SCIENCE AND SOCIETY

Ensuring the appropriate use of genetic tests

Wylie Burke and Ron L. Zimmern

Abstract | Ensuring the correct use of genetic tests is an important challenge for health-policy makers. Many new genetic tests will identify susceptibility to common diseases or adverse drug responses. Some will lead to new prevention opportunities, but others will have minimal clinical value. Statutory regulation alone cannot guarantee appropriate use. Other strategies, including resource allocation and matters related to clinical governance — such as practice-guideline development and health-provider education — are also important.

As a consequence of the completion of the Human Genome Project, an increasing number of genetic tests are becoming available to clinicians. New genetic tests will increasingly address clinical questions relevant to mainstream clinical practice, such as genetic susceptibility to common diseases and individual variation in drug response. Although some tests will provide effective new health-care alternatives, others will probably fall short of their promise, or entail substantial costs or risks. Defining and implementing genetic testing protocols that have a high chance of providing benefit, while avoiding questionable uses, represents an important health-policy challenge.

The promise of genetic testing — with its emphasis on 'PERSONALIZED MEDICINE' (see Glossary) and improved disease prevention — is intuitively appealing, and has been widely touted[1,2]. Genetic tests have traditionally been used to identify rare genetic conditions, but many new tests will identify relatively common gene variants that represent a new class of risk factors. With a large potential market for such tests, commercial incentives will have an important role in test development. Policy makers therefore have good reason to be wary of a technological imperative that might lead to the wide adoption of genetic tests without a considered assessment of the pros and cons.

There are several strategies for guiding the appropriate use of new medical technology; including evaluation procedures to define test properties, statutory regulation, decisions about the use of health-care resources, practice guidelines and health-provider education (FIG. 1). Here, we consider the application of these strategies to genetic testing.

The challenge of genetic testing

Given the diverse clinical applications of genetic tests, determining appropriate use can be challenging (TABLE 1). For example, a test used to diagnose a rare genetic condition might also be used to predict its occurrence in asymptomatic family members, detect carriers for the condition or aid in prenatal diagnosis. Testing can be done in the absence of effective treatment to provide a prognosis or determine reproductive risk. Conversely, some tests are done primarily to guide treatment. Newborn screening, for example, is done to identify newborns with genetic disorders that require rapid initiation of treatment, such as PHENYLKETONURIA (see also Online links box). However ANALYTIC VALIDITY, CLINICAL UTILITY and CLINICAL VALIDITY are important properties to be considered for all genetic tests[3,4].

The assessment of clinical utility poses particular challenges for genetic tests that assess drug response or susceptibility to common diseases. In contrast to tests for single-gene disorders, these tests have limited predictive value. For example, factor V Leiden, a gene variant of the factor V gene, confers an increased risk of venous thrombosis[5]. However, a population-based study indicates that the cumulative risk by the age of 80 is only about 12% (REF. 6). Other risk factors, including other gene variants and non-genetic factors such as cigarette smoking, immobility, pregnancy, surgery and oral contraception, influence whether venous thrombosis will occur in a person with factor V Leiden. Importantly, most cases of venous thrombosis occur in people without factor V Leiden.

For tests of this kind, a stringent approach to clinical utility would recommend that the test be used only when effective interventions are available to improve the health outcome of people with the gene variant. Without effective therapy, testing could result in adverse labelling of an individual as genetically susceptible, without any commensurate health benefit; and could also lead to the use of unproven therapy with its associated risks. Moreover, the resources used in such tests could be used for other health interventions with beneficial outcomes. However, this perspective contrasts with the emphasis that medical genetics has traditionally placed on the value of knowledge about risk.

