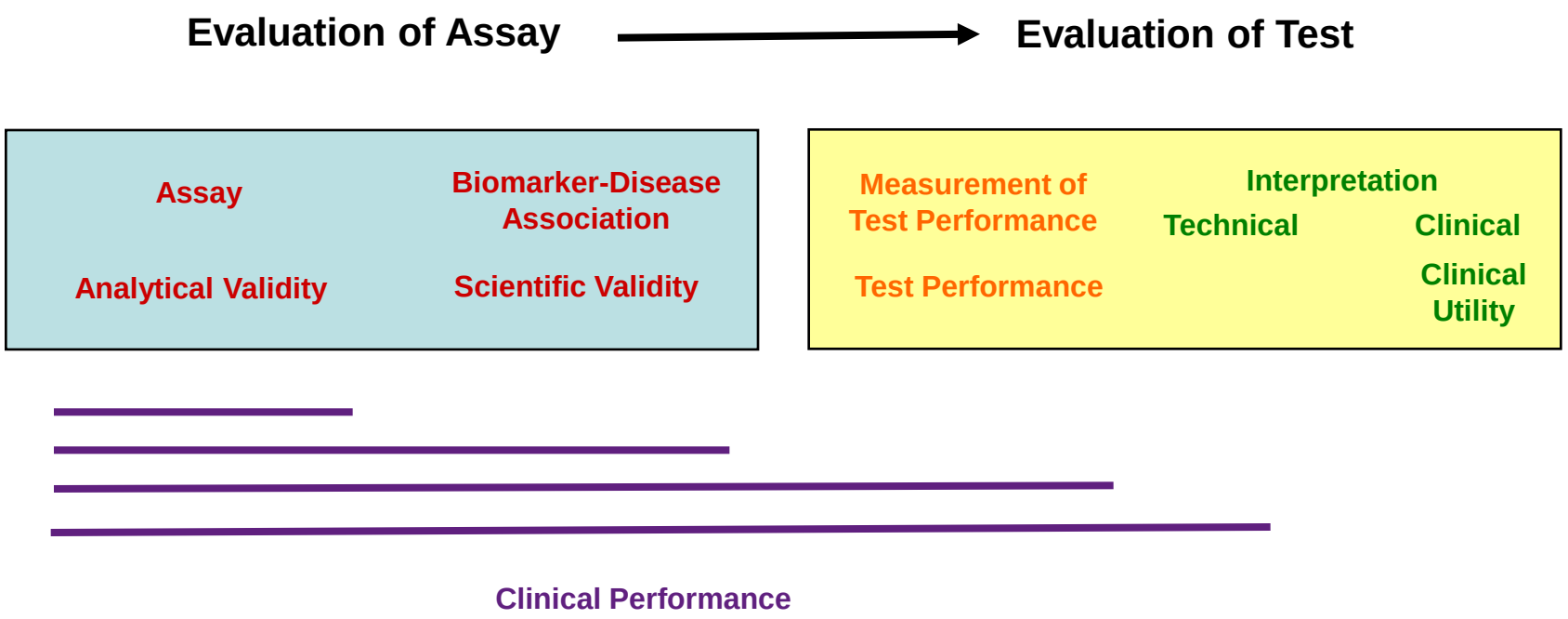
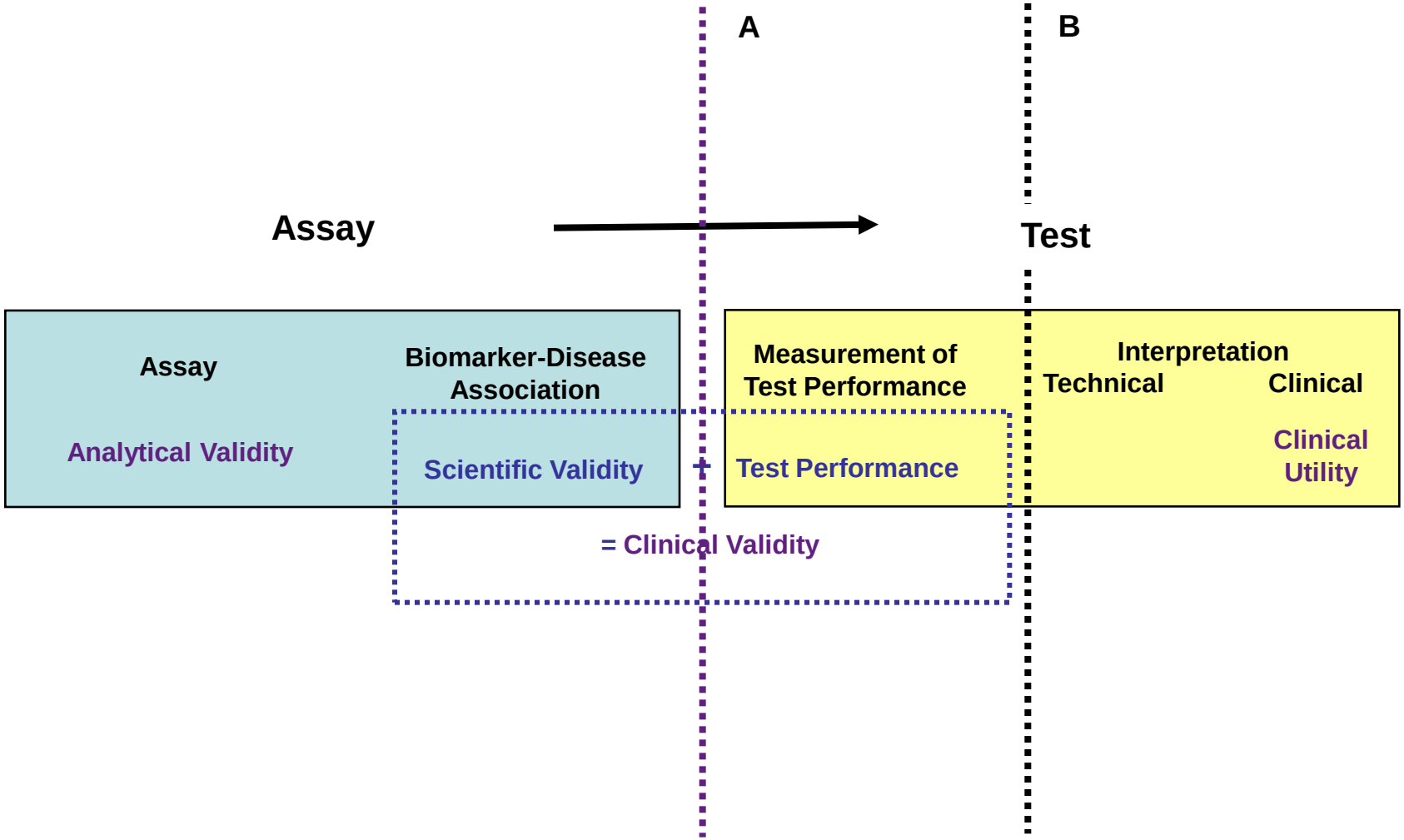
Clinical Performance from Regulatory Perspective



