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ANALYTICAL PAPER: REGULATION AND POLICY

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This analytical paper was submitted for discussion at the workshop on Policy Issues in the Development and Use of Biomarkers in Health held on 6-7 October 2008 in Hinxton, United Kingdom. It is submitted for information to the WPB.

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NOTE BY THE SECRETARIAT

This analytical paper was submitted as background material for discussion at the expert workshop organised by the Biotechnology Division on “Policy Issues in the Development and Use of Biomarkers in Health” held in Hinxton, United Kingdom on 6-7 October 2008. This workshop contributes to the fulfillment of Output Result 5 of the 2007-2008 PWB entitled “Analytical and policy reports on the impact of molecular markers and targeted therapies on Biomedicine”.

This analytical paper, written by the PHG Foundation, identifies the element necessary for a regulatory environment that is needed to ensure the safe and efficient commercialisation of innovative diagnostic tests based on biomarkers.

This analytical paper, along with others developed for the Biomarker Workshop, will be used as input for the Policy Report entitled “Policy issues in the Development and Use of Biomarkers in Health” that will be submitted to WPB in early 2009.

Delegates to the Working Party on Biotechnology are invited to:

- **Note** the analytical paper.

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1. Introduction

For years there has been a concern in many jurisdictions about the adequacy of the oversight of clinical tests involving genome-based and other biomarkers. As clinical genetics moves from the realm of rare diseases to mainstream medical care, advances in testing are outpacing the regulatory framework needed to assure its safety and effectiveness.

The use of tests in the absence of proper evaluation could trigger erroneous treatment and involve major hazards. For example, direct marketing of breast cancer tests to women at low risk has been criticised for causing unfounded anxiety and unnecessary preventive surgery. False reassurance from tests for common diseases could also cause individuals to ignore effective prevention measures, such as weight control and exercise. Problems with insurance or implications for other family members might also arise.

In addition to posing potential risks to the public, the absence of a mechanism for overseeing the clinical use of data and information arising from such tests creates an unstable business climate for manufacturers and laboratories that may deter investment in new and innovative tests. In addition, the international nature of health policy, scientific research and commercial activity all call for international collaboration on the development of a coherent framework for oversight to define an equitable and stable regulatory playing field that will be effective worldwide.

The growing need for harmonisation in regulation of medical devices has resulted in efforts by national device regulatory authorities and members of the regulated industry to encourage convergence in regulatory practices to ensure safety, effectiveness/performance and quality of medical device, promote technological innovation and facilitate international trade. The Global Harmonisation Task Force, for example, publishes and disseminates harmonised documents on basic regulatory practices, providing models for the regulation of medical devices that can be adopted or implemented by national regulatory authorities.

The focus of this paper is *regulation*. Its task is to consider the regulatory requirements and mechanisms that will ensure proper test evaluation, application and interpretation on the basis of full evidence of test performance. This needs to be accomplished without imposing undue regulatory burdens that would inhibit the development of new and useful biomarker tests. The paper considers some general issues and presents a framework, not by way of a definitive proposal, but as a mechanism for stimulating debate and discussion. It should be read in the context of the documents published by the Global Harmonization Task Force.

Issues arise therefore as to the appropriate *means* of regulation and level of accountability required in various contexts in the process of test development, evaluation and delivery. Stringent statutory criteria, for example, will generally be imposed on the manufacture of a test kit, while a requirement of disclosure of evidence might be appropriate in relation to clinical performance, and professional practice standards administered by an authorised body may be sufficient to ensure accountability for the interpretation of test results by a clinician. This briefing paper will address the following issues as they arise at each stage in the proposed evaluation framework:

- The potential harm
- The responsible party(ies)
- Possible solutions
- Regulatory mechanisms for implementing

The evaluation process has been covered in more detail in the accompanying paper on the clinical evaluation of biomarkers. In brief, three concepts are particularly pertinent to regulatory issues:

1. The distinction between an *assay*, the scientific measurement of a biomarker (the accuracy of which depends upon its *analytical validity*), and a *test*, its application in a particular population for a particular purpose.
2. The two-fold requirement for evidence of *clinical validity* where an assay is applied as a test in a clinical situation:
 - (i) A proven association between the biomarker and the disease of interest (*scientific validity*)
 - (ii) Evidence of test performance in a clinical setting (*test performance*), in order to assess whether the test is able to distinguish between those who have, or will develop, a particular disease, from those who do not
3. The *clinical utility* of a test, which relates to its interpretation within the context of an individual patient and its overall value to patients and physicians.