Disagreements can also occur about the evidence that is needed to document health benefit. For example, when is a randomized controlled trial necessary to prove a health-outcome benefit, versus less definitive observational data? Similarly, to what extent should tests be used as a means to motivate healthy behaviour? Many genetic tests can identify gene variants that increase the risk of heart disease; for example, apolipoprotein E4 (apoE4)

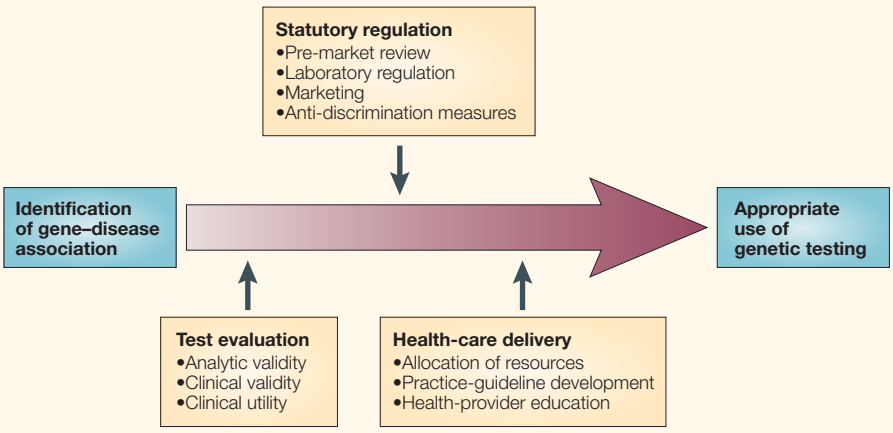

Figure 1 | **The discovery of a gene–disease association lays the groundwork for the development of a genetic test.** Technical evaluation is needed to define the test's properties. Both statutory regulation and mechanisms related to funding, practice-guideline development and health-provider education contribute to ensuring appropriate test use.

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Table 1 | **Diverse uses of genetic testing**

Test type	Examples
Tests for gene mutations with high penetrance*	
Diagnosis of genetic disease	Testing of patient, following indicative clinical findings, to confirm genetic diagnosis
Newborn screening	Testing of newborn to identify conditions that require immediate initiation of treatment to prevent death or disability
Carrier tests	Testing to identify an asymptomatic adult who is a carrier for autosomal-recessive or X-linked recessive conditions. Testing is usually initiated on the basis of family history or because the genetic condition is common among individuals of the patient's ethnicity
Prenatal tests	Testing to identify a fetus with a genetic condition. Testing is usually initiated on the basis of maternal factors or family history that indicate increased risk. Some prenatal genetic tests are offered routinely; for example, maternal serum screening to identify increased risk of neural-tube defects or Down syndrome
Tests for adult-onset genetic conditions	Testing of asymptomatic young adults to identify a genetic condition that will occur later in life, such as Huntington disease
Tests for gene variants that are associated with genetic susceptibility	
Assessment of genetic risk for common complex diseases	Testing to identify an increased risk of future health problems, such as heart disease or diabetes
Tests to predict drug response	Testing to identify an individual with less likelihood of response, or increased risk of adverse reaction, to a particular medication

*The proportion of affected individuals among individuals with a particular genotype. If all individuals with a disease genotype show the disease phenotype, then the genotype is said to be 'completely penetrant'.

(REF. 7). The health recommendations for people with this risk — avoidance of smoking, regular exercise, monitoring of lipid concentrations and blood pressure — are nonspecific, and whether knowledge of such risk will motivate healthier behaviour is still a matter of considerable debate[8]. In addition, testing might provide unsought risk information. In the case of apoE4, an increased risk for Alzheimer disease would also be identified[9].

Who should make the testing decision — the clinician, the health-care payer or the patient — and on what basis? How these questions are approached will affect the availability and use of genetic tests. Assumptions about a potential test's purpose and market, and the regulatory standards that a manufacturer must adhere to, will influence whether the test is developed. Expectations of health-care-systems providers and patients will influence the practice standards and payer decisions that determine test use over time. The regulation of genetic tests can be seen as a set of strategies — some of which are specific to genetic tests, whereas others are applicable to medical testing in general — that increase the consistency of these decision-making procedures.