Boundaries of Statutory Regulation



Epidemiological Study of DTC Tests

1. Seven companies offering predictive testing using multiple markers involving 69 polymorphisms in 56 genes
2. Literature review on 260 meta-analyses addressed 46 of the 69 polymorphisms and 32 of the 56 genes, encompassing 160 unique polymorphism-disease asssociations
3. Statistically significant associations were only found in 60 (38%) of these 160. These involved 29 polymorphisms and 28 different diseases
4. The odds ratios ranged from 0.54 to 0.88 for protective associations and from 1,04 to 3.2 for risk variants
5. The main commonly studied polymorphisms were found in the genes MTHFR, TNF-alpha, GSTP1, GSTT1 and VDR

Cecile Janssens et al (2008) Am J Hum Gen. 82, 593-599

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The Assay-Test Distinction - Implications

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

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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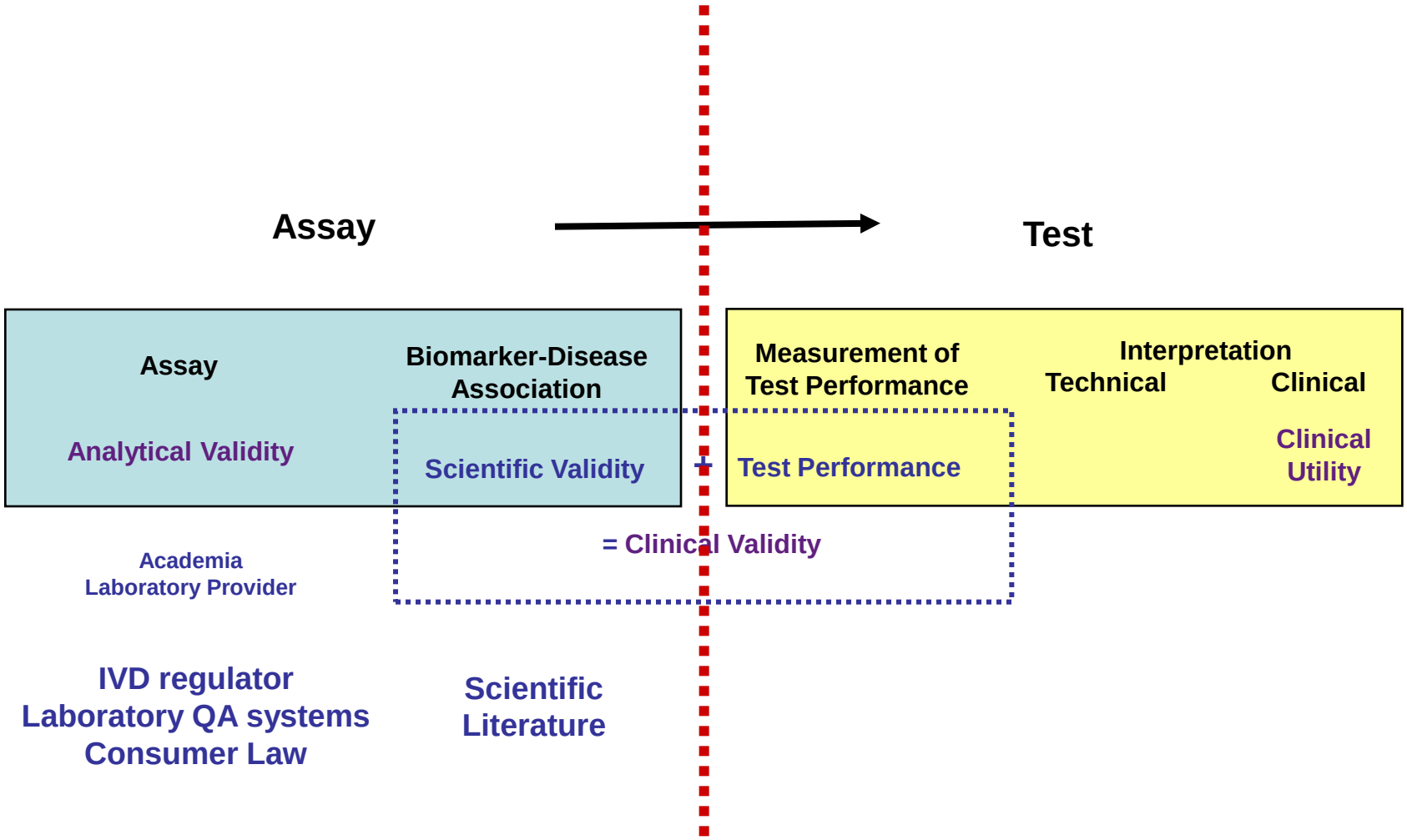
Boundaries of Statutory Regulation



Conclusion

The regulation of the clinical performance (test measurement and evaluation) of a test should, unless there is strong evidence to suggest otherwise, be by and large confined to:

(a) the regulation of the safety, reliability and analytic performance of the assay

(b) the determination of scientific validity (production of evidence about the prima facie association between the test and the disorder) and

