

Genetic testing: a conceptual exploration

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Abstract

This paper attempts to explore a number of conceptual issues surrounding genetic testing. It looks at the meaning of the terms, genetic information and genetic testing in relation to the definitions set out by the Advisory Committee on Genetic Testing in the UK, and by the Task Force on Genetic Testing in the USA. It argues that the special arrangements that may be required for the regulation of genetic tests should not be determined by reference to the nature or technology of the test, but by considering those morally relevant features that justify regulation. Failure to do so will lead to the regulation of genetic tests that need not be regulated, and would fail to cover other tests which should be regulated. The paper also argues that there is little in the nature of the properties of gene tests, using DNA or chromosomes, that in itself justifies a special approach.

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Introduction

The Advisory Committee on Genetic Testing (ACGT), in its *Report on Genetic Testing for Late Onset Disorder*¹ under the chairmanship of Professor Peter Harper, and the US Task Force on Genetic Testing, in *Promoting Safe and Effective Genetic Testing in the United States*,² have each attempted to define genetic testing. The Advisory Committee defines it as "testing to detect the presence or absence of, or alteration in, a particular gene, chromosome or gene product"; the US Task Force as "the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease related genotypes, mutations, phenotypes or karyotypes for clinical purposes". The latter explicitly states that the definition "excludes tests conducted purely for research, tests for somatic mutations as opposed to heritable mutations and testing for forensic purposes".

The ACGT carefully distinguishes between diagnostic genetic testing and predictive genetic testing, categorising the latter into presymptomatic testing and susceptibility testing, but the main body of the text is confined to "presymptomatic testing of healthy relatives with a family his-

tory of serious late onset disorder with a clear genetic basis and commonly following dominant inheritance". Issues connected with population screening, the use of genetic tests in symptomatic individuals and susceptibility testing for disorders involving multiple genetic and environmental factors are dealt with cursorily in three short appendices.

A recent paper by Peter Harper entitled, What do we mean by genetic testing?^{2,3} defines genetic testing as "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". This definition includes not only DNA tests but tests of its products and function. In the paper Professor Harper also argues that the concept of a genetic test should include not only the laboratory analysis itself, but the preliminary preparation and counselling of the patient and subsequent interpretation and support. In so far as it is possible to categorise tests as being genetic, as distinct from non-genetic, I believe his definition to be correct, including not only biochemical tests, such as those for phenylketonuria and hypercholesterolaemia, but others, such as the use of renal ultrasound in polycystic kidney disease or computerised tomography in tuberous sclerosis. For the sake of simplicity I shall, in the remainder of this paper, use the term *genetic testing* to refer to any type of test that indicates that a person is likely to have a genetic or familial disorder, and the term *gene testing* to refer to tests confined to the analysis of DNA, RNA or chromosomes.

The purpose of the reports from both the US Task Force and the Advisory Committee on Genetic Testing in the UK is to protect the public from indiscriminate genetic testing without proper safeguards and controls, and to ensure that genetic information obtained as a result of such tests is used in an appropriate manner, with adequate protection of its privacy and confidentiality. This purpose appears to be quite proper and rests on the view that genetic information is somewhat special and different from other types of health information, and requires a different and special approach from both health professionals

and society. One of the most important reasons behind moves to protect the public from indiscriminate genetic testing is a fear of genetic discrimination, and of the negative actions employers, insurers, mortgage and other lenders might take against people known to have a genetic disease or susceptibility to a multifactorial disorder.^{4,5} I shall attempt in this paper to look at four issues: first, to explore the meaning of genetic information and to ask if it can be adequately set apart from other types of health information; second, to explore in a similar fashion, the concept of genetic testing as a separate, identifiable category of medical test; third, to argue that the notion of regulating genetic testing as the means of addressing the problems of potential genetic discrimination and of protecting the patient and the public is misconceived, and that the morally relevant features that require certain aspects of medical practice to be regulated are not those which relate to the categorisation of a test as being genetic (as distinct from non-genetic), and fourth, to argue that the ACGT is mistaken in confining their definition of genetic testing to what I refer to as gene testing, that is tests which only involve DNA, RNA or chromosomes.