2. Scope

A clear definition of the scope of potential regulation is important in order to avoid ambiguity as to where obligations lie. The primary questions are: what sort of tests should come under regulatory scrutiny, and who are the parties responsible for their development, evaluation and application?

2.1 Biomarkers

The most widely accepted technical definition of the term *biomarker* is provided by the US Food and Drug Authority (FDA), and is reproduced at the start of this paper. Our use of the term is intended to be inclusive of (but not limited to) *genetic tests*, by which we mean tests that use nucleic acids as the analyte. We also extend it to predictive as well as diagnostic tests. Our paper will also discuss laboratory developed tests (LDTs) and *direct to consumer* (DTC) tests as these may generate special regulatory issues.

LDTs, for example, are developed and performed by laboratories for the purpose of providing testing services, commercial in many but not all instances, whereas test kits are developed and sold on a commercial basis. LDTs are addressed in Section 3.4.

DTC tests are directly available to the consumer without the oversight of a clinician either *over the counter* or from a foreign source, via the Internet or other means. The results are sent to the patient, sometimes with interpretation and advice about preventive strategies, but without the direct oversight of a clinician as would be the case if the tests were carried out in a conventional medical setting. Some commentators have expressed particular concern about genomic *lifestyle* tests that provide dietary and lifestyle advice purportedly based on analysis of an individual's genomic profile. An issue open for discussion is whether the public duty extends to attempts to regulate any aspect of Internet commerce in order to prevent harm to unwitting consumers. DTC tests are addressed in Section 3.5.

2.2 Stakeholders

A variety of parties will have a stake in the development and delivery of biomarker tests. For regulatory purposes, the concern is not so much with the balancing of their interests as with the definition

of their roles and responsibilities in relation to the evaluation and use of such tests. Such stakeholders will include:

- Test developers: academia, scientists, laboratories
- Manufacturers
- Laboratories: test performance / lab-based tests / 'interpretation' of results
- Clinicians: physicians, pathologists etc
- Retailers
- Consumers: over the counter/via the internet

2.3 *Means of regulation*

A wide range of regulatory vehicles is available to policy-makers: from codes of practice and informal guidelines to professional self-regulatory mechanisms and legal obligations.

Codes of practice and guidelines, although they do not have legal enforceability and can vary tremendously from jurisdiction to jurisdiction, may nevertheless be useful in the ongoing process of consensus-building, particularly at the international level.

Standards of professional practice are generally defined and enforced by authorised professional bodies in the national context.

Legally enforceable solutions will be conveyed either through the application of the existing common law or a legislative mechanism such as primary legislation (statute), or secondary legislation including regulations issued by a delegated authority. Legal requirements might dictate:

- Manufacturing standards
- Criteria for pre-market approval
- Mandatory disclosure of evidence
- Responsibility for administration of tests and results
- Standards for scientific validity and test performance
- Consumer protection laws: advertising, labelling
- Tort law: negligence, misrepresentation

International agreements require governments of signatory states to fulfil their obligations by implementation of their commitments in their respective national legal regimes, usually through an implementing statute.

3. Analysis

The distinction between an assay and a test has important implications for both evaluation and regulation. Whereas the evaluation of an assay is likely to be reasonably straightforward and allows

broadly applicable standards to be developed, the evaluation of the different parameters associated with a test is more complex and inherently less susceptible to standardisation.

3.1 *Analytical validity*

Existing statutory regimes for market authorisation of clinical tests are generally restricted to an examination of safety and analytical validity, and do not generally extend to the clinical validity or clinical utility of a test. In other words, they function primarily to regulate the integrity and safety of the assay.

Responsibility for analytical validity lies clearly with the manufacturer or developer of the test. Within the US, the FDA is responsible for the regulation of genome-based tests and molecular biomarkers. In Europe, such tests are treated as medical devices and the European *In Vitro* Diagnostic Medical Devices Directive provides the relevant statutory framework. The pre-market review mechanism is thought by some to be crucial to the effective regulation of analytical validity, yet in some jurisdictions such as the UK, except for a relatively small number of specified tests, there is no formal pre-market review and the system relies largely on self-certification by the test provider.