(c) the exact nature of the claims made in labelling the device or product

Regulating Services

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Regulatory Categories

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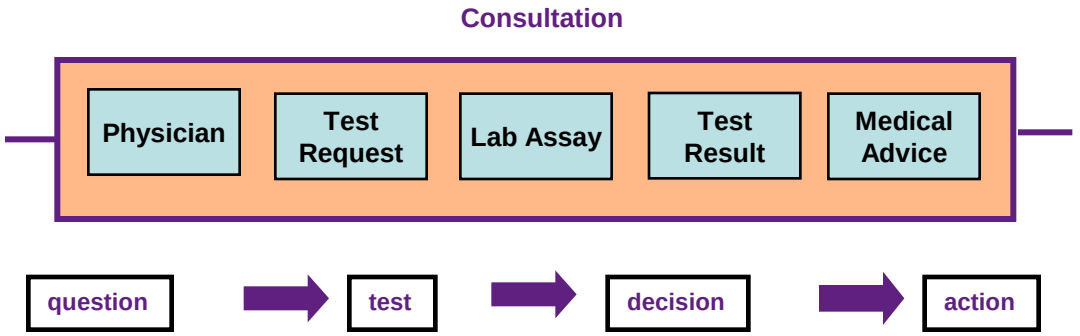
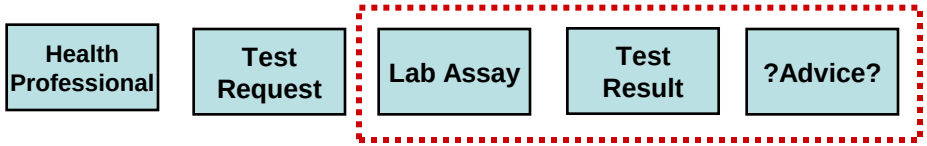
Pathways of Test Provision

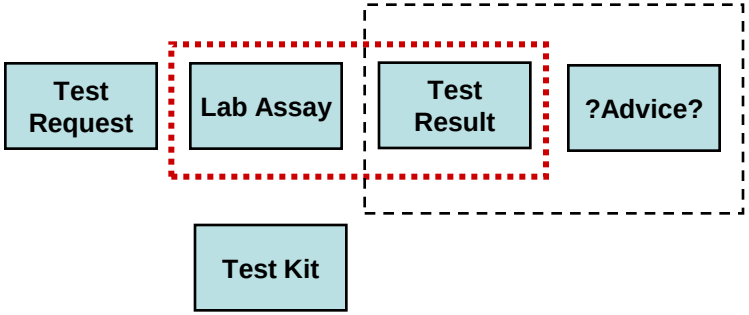
1. **Professional medical setting**



2. **Over the counter via non-medical professional**



3. **Direct to the consumer**
   - internet
   - test kit



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Interpretation and Professional Regulation

1. Technical interpretation

- Establishment of reference range
- Determination of significance of genetic variant

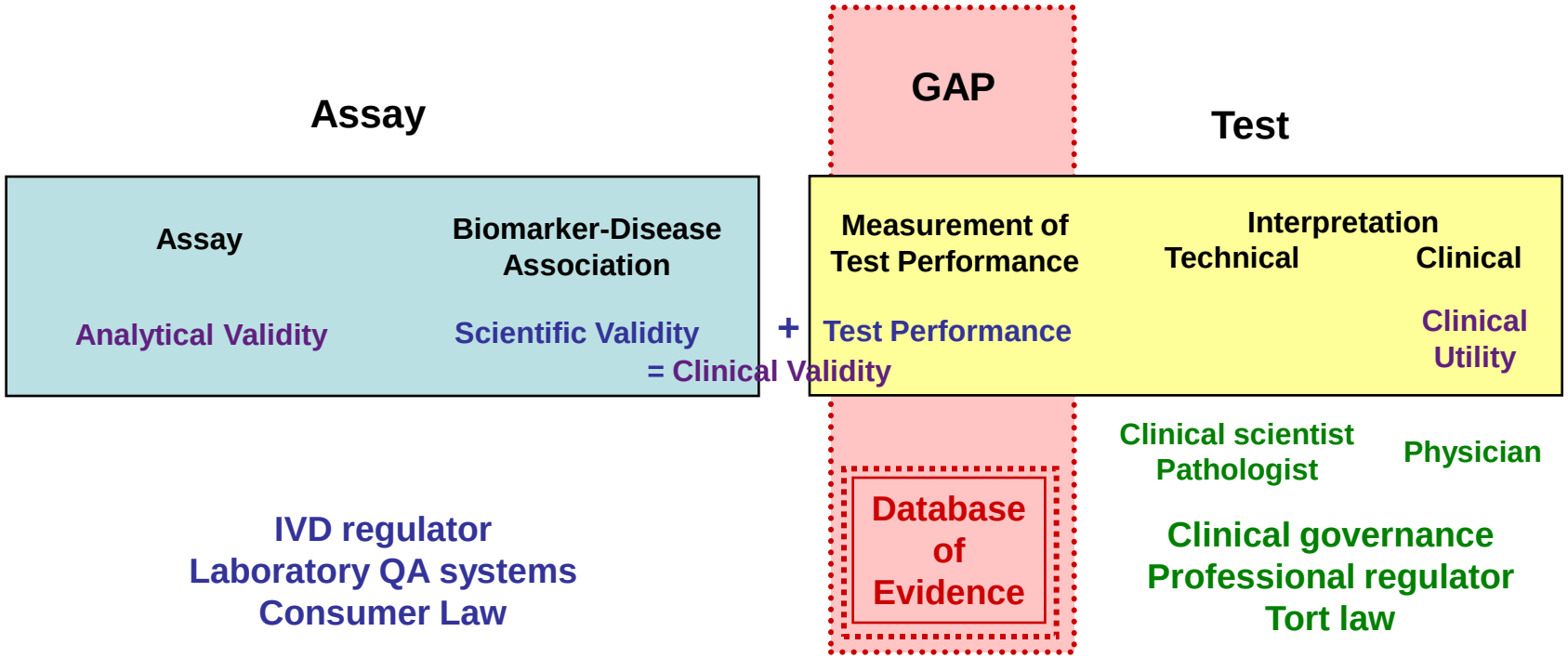
Carried out by laboratory scientist or pathologist