Statutory regulation

Statutory regulation — the development of rules and standards through legislation or other legal mandates — represents an important mechanism for controlling test delivery and use. We cite examples from the United Kingdom and the United States to show the current application of this approach (TABLE 2); similar approaches are being undertaken in most developed countries.

Laboratory regulation. Laboratory supervision and accreditation schemes are in place in the United States, Europe (including the United Kingdom), Canada and Australia. For example, in the United Kingdom, the Clinical Pathology Accreditation Co. Ltd (CPA) and the UK Accreditation Service (UKAS) carry out accreditation of pathology services, including molecular genetics and cytogenetics; the Clinical Molecular Genetics Society publishes best-practice guidance for laboratory procedure and audits the National Health Service (NHS) laboratories. Accreditation requires laboratories to conform to standards that address staffing, training and the physical environment of the laboratory, as well as laboratory procedure.

Current discussions of laboratory supervision focus on two issues: harmonization of regulatory and quality-assurance standards — for example, within the European Union[10,11] — and the question of extra supervision of laboratory procedures related to genetics. In the United States the advisory committee for Consolidated Laboratory Improvement Amendment (CLIA)[12], which governs laboratory supervision, has proposed the creation of a genetic testing specialty. The proposal stems from concerns about the technical complexity of many genetic tests. If enacted, the new regulation would impose specific staffing and quality requirements on laboratories that perform genetic tests.

Pre-market review of genetic tests. In contrast to laboratory regulation, pre-market review of genetic tests is variable and often limited. A key issue is whether this regulatory oversight should extend to 'home brew' tests — tests done in a laboratory using the laboratory's own reagents and protocol — which constitute the majority of genetic tests. In the United States, pre-market review is the responsibility of the Federal Drug Administration (FDA), the same agency that oversees drug safety. Currently, this agency reviews genetic tests that are manufactured as kits, but not home-brew tests. The primary focus of the FDA review is on the verification of the manufacturer's claims of analytic validity; the review also ensures standardized test-labelling, including a statement of the test's intended purpose. In 2000, a federal advisory committee recommended extension of the pre-market review to all genetic tests, a change that would have represented a significant increase in regulatory authority[13]. Although the FDA was instructed to begin exploring this added responsibility, the recommendation was controversial, and had not been put in place at the time when the advisory committee was disbanded[14].

In the European Union, the legislative instrument for test evaluation is the EU *In-Vitro* Diagnostics Directive 98/79/EC. In the United Kingdom, the directive is implemented by the Medicines and Healthcare Regulatory Agency (MHRA). Regulation applies both to test kits and to services provided in the marketplace. The directive does not cover home-brew tests that are used internally.

Arguments for pre-market review might be more persuasive for certain categories of genetic tests. For example, recent actions by the FDA indicate that this US agency is preparing for a more active role in overseeing PHARMACOGENETIC tests. In November 2003, the FDA issued a draft guidance for public comment, proposing voluntary collection and submission of pharmacogenomic data by pharmaceutical companies, because such data might in the future facilitate drug development and provide information for regulatory decisions[15]. The FDA also recently added a

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label to THIOGUANIONE tablets, noting that individuals with an inherited deficiency of the enzyme thiopurine methyltransferase (TPMT) "…may be unusually sensitive to the myelosuppressive effects of thioguanine and prone to developing rapid bone marrow suppression following the initiation of treatment. Substantial dosage reductions may be required…"[16]. This label, although not imposing a testing requirement, encourages genetic testing before thioguanine use, and illustrates how small actions by a regulatory agency have the potential to influence clinical practice.

Medical advertising. Direct-to-consumer and direct-to-physician advertising also offers opportunities for regulatory action. The United Kingdom does not allow direct-to-consumer advertising of pharmaceutical products, but has no such prohibition on test advertising. Consequently, there has recently been much concern about the direct advertising of genetic tests for over-the-counter use. In March 2003, the Human Genetics Commission (HGC) concluded that it was not appropriate for the state to intervene "…unless there is a risk of harm, particularly to vulnerable people like children or the elderly"[17]; so although stricter controls were recommended, the HGC did not wish to see a statutory ban.

