Comment

What do we mean by genetic testing?

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Genetic testing is a topic that stimulates widespread discussion and debate, not just among genetics professionals, but among clinicians and scientists generally, and increasingly involving the wider public. Views are expressed in the scientific and general press, and through other media, about the likely benefits and dangers that may result, while in Britain we now have an official government body, the "Advisory Commission on Genetic Testing",[1] with a counterpart in the United States, the "Task Force on Genetic Testing".[2] It should be noted that "genetic screening", as applied to large population groups, is the exception in relation to most current genetic testing activities, though this could change in the future.

As someone involved in the practice of genetic testing as a clinical geneticist, and also in some aspects of the general debate on the topic, I have frequently found that the term "genetic testing" means different things to different people and that this can confuse any discussion on its practical consequences and general implications. Since part of this confusion has at times existed within my own mind, I have been forced to think through the issues involved and hopefully to clarify them to some extent. Perhaps others will find it helpful to read some of my conclusions, even though they are largely personal views and do not represent those of any official body.

Some definitions

There are several possible definitions of the term genetic testing, each of which may be appropriate in one particular context, but unhelpful in others. They largely depend on the meaning attached to the word "genetic".

The first definition is based on a technological interpretation and would include any test involved in analysis of the genetic material, whether involving somatic cells or the germline. Such a definition could include the numerous changes seen in the genes and chromosomes of cancer cells, mostly non-heritable, as well as DNA analysis of pathogenic organisms involved in human disease, which play an increasing role in medical diagnostics. Such tests, however important, are not usefully considered together with tests involving potentially heritable genetic changes; they do notraise the same social and ethical issues and they can properly be left along with other laboratory medical tests to be assessed, costed, and implemented (or not) on their merits.

If a more restricted definition of genetic testing is accepted, confined to the germline and specifically to the human germline, the question still arises, why is a test any less genetic because it may be analysing the product or function of the gene rather than the gene itself? There are good reasons for not restricting our definition to the analysis of DNA, since testing procedures may shift between different technologies without altering the fundamental issues involved. Thus, for fragile X mental retardation, testing originally involved microscopic chromosome analysis, is now based on detection of the specific DNA mutation, but may well in future use the protein product of the gene.[3] All three approaches can reasonably be considered as genetic testing and the relevant factor is not the technology but the fact that the test is detecting a change directly related to an inherited disorder.

For purposes of discussion relating to human inherited disorders and the surrounding medical, social, and ethical issues, a useful working definition might be along the following lines. "Genetic testing is the analysis of a specific gene, its product or function, or other DNA and chromosome analysis, to detect or exclude an alteration likely to be associated with a genetic disorder". Perhaps the most important consideration is to make sure that the definition used is one appropriate to the activities and issues that one wishes to cover.

Why is genetic testing different from other forms of medical test?

This is a question that is often asked; indeed insurance bodies have specifically denied that it is different. For "known genetic diseases such as Huntington's chorea, cystic fibrosis or Duchenne muscular dystrophy ... the insurance industry already has experience of individuals who have had a genetic test because of medical history and insurers treat the report of such tests in exactly the same way as the results of any other medical test."[4]

Such a categorical statement makes it wise to ask whether genetic testing is actually a medical investigation at all? In some circumstances it is

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clearly not. DNA fingerprinting for paternity testing or forensic analysis provides an example, while study of the normal variations in human proteins and DNA used in anthropological and population genetics is similarly not regarded as a medical activity, even though such studies may involve human genes that may be as significant as those known to underlie specific genetic disorders. That this is a line that can easily be crossed is seen by the issues raised in testing for genetic variants of ApoE, widely used as a population marker, but now shown to have important correlations with susceptibility to Alzheimer's disease[5] and cardiovascular disease.[6] It is possible, indeed likely, that other markers previously considered "neutral" may prove to have important disease associations.

At the other extreme, many diagnostic genetic tests can readily be accepted as "medical" in nature, We have, however, to be clear as to what we mean by "diagnostic". I would restrict the term to those genetic tests done on people who either have or are suspected of having a particular disorder, and where the question to be answered is whether the patient has the particular disorder at present, not whether they may develop it at some time in the future. It is increasingly possible for genetic testing to answer this question in the absence of any known family history. Such tests will most often be requested by clinicians as part of their regular clinical practice, not just by those trained in clinical genetics. These tests will also increasingly replace other less accurate or more invasive (and often more costly) medical investigations.