Genetic information

The term *genetic information*, may be used in one of two ways. First it may be regarded as information about the genetic constitution of individuals, their genes or chromosomes, and their inheritance. Second, and by contrast, *genetic information* may be taken to refer to any information from which we may infer knowledge about the genetic constitution of individuals. In clinical practice geneticists, concerned classically (at least until recently) with Mendelian disorders such as Huntington's disease or Duchenne Muscular Dystrophy, or with chromosomal defects such as Down's syndrome, have used a detailed analysis of the family history and of chromosomes or DNA, as the information base from which to make a diagnosis or to predict the level of risk in their patients. These disorders have tended to manifest clear-cut patterns of inheritance and to confer a very high risk on family members. They may, without any confusion, be referred to as genetic diseases, and may also be distinguished relatively easily from other disorders where the patterns of inheritance are significantly less clear-cut.

Notwithstanding this distinction, it is also the case that genetic factors play a part in the pathogenesis of common disorders such as Alzheimer's disease, diabetes, breast and colo-rectal cancers and ischaemic heart disease. This has been known

for many years. In these disorders the genetic factors range from rare single genes which account for a tiny fraction of familial disease, for example, BRCA1 or BRCA2 in breast cancer or PS-1 in inherited Alzheimer's disease, to a number of as yet unidentified low-penetrance susceptibility genes or polymorphisms, which, interacting with environmental factors, account for the much larger proportion of familial cases of these common disorders. A woman with a first degree relative with breast cancer will be twice as likely as a woman without a family history to develop the disease, but would still be very unlikely to harbour gene mutations in BRCA1 or BRCA2.⁶

Infectious diseases such as tuberculosis and meningitis, behavioural traits, such as hyperactivity, and psychiatric disease, such as schizophrenia, have also been shown to have a significant genetic component. For these (non-Mendelian) disorders it would be more correct to speak of genetic susceptibility rather than genetic disease, but the genetic component nevertheless confers some degree of increased risk for the individual and some degree of heritability and implications for other family members. In these instances the concept *genetic information* is more problematic, at least if used in the first sense, unless it can be shown directly either (a) that genes have some part to play in the determination of the clinical features of a disease or trait, or (b) that some degree of heritability is conferred on family members.

In relation to the second use of the term, where phenotypic manifestations allow us to infer the presence of genetic factors, we may reflect on the fact that the most medically unsophisticated of us is able to elicit the difference between men and women, a clear-cut genetic trait. It is equally possible to imagine that an astute observer with clinical knowledge may make a diagnosis after the detection of scoliosis, café au lait spots and neurofibromata in a fellow bather on a beach. These features, visible to all, allow the inference of a genetic trait by simple observation. A physician in his surgery may elicit a family history of bowel cancer in one patient or of deaths from heart disease at a young age in another. In all these examples, whether through simple observation outside a medical setting, or the use of clinical history-taking and examination during a consultation, health information passes from one to another person; and in each a genetic component may be inferred.

The reality is that all human variation and all disease have both genetic and environmental determinants. The expression of the disease that results in illness is a consequence of both gene and

environment. A positive family history confers on an individual an enhanced risk of disease. In combination with harmful environmental factors, such as smoking, the risk may be further increased. Knowledge of these risks provides the physician with the clues that enable diagnoses to be made and prognoses to be discussed. All form part of the data-set that we call health information; and from each, to a greater or lesser extent, we may infer knowledge about the genetic make-up of an individual.

Genetic information is therefore a term which is coherent and sound, and refers to information about an individual's genes and his or her inheritance. But in as far as it may in practice be used in one of two ways, either directly, to refer to information about a person's DNA or chromosomes, or indirectly, to infer from some phenotypic feature, clinical, biochemical or radiological, the use of the term is often ambiguous. Any statement must show precisely in which of these two senses it is used.

Genetic testing

The same ambiguities of usage arise when we try to distinguish genetic from other medical tests. A test, whether in the form of information elicited by taking a history or a physical sign, a physical procedure such as a sigmoidoscopy, or a biochemical test or radiological procedure, is an intervention designed to alter the pre-test assessment of the probability of the subject having a particular disorder to a different post-test (whether greater or lesser) probability. A genetic test is no different from any other test in this regard.