The approach in the United States is to allow direct-to-consumer marketing of medical products, and advertisers are required to comply with 'truth in advertising" standards. The FDA oversees the advertising of the products it regulates and has occasionally requested changes in advertising messages. However, the FDA has been criticized as being insufficiently rigourous[18]. The Federal Trade Commission oversees advertising of other products, including health-related products such as dietary supplements, and the adequacy of this regulatory oversight has similarly been questioned[19].

Direct-to-consumer advertising might cross national boundaries, especially in media such as the internet or television, limiting the control of national regulatory schemes. Discussions that promote the harmonization of regulatory approaches might be of particular value in this area.

Regulation of test use. Several US states and European countries have introduced laws that limit employers' and/or health insurers' use of genetic information to a varying degree[20,21]. These laws indicate a consensus against the use of genetic susceptibility information in access to health services and employment. Whether genetic information is likely to be used for this purpose is not yet clear[22], and the optimal regulatory strategy remains uncertain. The UK HGC found little evidence for the systematic use of genetic testing by employers, but recommended that employers voluntarily notify the HGC of intentions to use genetic testing in employment decisions[23].

The use of genetic information in other non-medical settings — such as in life insurance decisions — is also under discussion. For example, the UK government has formed a Genetics and Insurance Committee (GAIC) to assess insurance providers' applications to use genetic test results for insurance underwriting purposes. It has enacted an agreement with the insurance industry for a voluntary moratorium on the use of genetic test results in assessing applications for life insurance policies, up to a value of £500,000; and for critical illness, long-term care and income protection policies, up to a value of £300,000. These limits will be reviewed in 2006.

Role of statutory regulation. These examples indicate that statutory regulation is an accepted element in the oversight of genetic tests, with a primary focus on the quality of laboratory procedures. Other uses of statutory regulation vary in scope in different locations, and are undergoing active development. Some efforts to promote harmonization of laboratory oversight are underway[10,11], and this approach is likely to be helpful in other areas of regulation as well.

In considering any further extension of statutory regulation, policy-makers will need to consider the underlying goal to be achieved. Is the goal to protect the public from unsafe products that can directly cause harm? Or does the state have a duty to protect its citizens from products that do not work ('snake oil'), or are too expensive for the benefit they provide, even if they are 'safe'? The latter task would be more challenging and more controversial, and would require regulatory mechanisms to consider the clinical validity and utility of tests. We believe that regulatory goals related to these aspects of test use might be better accomplished through other strategies within the health-care system.

Other regulatory mechanisms

Several mechanisms within the health-care system provide the potential for regulating the use of genetic tests on the basis of clinical validity and utility. Efforts to strengthen these mechanisms will encourage much-needed research and will probably have an important role in assuring appropriate use of genetic tests.

Allocation of health-care resources. Health-care payers, whether health maintenance organizations (HMOs), insurance companies or commissioning organizations within a national health-care system, have finite budgets. The need to obtain the best value from limited funds will motivate health-care payers to purchase only those tests that provide a health benefit and that are cost-effective. To accomplish this goal, however, mechanisms must be in place to determine

Table 2 | **Regulation of genetic testing: examples from the United States and the United Kingdom**

Area of regulation	United Kingdom	United States
Laboratory standards	Laboratories must meet the standards of the CPA and the UKAS	Laboratories providing results to patients or clinicians must meet the standards of the CLIA
Pre-market review of genetic tests	All genetic tests and services must meet the standards of the European directive on *in vitro* devices	Tests kits receive pre-market review by the FDA; 'home brew' tests are not reviewed
Direct-to-consumer marketing of genetic tests	Although direct-to-consumer advertising of drugs is prohibited, there is no statutory ban on advertising of genetic tests	Marketing must meet the general requirements of the FTC; or of the FDA for FDA-reviewed products
Test use	There is no statutory regulation of the use of genetic tests in employment or insurance. The GAIC assesses applications by insurance providers to use genetic test results for insurance underwriting purposes	Many states bar the use of genetic testing information in employment or health insurance coverage decisions

CLIA, Clinical Laboratory Improvement Ammendment; CPA, Clinical Pathology Accreditation Co. Ltd; FDA, Federal Drug Administration; FTC, Federal Trade Commission; GAIC, Genetics and Insurance Committee; UKAS, United Kingdom Accreditation Service.