2. Clinical interpretation

- Clinical implications of result
- Interventions and opportunities for prevention or management

Carried out by physician or relevant clinician

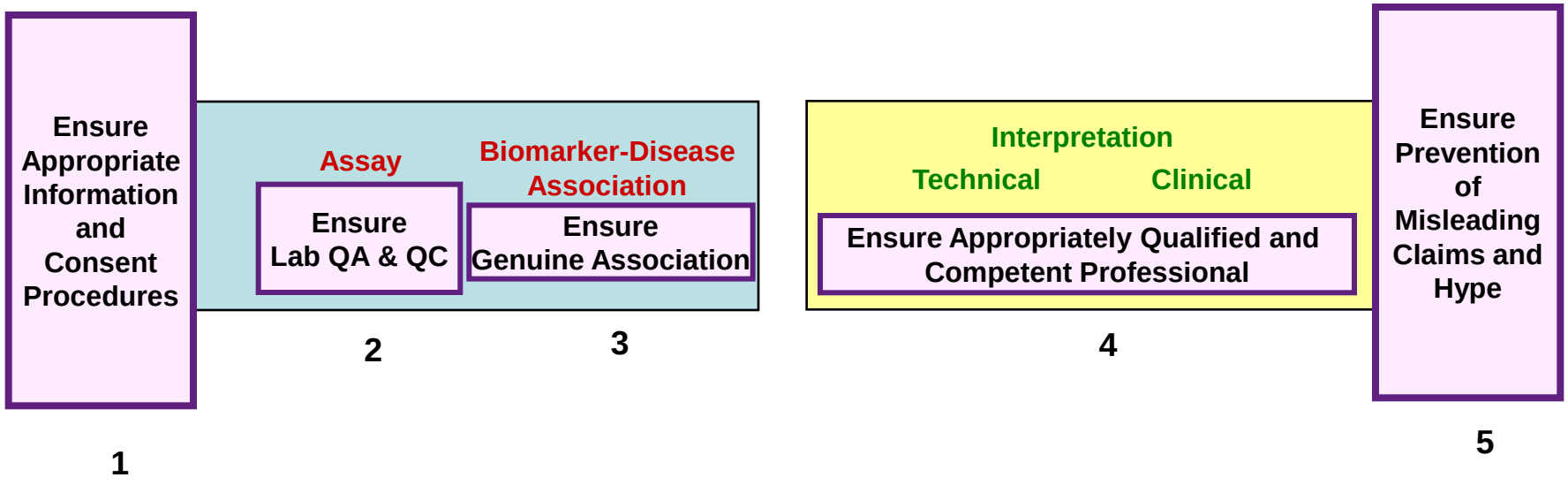
Service Regulation



Contextual Mechanisms

1. Train professionals
2. Educate patients
3. Empower commissioners
4. Prevent misleading claims

A Suggested Approach to Service Regulation



Conclusion

The regulation of a testing service is at present rudimentary and not well distinguished from the regulation of products and devices

Systems for regulating services may need strengthening and should include consideration of how professional regulation should be used to ensure proper interpretation of results

Regulation may be statutory or implemented through codes of practice. Will codes suffice or are statutory instruments needed?