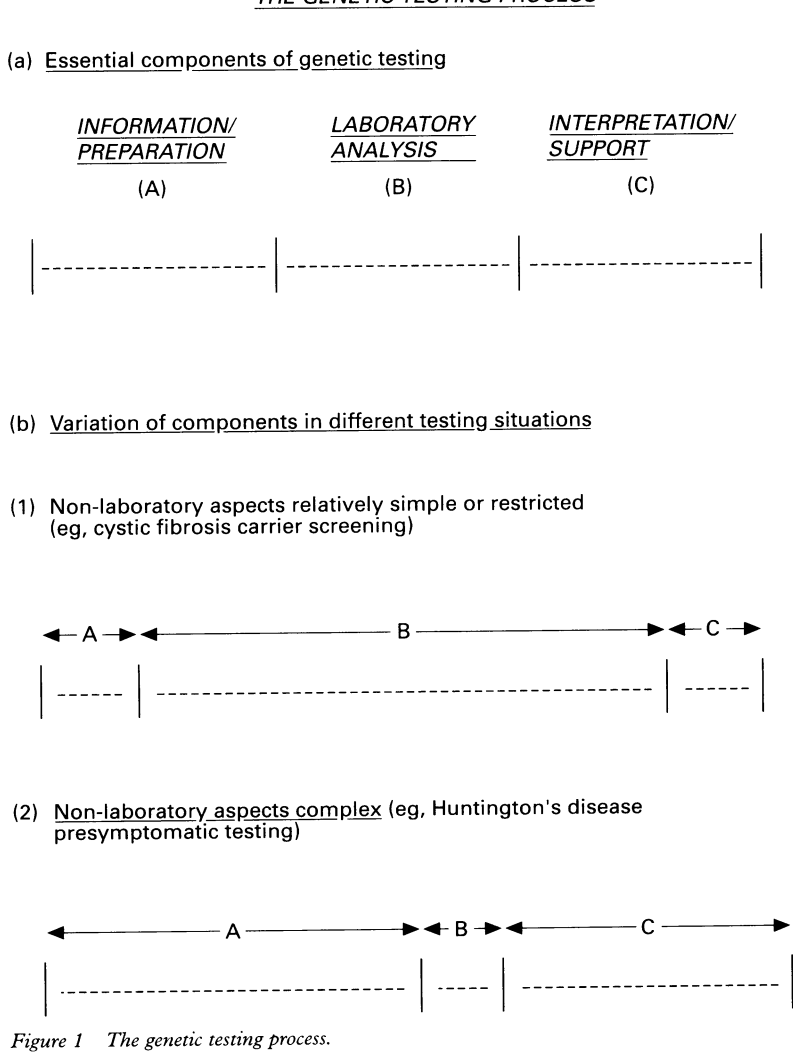

Figure 1 The genetic testing process.

It is extremely important to ensure that "diagnostic genetic testing" is not confused with "predictive" or "presymptomatic" genetic testing, discussed below, where the subjects concerned are usually not "patients" at all, but are healthy people. Even where symptoms are present, they must be relevant to the disease if testing is to be considered diagnostic. Thus, a test for the Huntington's disease mutation undertaken by a neurologist because of a movement disorder could be considered as "diagnostic", whereas the same test done on a patient with headache (not a feature of the disorder) and a family history of Huntington's disease would not be "diagnostic" but "predictive". Serious consequences will result if these fundamental differences in applying identical technology are not understood.

It is in the category of "presymptomatic" and "predictive" testing that most of the difficult issues involving genetic testing lie. Again, clear definitions are important here; "presymptomatic" testing is best reserved for those situations where an abnormal test result will almost inevitably lead to development of the disease at some point in later life (for example, Huntington's disease), whereas the term "predictive testing" covers a broader range of situations in which the risk of a disorder occurring is substantially increased or reduced, but with a much lesser degree of certainty.

Whether these forms of genetic testing are or should be considered "medical" in nature, and regulated as such, raises fundamental issues that have not been fully debated, let alone resolved. It may well be that there are strong reasons for medical involvement in some situations, but I see no reason why it should be assumed that all genetic testing in this group should automatically be "medicalised", whether by insurance companies, the medical profession, or others. One could perhaps point to the example of normal pregnancy as a process which has become medicalised without the full balance of benefit and harm being adequately assessed. Already one can see a progressive medicalisation in the language that is often used. Thus, healthy people undergoing predictive testing are referred to as "patients", while those with an abnormal test result are called "affected", even though onset of the disorder may be many years away or may not occur at all.[7]

The genetic testing process

Whatever we think of the matter, genetic testing is here to stay, both in diagnosis and prediction. It has been part of clinical genetics practice for almost a decade, and is now becoming widespread in the practice of most specialties. How can we ensure that it is delivered as efficiently and appropriately as possible and to the highest standards? Perhaps the most

important factor in this will be to ensure that genetic testing is looked at as an overall process, not simply as a laboratory activity.

Many lay people's concept of a test is of something that starts when a sample is taken and ends when a result is produced, but this is far from the case and in no situation is it more important to recognise this than in the process of genetic testing. This process can be illustrated diagramatically in fig 1, where the laboratory aspects of the test are represented in the central portion (B), while the equally important aspects of preparation, information, and consent and the subsequent aspects of interpretation and support are shown as the outer portions (A and C).

