ABSTRACT – Through the lens of public health genomics, this article probes certain issues that concern the evaluation of diagnostic tests and molecular biomarkers, and the accompanying policy and regulatory implications. It begins with some conceptual remarks followed by a discussion of evaluation, translation, and regulation, and their importance for public health.

KEY WORDS: biomarkers, diagnostic tests, translation, regulation

Conceptual issues

Diagnosis is about classification and how it may be used as a label to aid prediction, prognosis and treatment.1 The label, the diagnosis, is not an end in itself but an intermediary, a means to an end. Diagnosis is no use in itself; there must be a purpose, an objective. Tests, including the use of clinical symptoms and signs, are the means by which a diagnosis is made so that a decision or an action can be taken. It is also the case that one can make no statement about the effectiveness of a test without knowing its purpose or objective since purpose is inherent in the formal definition of the effectiveness of a healthcare intervention. But it is not just purpose that is important in test evaluation. The nature of the disease is also important. The effectiveness, validity or utility of a test is dependent on the disease or disorder under consideration. The third factor that has a bearing on test interpretation and evaluation is population and, in particular, the effect that the disease prevalence in the studied population critically affects the test’s predictive value.2

The term ‘biomarker’ is often used in this context rather than diagnostics or diagnostic tests. It has been more broadly defined by the Food and Drug Administration as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. There are many reasons for carrying out a test, of which the making of a diagnosis is but one (Fig 1).

These considerations lead to the most important conceptual insight into biomarker or diagnostics evaluation, the distinction between an ‘assay’ and a ‘test’. The assay is a method for determining the presence or quantity of a component whereas the test is its use in the context of a particular disease, in a particular population, for a particular purpose. The distinction has an important practical implication. 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 and interpretation depending on how the test is to be used in the particular context of disorder, population and purpose.2

Evaluation

Various frameworks have been developed for this process. The genomics community has settled on the ACCE framework to guide its activities (Fig 2).3 The analytical validity is essentially a measure of the technical evaluation of the assay used in the test. It defines the ability of the assay to measure accurately and reliably the component of interest. Its performance is judged against an agreed reference standard. The clinical validity of a test by contrast defines the ability of the assay to detect or predict the presence or absence of clinical disease or risk of disease in the context of population and purpose. It is of the utmost importance to understand that there are two separate aspects to clinical validity. First, there is the need to show evidence of biomarker-disease association. This is essentially a matter for epidemiological studies which are normally carried out by the scientific community. Second, assuming that such an association has been demonstrated and validated, it will additionally be necessary to ascertain test performance using measures such as sensitivity, specificity,
positive and negative predictive values, likelihood ratios (both positive and negative), and area under the receiver-operator curve (ROC). The fact that there is well confirmed biomarker-disease association does not entail that the performance of the test is necessarily valid, that it necessarily serves to discriminate accurately between an individual with or at risk of a disease from one who is without disease or at lower risk. Validity cannot be assumed; it must be empirically determined.

Clinical utility refers to the likelihood that the test will lead to an improved outcome. It is here that the purpose of the test becomes an essential element. To date, this has been a much neglected area, but recently ways by which to set out dimensions of clinical utility have been explored.4

This analysis holds true for diagnostic tests, but its application to predictive tests will need some modification. Whether predictive or diagnostic the actual reality is that for many tests in use formal evaluations along the lines suggested above have not been carried out. It has been proposed that for simpler tests, such as serum sodium or a white blood count, such formality is not required. The failure to evaluate the newer complex molecular biomarkers will be highly detrimental for the proper care of patients and for the financial health of the NHS.

Translation

This section discusses the translation of scientific advances, in particular biomarkers and diagnostic tests, into effective technologies and interventions for individuals and populations. The Cooksey Report, published in December 2006, set out a strategy for the funding of UK health research.5 It outlines a pathway from basic research through preclinical development, clinical trials, health technology assessment and health services research into healthcare delivery. It identified two gaps in translation: the first arising from the translation of the results of basic scientific or clinical research into products that might, in due course, be disseminated into wider healthcare practice – a process that has been summarised in the phrase ‘from bench to bedside’ and called by others ‘type I translation’; the second relating to the evaluation of these new products and their implementation into routine clinical practice – ‘research into practice’ referred to by some as ‘type II translation’. Both gaps, it suggested, needed to be addressed through translational research.