Proposals for regulatory change might involve refinements to specific national market authorisation mechanisms to ensure their application to biomarker tests. Regional and international harmonisation of quality and safety standards is a further objective that might be pursued.

3.2 *Clinical Validity*

Clinical validity comprises two elements: the link between genotype (biomarker) and disease, which we call *scientific validity*; and the determination of the parameters of test performance, such as sensitivity, specificity and predictive value, which we refer to as *test performance*.

The approach to clinical validity is often confused, and the extent to which regulators are concerned with such matters differs from one jurisdiction to another. The FDA in the United States, for example, purports to require evidence of clinical validity, while in the UK such evidence is not required unless clinical claims are made in regard to a test. In neither country, however, are the standards of evidence and the nature of the requirements clear and transparent.

3.2.1 *Scientific Validity (Biomarker-disease association)*

A biomarker-disease association is established through scientific and epidemiological research involving high levels of statistical significance and independent replication of association in more than one population. Although standards now exist by which it is possible to demonstrate that such associations are real rather than anecdotal, tests have been made available to the public where such standards have not been met. A study by Cecile Janssens and colleagues, for example, showed that of 160 biomarker-disease associations culled from tests provided by seven companies selling tests directly to the public, statistically proven associations had been found in only 60 (38 percent).

In many cases, the effect of the association, as measured by relative risk, is small, and unlikely, on its own, to show anything but poor test performance. Despite the size of the effect, if the association is real it nevertheless has potential, most likely in combination with other factors, to serve as the basis of a test with some degree of clinical utility. By contrast, any putative test established in the absence of such association will in effect be based on a false premise, and doomed to failure.

Any regulatory mechanisms must therefore draw a clear distinction between the two components of clinical validity. We suggest that it might be useful to regard *scientific validity*, which is necessary but not sufficient for a test to be clinically valid, as a property closely associated with the assay itself, and might

therefore be appropriately regulated through similar mechanisms. One possible approach would be to require that evidence of the biomarker-disease association be made a mandatory requirement within the framework of device regulation. Responsibility for providing this evidence would need to be considered, but would presumably fall upon the developer or manufacturer of the test, based on the work of academics and scientific researchers.

3.2.2 *Test Performance*

Test performance refers to the elucidation of a number of established test parameters such as sensitivity and specificity, in which the ability of the assay under investigation to successfully distinguish between healthy and diseased individuals, or those at higher risk from those at lower risk of future disease, is compared to a reference assay. Evidence of test performance plays a crucial role in informing the professional practitioner in the clinical application and interpretation of a test, thus avoiding potential harm and increasing benefits to patients. The absence of sufficient performance data is considered to be the greatest 'gap' in the effective translation of biomarker technologies into clinical practice. Without such evidence clinicians will in effect be unable to interpret the test results with any degree of certainty or consistency. Funders of health services, and clinicians, should be discouraged from using tests that are not backed by evidence of appropriate performance in a clinical context.

A solution, therefore, would be to encourage the generation of adequate evidence of test performance, and to ensure a system for collating it and making it publicly available in a way that is transparent and accessible. Responsibility for the generation of these data is therefore an important consideration in relation to the oversight of test performance. Population trials are lengthy and costly and a clear assessment of cost-benefit is difficult to obtain. To what extent should there be public support and investment into the conduct of such trials? Should it be the sole obligation of the test developer or manufacturer? Might public-private partnerships provide a workable option? Do laboratories and clinicians have a role in generating this sort of evidence-base?

The proposed vehicle for making evidence of test performance readily available to practitioners and consumers is a database or test registry, made mandatory by a statutory requirement of disclosure of evidence. The proposal raises a number of preliminary questions for discussion:

- Even if such a comprehensive database could be achieved, is 'transparency' sufficient to ensure appropriate and effective clinical use of tests?
- Who would be responsible for establishing and maintaining the database and who would pay for it?
- Are there sufficient incentives to ensure that the database would be accessed? Who would seek to use it and for what purpose? Clinicians? Practitioners? Consumers who purchase tests over the counter, or via the Internet? Laboratories or researchers?
- Would the evidence contained in the database be in a form that is understandable and useful to the average practitioner or consumer if they were to access it?