Naturally the central laboratory portion of the testing process is crucial to the whole and needs to be assessed in terms of scientific validity, accuracy, efficiency, and cost, all of which form part of what is usually considered "quality control". As genetic testing moves from being a research activity to an established service, these issues are being addressed, often on a national or international basis. Improved technology, cost pressures, and increasing commercial involvement are all powerful factors ensuring progress. The danger, however, is that the evolution of this part of the testing process may become detached from the essential preceding and subsequent parts, unless we think about, plan, evaluate, and cost the testing process as a whole.

In proposing an integrated approach to genetic testing, I would argue that there is ample precedent for this and that it is dangerous, even negligent to do otherwise. Precedent comes from several sources: thus, in HIV testing it is generally accepted that laboratory testing should only be done in the context of counselling, while much of the skill of those in laboratory medicine as pathologists lies in the interpretation of results in a clinical context and the determination of which investigations are most appropriate; pathologists have rightly warned against the dangers of "results only" test procedures.[8]

If we think of genetic testing as analogous to a surgical procedure, one could reasonably ask what body instituting or commissioning such an operative procedure would do so unless the framework of preoperative assessment and postoperative care had been evaluated, costed, and put in place to the same standards as the operation itself. Any surgeon or hospital failing to do this would rightly be considered negligent.

Of course it is unnecessary and unrealistic for all genetic testing procedures to be surrounded by a forest of associated activities. As indicated in fig 1b, there will be many situations, especially in diagnostic or carrier testing, where these aspects will be quite limited, and where written information may appropriately replace expensive professional time. In other genetic testing situations, however, it may prove that the associated risk estimation, preparation, information, and support, all part of what is generally recognised as "genetic counselling", will be as important and as or more expensive as the actual laboratory procedure. Presymptomatic testing for late onset disorders, such as Huntington's disease and familial cancers, are cases in point. The balance will clearly vary between different situations as will the question of whether specialists in clinical genetics, other hospital clinicians, or those in primary care should be responsible; what is essential is that all the aspects are considered together as integral parts of the genetic testing process.

The future of genetic testing

Those who have expressed concerns about genetic testing have been worried not so much about the present but about the future. These concerns have included such issues as: what will happen when genetic testing becomes widespread and commonplace? Will commercial interests and cost pressures result in numerous tests being done without the understanding and consent of those involved? How will access to genetic test results be controlled? Will testing result in widespread discrimination in employment, insurance, and access to health care? All these are valid concerns and it is as well to address them now, before genetic testing becomes more widespread.

Some with whom I have discussed these aspects are fatalistic and see widespread misuse as inevitable. I disagree, and take the view that, provided that professionals in the field, both clinicians and scientists, take the lead in setting standards of practice, and involve both the general public and government bodies in this, we should be able to avoid the widespread abuse of genetic tests that might otherwise occur. I can point to some hopeful signs.

A small but significant pointer is our experience of presymptomatic testing for Huntington's disease, an activity that was widely forecast as likely to have disastrous effects. Over 1500 such tests have now been carried out in the UK alone,[9] and the experience of most countries, including the UK, Canada, The Netherlands, and Belgium, is that harmful effects have been few[10 11] and that most people tested, regardless of the result, have felt benefited by being tested. Widely accepted international guidelines have been produced and followed, and it has generally been accepted that presymptomatic testing in other serious late onset disorders should follow comparable lines. Given the gravity of the issues involved and the potential for disaster, I regard this as a considerable success. The challenge is how to maintain standards as testing encompasses increasing numbers of diseases and pressures to contain costs of genetic services increase, particularly since the cost of pre- and post-test activities may equal or even exceed the laboratory costs of the test itself.

A second favourable pointer is the establishment of regulatory bodies, such as the Advisory Committee on Genetic Testing in the UK and the US Task Force on Genetic Testing. Such bodies may lack legal powers, but the influence of the guidelines they produce and the likely legal consequences of ignoring them are considerable. Such influences extend well

beyond their countries of origin and can encourage good practice in those countries where there may be less awareness of the issues involved.

Can commercial pressures be overcome? Again I am optimistic that this can be achieved, with one important proviso, that commercial interests, whether pharmaceutical, technological, or insurance related, are not in unfettered control of health or research policies. Provided that governments do not give up their regulatory or planning powers completely, I think it likely that most commercial organisations will generally prefer to work within a framework acceptable to governments and society. Although the less responsible may be influenced by the desire to achieve volume rather than appropriateness in genetic testing, the recognition that a few lawsuits could neutralise large profits is likely to be a powerful reminder of the advantages in maintaining responsible codes of practice.

I am in no doubt that, even 10 years from now, the patterns of genetic testing that will have evolved will be widely different from those that can be predicted now, and that what we mean by the process will equally have changed. By thinking and planning ahead, by trying to set high standards of practice now, and by insisting on rigorous evaluation of all aspects of genetic testing, we should be able to ensure that current concerns over its future misuse do not become reality.

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