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the clinical validity and utility of different tests and to evaluate their implications for clinical practice.

Regulation by health-care resource allocation is crucially dependent on building and strengthening systems for genetic test evaluation developing authoritative practice guidelines and ensuring well-informed health-care providers. For example, attempts are being made by the National UK Genetic Testing Network to establish a 'menu' of molecular genetic tests that are judged, following some basic evaluation, to be of sufficient validity and use to warrant funding by commissioners within the NHS.

Practice guidelines. Historically, practice standards for the use of genetic testing were formulated on the basis of expert opinion. More recently, formal methods to develop clinical practice guidelines that use the concepts of 'evidence-based medicine' have been proposed[24–26]. In this approach, testing or other medical interventions are generally not recommended unless high-quality evidence shows that they result in improved health outcomes.

The application of evidence-based medicine to genetic testing has been controversial. For example, Childs and Valle[27] argue that the data most valued in the evidence-based medicine model — derived from large population-based clinical trials — are inherently insufficient for the clinician attempting to individualize care on the basis of genetic risk. In addition, Wilcken[28] has argued that randomized clinical trials might be either unfeasible or unethical for many genetic conditions. If a condition is rare, and complications can occur over the course of several years, the logistical requirements for a randomized clinical trial might be difficult to meet. In these circumstances, basic science and clinical observation might provide sufficiently compelling information about treatment options to justify testing. For example, people shown by genetic testing to have multiple endocrine neoplasia type 2, an inherited condition causing a high lifetime risk of medullary thyroid cancer, are treated with prophylactic thyroidectomy, on the basis of clinical observation rather than controlled outcome studies[29]. Medical geneticists can point to substantial evidence that this approach is beneficial[27,28].

It is questionable whether this traditional approach will prove acceptable for most new genetic tests, given the concerns about health-care costs and the availability of evaluation strategies such as those used by the NHS Health Technology Assessment programme and the US Preventive Services Task Force[30–32]. In particular, a strong argument can be made for the use of an evidence-based approach in the evaluation of genetic susceptibility and pharmacogenetic tests, because the claims for these genetic tests are made on the basis of their potential to provide a new route to disease prevention[1,2].

However, lack of data represents a substantial barrier to the development of practice guidelines for new genetic tests. For example, two recent guidelines on the use of factor V Leiden testing rely largely on expert opinion for resolving questions related to clinical utility[33,34]. Similarly, the assessment of newborn screening tests is limited by lack of data on the outcomes of screening[31,32]. The development of efficient research strategies to investigate health outcomes associated with genetic testing is therefore a crucial factor in ensuring appropriate test use.

Objective investigation of the health consequences of tests to predict common disease risk or drug response will allow those with clinical utility to be identified. Many potential tests will have only modest effects on risk status, because both disease aetiology and drug response are complex phenomena that are influenced by multiple genes and environmental factors[35,36]. As a result, it is probable that only a minority of gene variants that are found to have clinical associations will provide information on susceptibility that is relevant to clinical practice.

Education of health-care providers. Even with well-reasoned clinical-practice guidelines, effective use of genetic tests will depend to a substantial degree on the ability of providers to collect relevant clinical data, such as family history, and make confident recommendations about the use of testing in particular clinical situations. Current research indicates that health-care providers are poorly prepared to integrate genetics into their practice[37]. Strategies to develop the genetics competencies of the health-care workforce therefore represent another way to ensure appropriate test use[37,38], potentially backed by regulation through professional governance procedures. Achieving this goal will require studies to identify the best methods for providing genetics education, as well as an infrastructure to support the development and dissemination of educational materials. Important pilot efforts are in place[39,40], but substantial, continued investment is needed.