By convention, the term, *genetic test*, is usually taken to refer to tests made directly on genetic material such as DNA or on chromosomes, and which, in this paper, I have referred to as a *gene test*. This usage suggests that there are differences between *genetic tests* and, by inference other tests, and applies the distinction between that which is called "genetic" or "non-genetic" to the test itself. By analogy with the discussion of the use of the term, *genetic information*, it is possible to conceive of another use of the term, *genetic test*, and to regard any clinical, haematological, radiological or biochemical test, from which information about the gene or the inheritability of a disorder to be inferred, as a form of genetic testing.

The reason why in conventional usage the term *genetic test* is used in the narrower sense, the sense which I call a *gene test*, is that it is argued that the regulation of gene testing will protect patients and society from certain ethical and social implications of the diagnosis of genetic disease. This objective, in my view, cannot be achieved by refer-

ence to the nature and technology of the test procedure, but must relate to morally relevant features which are more likely to be associated with the nature of the disorder or disease itself. I will deal with this issue in the next section of the paper, where I will attempt to argue that neither the regulation of genetic testing nor of gene testing is likely to achieve the desired result.

Genetic testing and the prevention of genetic discrimination

I start from the premise that the prevention of genetic discrimination and of adverse ethical consequences to families and individuals, including those of privacy and confidentiality, of the ability to predict in advance of its clinical appearance the onset of genetic disease, is worthwhile. A society which supports institutions and structures which adversely affect people with genetic disease more than those with disease that is not primarily genetic in origin is clearly undesirable and should be discouraged. To the extent that there is evidence for the contention that certain groups in society suffer discrimination, one may argue that steps should be taken, through voluntary codes of practice or through regulation and legislation, to minimise or prevent such discrimination. Within the UK, evidence of racial and of sex discrimination led to the Race Relations Act 1976 and the Sex Discrimination Act 1975; the advent of HIV and AIDS led to codes of practice regarding the use of HIV-testing and a more stringent requirement to protect confidentiality that did not extend to other medical tests.⁷ In each of these instances there was evidence or a prima facie reason to believe that, without explicit action, discrimination, with documented adverse consequences for individuals, would occur.

In the case of late onset Mendelian disorders such as Huntington's disease the role played by geneticists and the ethical issues surrounding genetic testing, whether through linkage analysis or direct gene testing, has been exemplary⁸; but it is very much to be doubted whether a blanket extension of those principles through codes of practice or regulation of genetic tests to non-Mendelian disorders would be of use. The morally relevant circumstances in which regulation is warranted, whether voluntary or statutory, are, in my view: (a) where there is already de facto evidence of significant discrimination or (b) where the predictive value of a test and the probability of developing the disease, or phenotypic manifestations, attributable to the genetic defect is high enough to give employers, insurers or others in society a reason to justify discriminatory policies.

These morally relevant conditions apply to all tests from which a genetic predisposition might be inferred, not just *gene tests*. However, it does seem to me that a practical distinction for deciding whether regulation is required, using the conditions specified above, might be made by distinguishing between those tests which confer very high risks on individuals and a high probability of being inherited by other family members, such as Mendelian disorders, and tests for other diseases.

Pre-test risks associated with Mendelian disorders in first degree relatives, parents, children and siblings, are usually either of the order of 1 in 2 or 1 in 4. Genetic testing may either reduce the risk of having the disorder to zero (or almost so) in a particular individual or increase it to a certainty (or almost so). For them, the very high predictive value of the test could well give society reasons to justify discriminatory policies. It is for this reason that Peter Harper has so cogently argued for the need to conceptualise a genetic test as one which includes pre- and post-test information and advice. It is for the same reason that I believe that in these circumstances regulation might well be required, but, if required, it should be applied to all *genetic tests*, and not just *gene tests*, and where ethical considerations do not dictate the need for regulation, it should not be used at all.

By contrast, individuals with multifactorial diseases such as diabetes or heart disease have lower pre-test risks than patients with Mendelian disorders. The test may also lead to the formulation of a post-test risk which, whether higher or lower than the pre-test risk, will nevertheless not increase to near certainty or decrease to near zero. For this and other reasons, the ACGT report attempts to distinguish (a) “pre-symptomatic testing”, defined as “testing carried out in asymptomatic individuals to provide definitive information about that individual’s future health”, from (b) “susceptibility testing”, defined as “testing which provides information about the genetic component in a multifactorial disorder”.² In relation to “pre-symptomatic testing” the report goes on to say: “Such a test result may indicate that the individual has a high likelihood of developing the disorder or excluding it. Predictive testing is most frequently used in late onset autosomal dominant disorders such as Huntington’s disease”.