These ideas are, of course, not new. The Shattuck Lecture in 2003 in the New England Journal of Medicine was entitled ‘Clinical research to clinical practice – lost in translation?’. It bemoaned the fact that it took far too long before clinical practice caught up with the results of research findings.6

Elias Zerhouni, Director of the National Institutes of Health (NIH), proposed a new vision in 2003, the NIH Roadmap, in which he stated that it was necessary to ‘re-engineer the clinical research enterprise’ such that ‘translational and clinical research are core components of a full-spectrum biomedical research enterprise’.7 Despite all this, the emphasis and research funding continues to be directed at basic research and at type I translation, as evidenced by research on publications in the genetic literature, which showed that under 3% was on research that fell outside the range of type I translational activity. Indeed Lawrence Green from the University of California dubbed type II translation as ‘the roadmap less travelled’.8

The other point that might be made about Cooksey and translation is that it failed, first to mention the importance of the population sciences, especially biostatistics and epidemiology, in the translation process; second, that there was a social, legal, ethical and policy context to consider; and third, that outcomes could not be confined to service delivery but had to include policy development.

Jonathan Lomas was quite explicit in stating, ‘For research findings to effectively influence health services’ delivery of care needs an ‘intermediary’.9 This intermediary is the knowledge broker; in Lomas’ view, an entrepreneurial, trusted, credible communicator who understands the cultures of the research and decision-making environments and is able to facilitate, mediate and negotiate the way between the one and the other culture. Both research and decision making are complex processes, not products or events, which need active management by an agent who is able to interpret between the two cultures in order to drive the change necessary to get research into practice. The literature on translational research has not attended adequately to the concepts in Lomas’ paper, and policy makers have on the whole failed to distinguish (and have even conflated)

**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
translational research from the process of translation as envisaged by Lomas. This failure (seen also in Cooksey), to distinguish and to adequately fund, is particularly starkly seen when considering diagnostics and biomarkers.

**Regulation**

Regulation is a term that is often used synonymously with statutory regulation – in effect, a legal restriction promulgated by government and supported by a threat of sanction or a fine. This, however, is far too narrow and the word should be used (at least in the context of public policy) to encompass any form of control or governance of behaviour. It has been suggested that in the context of genetic tests, essentially their regulation could be thought of as taking place in three separate domains – through statutory mechanism, through control of resources by funders or reimbursers of healthcare, and through mechanisms of clinical governance at the level where physicians and patients interact. Over the past three years, working with David Melzer at the University of Exeter on a project funded by the Wellcome Trust, the policy issues in genetic testing have been explored. Key players in this field on both sides of the Atlantic were interviewed, individually and in focus groups. The conclusions reached in this study were echoed and reinforced by the deliberations of a diagnostic summit organised by the PHG Foundation and the Royal College of Pathologists in January 2008. A summary of its key recommendations are shown here (Fig 3).

**Statutory regulation**

Biomarkers are regulated as medical devices and, in the UK, this is carried out by the Medicine and Healthcare products Regulatory Agency (MHRA). The regulatory framework is based upon the European In Vitro Diagnostic Medical Devices Directive 98/79/EC. The language that is used suggests that it is statutory regulation – in effect, a legal restriction promulgated by government and supported by a threat of sanction or a fine.

There is much that can be said about this matter. But in brief, first, some reliance has to be placed on the other two domains of regulation – reimbursement and clinical governance; and second, the mechanism that will allow these domains to be effective in their task is the establishment of an open and transparent database of evidence.

**Public health implications**

It is now no longer acceptable to take the view that physicians can, purely as a result of their training, interpret all test results effectively without some help. One reason is that commissioners and funders of health services throughout the developed world are under extreme financial pressure and will require evidence of effectiveness before funding a test. This is essentially the reason why an evidence base is necessary. A second is that tests are more complex, being made more generally available, and have been increasing in numbers. I suggest also that tests that predict the risk of disease, or allow the prognosis of disease to be determined, will be of increasing importance in the coming decades.