Conclusions

Genetic tests are used for various purposes, with hypotheses about the benefits of these tests actively evolving. Many tests with potential commercial value — for example, tests to predict drug response and risks for common, complex diseases — will pose particular problems with respect to measurement of clinical validity and utility. Evaluation of these properties will be difficult, but this process is necessary to distinguish tests that lead to health outcome benefits (most probably a minority) from those that will provide limited risk information without an associated health benefit.

There is no accepted methodology for establishing the clinical utility of a genetic test. Although the technical evaluation of test properties might be a scientific matter, the standards for test use are influenced by societal values. Many competing interests are at stake, including the value that consumers and health-care providers place on genetic risk information, the relative weight that is attached to preventive and primary care within a health-care system, the costs of genetic services relative to other health-care services, and the commercial interests of test developers.

An example might be the pre-test probability of finding a breast cancer types 1 and 2, (BRCA1 or BRCA2) mutation in an asymptomatic family member. Should the recommendation for testing occur with a probability, on the basis of pedigree analysis, of 15%, 20% or

Glossary

ANALYTIC VALIDITY
The accuracy with which a particular genetic characteristic — such as a DNA sequence variant, chromosomal deletion or biochemical indicator — can be identified in a given laboratory test.

CLINICAL UTILITY
The risks and benefits resulting from test use.

CLINICAL VALIDITY
The accuracy with which a test identifies or predicts a patient's clinical status.

PERSONALIZED MEDICINE
The use of genetic susceptibility or pharmacogenetic testing to tailor an individual's preventive care or drug therapy.

PHARMACOGENETICS
The study of drug responses related to inherited genetic differences.

PHENYLKETONURIA
A genetic condition resulting in the inability to metabolize normal amounts of the amino acid phenylalanine. Mental retardation occurs if the condition is untreated, but can be prevented by the initiation of a phenylalanine-restricted diet in the newborn period.

THIOGUANIONE
An anti-metabolite medication used to treat some kinds of cancer.

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25%? Should testing only be done when clinical management will change on the basis of the test results, or is there intrinsic value to the genetic risk information provided by the test? How should the cost-effectiveness of the test be defined, and what weight should be placed on cost analysis[41]?

Genetic test evaluation should ideally include the promotion of a multidisciplinary consensus on these questions, with involvement of members of the public. Once a consensus has been achieved regarding clinical utility, issues related to access should be addressed. Without equitable access to beneficial tests, their use will contribute to health-care inequities.

Although statutory regulation of genetic testing occurs in most developed countries, it generally focuses on assuring the accuracy of laboratory procedures. A more rigourous evaluation process through statutory regulation might be considered for some tests — for example, when a test poses important safety concerns — but there are good reasons to be cautious about over-use of statutory regulation in the control of genetic test use. In particular, arguments that genetic tests require more regulation than other predictive and diagnostic tests are generally weak. Many products on the market, including vitamin pills and homeopathic remedies, are at present heavily marketed and widely used, but have little evidence to recommend them. If policy-makers were to advocate the regulation of genetic tests on the basis of the model used for medications, with careful pre-market review of all tests to assure test efficacy and usefulness, they would need to justify why other medical tests, including biochemical, radiological and other modalities, are not similarly regulated.

Indirect genetic test regulation, through guidance for health-care payers and providers, seems intrinsically more acceptable than legislative control. Furthermore the use of clinical governance as a tool for changing practitioner behaviour is probably more effective and efficient than statutory regulation. Several important steps can be taken towards implementing this regulatory strategy, including promoting consensus on the evidentiary standards needed to justify test use, ensuring adequate funding of research to assess the outcomes of testing, developing procedures for guideline development that ensure the input of all stakeholders, including the public, and developing authoritative information sources to promulgate the findings of these efforts. Health-care payers and clinicians are likely to respond positively to robust professional and public consensus concerning genetic test use.

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