Assuming that a collection of performance data on biomarker tests is desirable, how would such a database be defined and established? The following list of parameters might be discussed:

- Administration: public/private; centralised/decentralised
- Jurisdiction: national/international
- Evidence: international standardisation
- Accessibility. International interoperability

- Participation: mandatory/voluntary. Enforcement

3.3 *Clinical utility*

Clinical utility is demonstrated by evidence that the use of the test is not only safe to administer and produces both technically accurate and clinically relevant results, but also provides information that will assist in the management of a patient and lead to an improved clinical outcome. In a conventional medical context, responsibility for so doing will lie with the physician or other health professional caring for the patient. He or she will interpret the test results in the context of the patient's problem and with regard to the purpose of the test. Proper interpretation and decisions will require access to evidence of test performance, and is likely to be impaired if such evidence is lacking. The establishment of a transparent evidence-base, as discussed above, is the means by which the health professional may be given access to such evidence.

Problems of interpretation may also arise because of the limitations of the party positioned to interpret or apply the results. Utility would therefore be enhanced by ensuring that those who interpret test results and make decisions about prevention and treatment have the proper technical qualifications to do so.

What then is the appropriate *regulatory mechanism* for overseeing clinical utility? By definition, it cannot be the subject of a statutory pre-market regime although certain legal requirements such as marketing and labelling laws, might have some bearing on the application and interpretation of commercial products. A strong argument can be made for incorporating governance of clinical utility into existing mechanisms of professional regulation, which define and enforce the practice standards of physicians, nurses, pathologists, pharmacists and other relevant professional groups. Professional regulatory bodies would have to ensure that ongoing educational resources were made available to its members and that there was a means of ensuring their competence for carrying out this task.

This mechanism will, however, need modification and possibly supplementation with other regulatory devices if it were to play a role in the administration and interpretation of tests provided directly to the consumer. This will be discussed in Section 3.5 later in the paper.

3.4 *Laboratory developed tests*

Lab-developed tests (LDTs), also known as *in-house* or *home brew* tests, are developed and conducted at a single clinical laboratory; they may also be developed by a third party and licensed exclusively to the conducting laboratory. Tests may, on the other hand, be packaged as complete testing systems ('kits') for wide commercial circulation, including sales to multiple laboratories. LDTs raise two main regulatory problems: the *level-playing field*, and the regulation of laboratory standards.

The *level-playing field* issue is that commercial test kits are generally subject to a statutory regime of pre-market criteria that is not imposed on LDTs, resulting in a discrepancy that creates a regulatory imbalance between test kit developers and providers of laboratory services. This is particularly important in the US, where LDTs are now the primary avenue for test development. Having come to the attention of federal oversight committees, the US FDA has now taken steps to provide preliminary guidance on a sub-category of LDTs known as *In Vitro* Diagnostic Multivariate Index Assays ('IVDMIAs'). Questions remain, however, about the legal (constitutional and statutory) authority of the FDA to expand its oversight in such a way, and what the proper regulatory boundaries might be. The long-standing policy against interfering with the 'practice of medicine' has been proposed as a limiting principle in the regulation of these tests, arguably allowing the FDA to ensure test quality – in effect the quality of the *assay* – while avoiding the damaging effects of excessive regulation on developing technologies. In the UK, while the same double standard for LDT and test kit regulation applies, the situation is not perceived to be quite as urgent in the context of the National Health System, which closely monitors laboratory standards. For

example, in the case of tests for inherited and heritable disorders, the UK Genetic Testing Network (UKGTN) has established procedures additionally to ensure that a test has the appropriate level of clinical validity and utility.

The regulation of laboratories is a separate issue that should not be confused with the regulation of individual tests. Laboratory regulation concerns standards for the conduct of laboratory processes, which in the UK and Europe are covered by a number of well established quality assurance schemes. The situation in the US is somewhat different, where this matter is addressed through the Clinical Laboratory Improvement Amendments (CLIA), which seeks to establish quality standards for all laboratory testing to ensure accuracy and reliability.

Table 1: Regulation of Biomarker Tests

	Technical Barrier	Potential Harm	Responsibility	Regulatory Solution	Regulatory Mechanism
Analytical validity (assay)	Technical performance.	Failure to validate analytical ability of the assay. Misleading or inaccurate results/ injurious consequences.	Test developer/ manufacturer. Laboratory	Pre-market quality and safety criteria. Laboratory quality assessment systems. IVD regulation. Consumer protection.	Statutory regime.
Scientific validity (biomarker-disease association)	Power of trials. Reproducibility of result.	Failure to validate biomarker-disease association. Misleading or inaccurate results/ injurious consequences.	Academia/ scientific researchers.	Pre-market criteria. Generation of biomarker-disease association data. Transparency.	