Although the NHS keeps very little data on tests and test costs, it has been estimated by the Audit Commission that the total number increased by 6.4% per year (in biochemistry and haematology) and 9.5% per year (in
evaluation of novel diagnostics and molecular biomarkers

between 2000–1 and 2005–6. In East Anglia there
has been a 14% per year compound growth in molecular genetic
testing between 2002–3 and 2007–8. These numbers, between
2,500 and 6,000, can be put into context. Addenbrookes
Hospital carried out 3,252,590 pathology tests in the 2007–8
financial year of which 1,921,273 (59.1%) were for biochemical
tests. In financial terms, pathology accounted for £18m (4.97%)
of the trust’s £362m expenditure.13

A third reason is that predictive tests bring their own chal-
lenge and should be handled differently to conventional diag-
nostics. There is a real sense that predictive (pre-disease) bio-
markers differ from post-disease biomarkers where, in effect, the
disease is already present. The diagnostic biomarker, whether
radiological, biochemical or physiological, serves as a conse-
quential indicator of the disease process. The predictive bio-
maker, by contrast, is an indicator of future disease; disease
which, by definition, is not present and where the biomarker is
not a consequence of disease. It is a risk factor which may either
be on the causative pathway to disease or is linked with some
other factor that is on that pathway. The standard performance
characteristics used for diagnostic tests, such as sensitivity or
specificity and the dichotomisation of test results into positive
or negative may not provide the correct approach for conceptu-
alisng how such predictive tests should be evaluated and used.

The new genetic and molecular biomarkers, unlike conven-
tional diagnostics, also tend to be characterised by low relative
risks (RRs) or odds ratios (OR). Effect sizes are usually less than
1.5 and often in the range of 1.05 to 1.2. These are certainly the
sorts of numbers that are seen emanating from whole genome
scans in various complex disorders. Sceptics have correctly
pointed out that the low RRs of 1.0 to 2.0 will never allow one,
using a single marker, to distinguish (with acceptable levels of
false positives and negatives) those who will develop disease
from those who will not.14 By contrast, multiple biomarkers
may have some utility.

An example is provided from the field of prostate cancer
where the RR of individuals with a family history and one
abnormal allele is 1.62, whereas with five or more abnormal
alleles the risk goes up to 9.46.15 A

Fig 4. Regulation of biomarkers. HSR = health services research; HTA = health technology
analysis; IVD = in vitro diagnostic.

example, might not recommend prostrate-specific antigen
testing in an asymptomatic male, but would that advice hold for
those who have all five of the abnormal alleles in the example
cited above? The answer is unknown.

Direct consumer testing

There has been much anxiety over their lack of regulation and
the fact that these tests are offered to the public with a very poor
evidence base. Caroline Wright has reviewed 29 companies and
the level of information that they provide against guidelines for
direct to consumer testing from the American Society of Human
Genetics. Wright has shown that none provide evidence of clinical
validity and few point out the risks. Scientific publications are
only cited in 50% of cases. At an epidemiological level, Cecile
Janssens and colleagues have studied the gene-disease
association of tests offered by seven companies directly to con-
sumers. The salient result from their study was that significant
associations were only found in 38% of those polymorphism-
disease associations that they investigated.17

A regulatory gap does exist but I am not convinced that the
statutory regulators of in vitro devices such as the MHRA can
easily carry out this function on their own. To the extent that
claims are made for biomarker-disease association by test manu-
ufacturers, it would not seem unreasonable for the regulators
to require evidence of scientific validity, namely that such claims
are substantiated in the scientific literature – since by definition
a false or unsubstantiated association cannot result in a clinically
useful test. But once an association is substantiated, no matter
how small, it would seem that there is a small chance that the
test may be clinically valid or useful.