A case might therefore be made for having different principles and a different approach to dealing with tests and information obtained from people with a predisposition to a Mendelian disorder from those with genetic susceptibility in multifactorial disease. However, it is not the distinction between *genetic tests*, however defined, as distinct from non-genetic tests, that confers the need for a

different approach in the two instances. The contention that all *genetic tests* should be subjected to a regulatory framework, irrespective of whether the morally relevant indications outlined above exist or not, seems far too wide and unnecessary. It would theoretically include within its remit the taking of a family history, the measurement of a blood pressure, and the use of biochemical and other pathological tests, such as cholesterol or HLA typing, as well as *gene tests*, as narrowly defined. However, an approach which requires only *gene tests* to be regulated is equally without foundation. It would lead to a situation in which many tests, not based on gene technology, escaped regulation when they ought to be regulated; while some gene tests would be regulated, for which no morally relevant reason exists.

Gene testing

The social and ethical issues that are raised in genetic disease, including the potential for discrimination by insurers and others,^{9 10} arise as a consequence of making a diagnosis in a patient with symptoms, or in establishing an increased risk in pre-symptomatic individuals, or in family members. The social and ethical consequences arise from the making of the diagnosis of a familial disease. In Peter Harper’s words: “The relevant factor is not the technology but the fact that the test is detecting a change directly related to an inherited disorder”.³ This statement alone is adequate to raise in my mind the difficulties of according special status, including the need for counselling, when a diagnosis or an increased risk of genetic disease is predicted through the use of DNA technology but not when it comes about as a result of a biochemical or a radiological test. An asymptomatic adolescent from a family with known polycystic kidney disease is at the same risk of discrimination, and the diagnostic procedure is just as worthy of regulation (or not) whether it is an ultrasound scan or a DNA test.

The ACGT report outlines a number of differences between *genetic tests* (meaning *gene tests*) and other medical tests, stating that while these others “may detect changes in those at risk before symptoms occur, they still reflect an early stage of the pathological process”.¹ I list some of these. We are told that DNA is extremely stable, that DNA analysis can be carried out at any point from conception to old age, and that the presence or absence of an abnormality in a gene test is unaffected by whether the individual has symptoms or not. Testing for inherited disorders is said to be different from other clinical tests because such testing may reveal important information about relatives. Another important feature of

testing for inherited disorders is said to be the power of such testing to predict the potential future health of the individual and that the test result may cause anxiety in an otherwise healthy individual, so that the consultation before and after a *gene test* may be different from that needed in many other types of medical test. These properties, said to be those which relate to analysis of DNA itself, may be described by the terms *stability*, *heritability*, *predictiveness* and *sensitivity*. I find it difficult to convince myself that any of these are properties of DNA or *gene tests* that are not shared by other diagnostic interventions in medical practice.

The *stability* of DNA is a feature which does give rise to concern, particularly when specimens are stored and subsequently used for purposes not covered by the original consent. However, this particular ethical issue is about regulating the use of DNA, principally by third parties, and its relation to the law of consent and of proprietary rights to human tissue, rather than to diagnostic or pre-symptomatic testing in the clinical situation. *Heritability* is the defining feature of familial and inherited disorders. But conceptually, the degree of heritability is a feature of the condition under study, highly heritable in Mendelian disease, less so in multifactorial disorders. The phenotypic manifestations of heritability, referred to as the penetrance of a gene, is as likely to be determined by environmental as genetic factors. Whatever the mechanisms, heritability is certainly not a feature of the technology used to diagnose the disorder.

Predictiveness, the ability to predict the risk of disease in asymptomatic individuals is a feature of all tests. The likelihood of myocardial infarction can be predicted from knowing the risk factors to which the subject is exposed. DNA information does allow an individual to know if he or she is with or without a deleterious gene mutation, in a family where the mutation exists, and may confer a degree of knowledge that cannot be obtained from phenotypic information directly. In that sense *gene testing*, in certain circumstances, may give important data about the heritability of the disease in an individual. In many other instances, phenotypic information is much more useful as a predictor of disease manifestation. The predictive potential of a family history in genetic disease is well known to geneticists, whereas information about the presence of a mutation in a gene, or of its exact DNA sequence, may not always allow one to know if the mutation will give rise to manifestations of disease. Put in a different manner, the ability of a test based on genotypic information, to change the probability that a patient is at risk of disease, may, in most cases, be lower than that of

an appropriate test based on phenotypic information.