Table 1(con'td): Regulation of Biomarker Tests

<p>Test performance (measurement of clinical test performance)</p>	<p>Lengthy clinical trials in target population.</p> <p>Variation of results with disease prevalence and populations</p>	<p>Failure to demonstrate utility of test using clinical trials in target population.</p> <p>Clinical application of tests on basis of inadequate information.</p> <p>Misleading results.</p> <p>Consequential action resulting in physical and/or psychological injury to patient.</p>	<p>Test developer/manufacturer.</p> <p>Public-private partnerships?</p> <p>Laboratory?</p> <p>Clinicians?</p>	<p>Population trials.</p> <p>Transparency.</p> <p>Database(s).</p> <p>International collaboration re standardisation of evidence</p>	<p>Statutory requirements:</p> <ul style="list-style-type: none"> • conduct of trials • participation in data collection
<p>Clinical utility (in patient care)</p>	<p>[Absence of adequate evidence of test performance.]</p> <p>Lack of technical ability to read or interpret test results.</p>	<p>Decisions are prevention or treatment on basis of inaccurate interpretation of test results.</p> <p>Consequential action resulting in physical and/or psychological injury to patient.</p>	<p>Test developer/manufacturer?</p> <p>Policy-makers?</p> <p>Health care commissioners?</p> <p>Physician Clinician Pathologist</p> <p>Patient?</p>	<p>[Transparency re evidence of scientific validity and test performance.]</p> <p>Education of medical practitioners.</p> <p>Certification of clinician/test provider.</p>	<p>Professional self-regulatory mechanisms.</p> <p>Mandatory certification process.</p> <p>Tort law.</p>

3.5 Direct to Consumer Tests

DTC tests raise issues that differ from those encountered in relation to tests administered through a medical professional. Leaving aside the question of regulation of internet commerce, what is the cause for concern? Is it the action of market forces on the 'home consumption' of tests, or a decrease in the standard of health care, as a result of misapplication, misinterpretation or inadequate action on the basis of the results of DTC tests?

At one extreme, a liberal society would impose no requirements on test providers, except perhaps a safety assessment, and leave it to the consumer to decide whether a test is valid or useful. At the other extreme, an authoritarian or paternalistic society might ban the sale of tests for which insufficient evidence of clinical validity or even utility exists. In most jurisdictions the situation lies somewhere in between these extremes, with analytical validity generally regulated pre-market through *In-vitro* diagnostics legislation regarding laboratory certification and quality assurance, and scientific validity partially regulated through trades description acts and advertising laws. Nonetheless, some states and countries have banned sales of certain DTC tests, particularly genetic tests, due to lack of evidence of clinical test performance or usefulness and fears of incorrect interpretation by the consumer. Full and transparent evaluation of all tests is still clearly the ideal situation, but the political environment in which the tests are sold will have a significant effect on *requirement* for evaluation and therefore the level of regulation.

How then should the question of regulation of DTC tests be approached? Let's assume, to begin with, that despite being sold directly to the consumer, an assay provided DTC is 'commercially available' indicating that it has received statutorily required pre-market approval, at least as to safety and analytical validity. This might itself be a subject of discussion. Insofar as there are issues in relation to the regulation of scientific validity and test performance of DTC tests, these will be largely the same as those for tests offered by a medical clinician. This also might need further analysis,

The concern with respect to DTC tests is largely about the clinical interpretation of the information provided by the test results and any potential for physical harm that might happen as a consequence. Whereas interpretation would otherwise be handled with the discretion of a medical specialist, a DTC test requires the lay person to discern the appropriate course of action to be taken on the basis of test results. The potential harm to the individual in the event of misconstruing the results cannot be generalised, but will vary depending on the test, the results and the personal circumstances of the individual.