The question of how and where the responsibility for regula-
tion should lie may be discussed in the light of the distinction
between the assay as the measurement, and the test as the inter-
pretation of that measurement. It has already been noted that
the assay is the responsibility of the statutory regulator of in vitro
devices. Interpretation, by contrast, has always been the respon-
sibility of the clinician, and where it is the interpretation of the

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Implications to health promotion and disease prevention

As a consequence of the growth in complex molecular biomarkers, a shift in the paradigm in terms of how health is promoted and disease is prevented may need to be considered. Public health interventions have classically been directed at the external environment – matters such as water or air quality – or to economic, political and social factors, such as fiscal policy in relation to alcohol which affect whole populations and communities. In recent years, attention has been additionally directed at behavioural determinants of health. By so doing the idea of a population has been altered in a subtly different way – conceptualising it not as a single entity but as collections of individuals.18

The development of genetic and molecular biomarkers allows us to differentiate individuals within populations even further by categorising them into groups based on estimates of their absolute risk of disease. The preventive intervention would not be uniform across a population but would vary according to an individual’s risk. Cardiovascular risk assessment based on age, sex, cholesterol levels, blood pressure (BP) and smoking history provides an example of this type of preventive intervention that is already being used in general practice. Although all three approaches may be characterised as preventive interventions they have different social, legal and ethical implications (all of which need further exploration), and with the progress in genetic, cell and molecular science, the move towards such individualised or stratified prevention will accelerate – with profound implications for the practice of public health and health promotion.

Margaret Pepe suggested that by comparing the probability density function of a risk factor among persons who will develop the disease and those who will not, biomarkers of low RRs necessarily fail to meet the standards for a credible and valid test. In the case of preventive biomarkers, this may not be so. Indeed, raised cholesterol or BP levels that are used routinely in practice probably confer ORs of between 2 and 10, depending on the magnitude of the rise.19

Paul Pharoah uses as an example a scenario that once the main genetic determinant of a disease, such as breast cancer, have been elucidated, it will be possible, for example, to divide the female population into different groups according to genetic or biological risk; and to give different advice about mammography according to where the individual sits on this continuum.20

The generalisation of this insight is that more attention should perhaps be paid to an understanding of absolute risk and the levels at which individuals undergo particular interventions for certain diseases. The critical factor then becomes not so much the RR that the possession of a biomarker will impose (since with most the ORs will be relatively low) but an understanding of the baseline absolute risk of the individual and the absolute risk threshold for a particular intervention. This approach accords closely with how clinicians take decisions, and the notion that all tests are done for a particular purpose and with some action in mind.

Using this notion, predictive biomarkers may be viewed as genetic variants with low ORs, not as a diagnostic test in the conventional sense, but as extra pieces of data that will serve to modify absolute risk estimations. On this interpretation, all biomarkers, no matter how small the effect size, provided the disease association has been shown to be real, may have a potential use.

Conclusion

1 The distinction between an ‘assay’ and a ‘test’ is crucial to understanding the roles of statutory regulators and others in test evaluation.
2 Clinical validity requires more than evidence of gene-disease association; it also requires evidence of test performance such as sensitivity, specificity, positive and negative predictive values.
3 The main problem is lack of data; policy is urgently needed to establish systems and resources to generate evidence of test performance, and to agree the respective roles and responsibilities of government, statutory regulators, public bodies, academia and the commercial sector.
4 Systems should be established to ensure that the data are appropriately analysed and evaluated against agreed standards and that the evidence is placed in the public domain.
5 Funders and reimbursers of health services and clinicians should be discouraged from purchasing and using tests that are not backed by appropriate clinical evidence.
6 The role of statutory regulators should be confined to (a) ensuring the safety of all tests and biomarkers (b) ensuring that claims for biomarker-disease associations are genuine and real, and (c) requiring all evidence of test performance (or lack of it) to be placed in the public domain.
7 The public health community should anticipate the advent of stratified prediction and prevention and its implications for health promotion messages.
8 The conventional model for diagnostic tests may not be appropriate for predictive biomarkers. Instead attention should be directed at understanding absolute risk and how biomarkers may alter such risk in the context of preventive interventions.

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