It is said also that the use of DNA testing is ethically much more sensitive and will lead to anxiety, both for the patient tested and potentially for other family members. The *sensitivity* which leads to anxiety is there whenever a test result is conveyed to a patient, and is not a specific feature of gene testing. It is also a feature of participation in screening programmes. The capacity to create anxiety is not a specific feature of gene tests.

Conclusion

The fact that I have attempted to explore the concepts of genetic information and genetic testing, and to suggest that the use of a regulatory framework to control such information and tests, as conventionally and narrowly defined, is illogical and without foundation, does not mean that I am against the construction of a regulatory framework in circumstances where discrimination is likely to exist. The purpose of my analysis has been to demonstrate that:

- (a) the special arrangements that may be required for the regulation of tests which lead to the diagnosis of genetic disease should be determined not by reference to the nature of the test but by morally relevant features which should apply to all *genetic tests* and not just to *gene tests*

and

- (b) a regulatory framework which applied to all forms of *gene tests*, and only to *gene tests*, would lead to the regulation of tests that should not be subject to special regulation, and would fail to cover other tests, from which a diagnosis of genetic disease may be inferred, which should be so regulated.

The attempt by both the US Task Force and the ACGT to prevent the abuse of genetic information by regulating *gene testing* is the result of the very clear and genuine concerns of geneticists, based on their experience of Mendelian disorders. I suggest an alternative practical basis for the prevention of discrimination might lie in differentiating Mendelian (and other disorders where the degree of genetic risk is of the same order of magnitude as Mendelian traits) from other disorders, or whenever there is *prima facie* evidence that discrimination occurs or is likely to occur; and that this distinction should be irrespective of the technology or the type of test used to make the diagnosis or to categorise the risk.

Although my motivation in undertaking this analysis has been to stimulate debate there are two important practical consequences which arise if my arguments are accepted. First, in relation to the multifactorial or polygenic disorders, the question of whether a specific regulatory framework will be required will depend on whether de facto there is likely to be discrimination, or other social and ethical implications, as a consequence of making clinically and ethically relevant predictions in either a symptomatic or an asymptomatic individual. I do not at present see much evidence that conventional risk prediction in medical practice has resulted in significant problems. Second, in relation to Mendelian disorders, I believe that regulation, if deemed necessary, should cover all forms of diagnostic tests and not just *gene tests* based on DNA analysis. In these cases, arrangements for counselling and pre- and post-test consultation and for specific consent should be available irrespective of whether the consultation is made with a geneticist who uses DNA technology or a physician who uses biochemical or radiological techniques in reaching a diagnosis.

In spite of my analysis there may be some who would argue that, notwithstanding the logic of my arguments, the practical reality of the fear and mistrust of DNA technology by the public requires that society acts to regulate the technology itself. For these reasons they might argue that the narrow definition of *genetic testing* used by the ACGT should receive support. In favour of this view is the contention that the stability of DNA and the possibility of third parties using it in circumstances outwith the original consent gives rise to important ethical concerns which need to be addressed and for which codes of practice have to be established. I would not necessarily dissent from this argument, but I would wish those who use it to be clear that the motives for applying a distinction based on technology are pragmatic. I would also subscribe to the view that DNA testing, like all other pathological tests, should be subject to national quality control mechanisms. However, whether the use of *gene tests* needs any greater degree of regulation than any other form of medical test, and whether such regulation would in itself prevent discrimination is questionable. The experience of HIV-testing suggests that

the procedural restrictions on the collection and the dissemination of information about HIV status have not proved very effective in eliminating discrimination against HIV-positive individuals and against those afflicted with AIDS within our society. These comments are an attempt to expose what I believe to be an analytical flaw in the debate about genetic testing. I doubt very much if the practical outcome which I seek to achieve differs greatly from that desired by those who argue for the distinction between genetic and other tests. I hope that this paper might provide an interesting alternative viewpoint and generate some debate about the definition and nature of genetic testing.

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