Questions for consideration are therefore:

- Is the potential harm to individuals such that tests involving complex biomarkers should be administered through a medical professional in all cases? Should the DTC sale of such tests be entirely prohibited?
- If not, what principles should be applied to determine which tests require the oversight of a physician and which do not? Who should be responsible for establishing such principles?
- By what mechanism should this decision-making process (which tests might be suitable for DTC delivery) take place? Is it necessary to assess each test individually as to the potential for consumer misinterpretation and harm that might result? What body should be responsible for making such decisions?
- Are specific marketing requirements, apart from generally applicable consumer protection legislation, necessary in regard to tests for DTC sales? What might be considered adequate consumer protection against the use of biomarker tests: warning labels, instructions about

application and interpretation, instructions to obtain an opinion from a physician in certain circumstances?

- At the other extreme, are there any biomarker tests that in no circumstances *require* the oversight of a medical physician?

The responses to these questions will, to a significant extent, determine how we might wish to approach the regulation of DTC tests in order to ensure the proper balance between innovation and the protection of citizens. If the central problems are perceived to involve issues concerning the assay and its scientific validity, it might be appropriate to use device regulation; if interpretation is believed to pose the main risk, then the solution might lie in establishing a link to existing forms of professional regulation.

4. Policy Considerations

Policy considerations in the economic, social, and public spheres inform the development of oversight mechanisms. In addition to the promotion of public health and confidence in the health care system, these include:

- Economic issues such as the responsibility for and the costs of establishing platforms and systems for the generation of test performance data
- The logistics and costs associated with administration of a national or international test registry
- Professional education of clinicians in specialist technologies.

Policy considerations associated with possible regulatory mechanisms for tests are summarised in Table 2.

Ethical, legal and social implications of the clinical use of biomarker tests are not the focus of this paper, although they will to some extent inform clinical utility. Certain social factors such as access to testing and treatment and their cost are critical determinants of medical outcomes. The potential for a testing program to cause long-term psychological harm is also relevant, but very difficult to assess. The fact that self-directed counselling is often used in the clinical context indicates that many testing decisions are based on personal values although clinicians will make recommendations on testing based on a combination of test validity and potential treatment options.

5. Conclusion

A variety of regulatory issues and potential solutions must be considered by the policy-maker seeking to ensure that sufficient evidence is available in support of proper interpretation in the clinical use of biomarker tests. The risks, *means* of regulation and necessary accountability will vary at each stage and in different contexts within the process of test development, evaluation and delivery. A wide range of mechanisms of oversight are available: from codes of practice and informal guidelines to professional self-governance and legal obligations. Determining the most appropriate mechanism requires a considered assessment of a number of factors, including the potential harm to be avoided, attribution of responsibility to stakeholders, and the level of enforceability required of the regulatory solution. Some of this work has already been started by the Global Harmonization Task Force in the wider context of medical devices. Finally, this needs to be accomplished without imposing undue regulatory burdens that would inhibit the development of new and useful biomarker tests.

Table 2: Policy considerations in formulation of regulatory framework

	Individual	Social/Society	Economic/ Industrial	Government/ Public
General (clear and coherent framework of regulation)	Promotes health and safety.	Public confidence.	Certainty supports innovation and strengthens market potential.	Administration of regulatory regimes. International collaboration
Analytical validity (assay)	Protection of consumer safety.		Cost of administration of pre-market approval mechanism	Promotion of public health Increase public confidence
Scientific validity (biomarker-disease association)	Protection of consumer safety.	Public confidence.	Cost of administration of pre-market approval mechanism Support for innovation & industry	Promotion of public health
Test performance (measurement of clinical test performance)	Individual access to all data on performance of tests: evidence base informs clinical use and ‘direct to consumer’ choices Appropriate form of consent to individual participation in population trials, use of results.		Funding for lengthy population-based trials. Public/private costs associated with building, maintaining and enforcing use of database.	Facilitating transparency. Public confidence Public (?) administration of database of biomarker test evidence
Clinical utility (interpretation of tests in patient care)	Sufficient evidence means test results can be properly applied and interpreted.	Certainty strengthens physician/ patient relationship.	Use of tests in absence of evidence of test performance = inefficient use of resources.	Public confidence in/public responsibility for health services delivery.

	<p>Avoidance of physical and /or psychological harm to patient.</p> <p>Ultimately patient health benefits.</p> <p>Appropriate form of consent to application of test, use of information.</p>	<p>Confidence in results extends to use of information by family members.</p>	<p>Cost of education and certification of clinicians.</p>	<p>Difficulty of assessment of impact of tests on service and true cost/benefit.</p> <p>Transparency re evidence of scientific validity and test performance.</p>
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