Issues concerning the evaluation and regulation of predictive genetic testing

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Abstract This paper is a précis of my keynote address at the Symposium on Predictive Genetic Testing organised by the Robert Koch Institute in Berlin. The talk is based on reflections which I have had over a number of years on genetic testing and its evaluation and regulation. It presents a thesis, which I hope will generate discussion and comment. A theme which will run through the paper is the need for precise definition of terms before making any normative statement about such terms. Our failure to do so in genetic discourse is at best confusing and at worst capable of resulting in inappropriate (and sometimes harmful) regulatory responses.

Introduction

This paper is a précis of my keynote address at the Symposium on Predictive Genetic Testing organised by the administrative office of the German Commission on Genetic Testing at the Robert Koch Institute in November 2011 in Berlin. The talk is based on reflections which I have had over a number of years on genetic testing and its evaluation and regulation. It presents a thesis, which I hope will generate discussion and comment. A theme which will run through the paper is the need for precise definition of terms before making any normative statement about such terms. Our failure to do so in genetic discourse is at best confusing and at worst capable of resulting in inappropriate (and sometimes harmful) regulatory responses.

But even if one does make precise definitions, problems can arise. Within a policy or regulatory framework, there may be inconsistency in the way terms are used in different parts of the document. The definitions used may themselves be problematic. Some of these points will be illustrated with reference to the German Genetic Diagnosis Act (Gendiagnostikgesetz) 2009.

Definitional issues

I start by giving two early examples of failure to define in a legislative context. First, the European Parliament Resolution on the Commission Communication on Life Sciences and Biotechnology of 21 November 2002 called on the Commission to draft a regulation for the introduction of a standard for *genetic tests* (para 51), to take the necessary steps for an EU-wide regulation on *DNA testing*, and to consider drafting an own-initiative report on the legal aspects of *genetic testing* (para 55) (European Parliament 2002). Second, Hansard reported a debate in the House of Commons on Genetic Discrimination on 15 March 2006, where it was said that the government would at some time in the future have to consider legislation making it illegal to discriminate on the grounds of *genetics*; that the subject of *genetic discrimination* had come to the attention of the speaker when he realised that those with diagnosed *genetic conditions* were receiving unfair treatment when applying for insurance; and stating an intention to extend discrimination law into new areas, including *genetic predisposition* (Hansard 2006).

The terms in italics were not formally defined. What exactly is meant by a *genetic test*? Is it equivalent to a *DNA test*? What do we mean when we say discrimination on the grounds of *genetics*? What is a *genetic condition*? The purpose of speech and of writing is to communicate, to pass on to the recipient the views of the speaker or writer, so

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that the recipient has the same understanding. Can we really agree that this purpose was achieved in these two examples?

In other contexts, terms have been defined, but regrettably with no consistency. Table 1 shows various definitions of the term *genetic testing*. The first four of these are culled from documents that emerged from various committees within the UK Department of Health between the years 1997 and 2000. They all differ one from the other, and also from the fifth, which is the definition used by the US Task Force on Genetic Testing (Zimmern 1999).

In the paragraphs below, I set out my personal views on the meanings of certain words. I would gladly defend such use in the public domain if challenged, but I understand that others may take a different view in their own use of these terms. Whether, as a community, we should accept multiple definitions and usage for a particular term is a matter that can be debated. It is certainly the case that as a matter of fact there are multiple definitions of such terms. We may therefore have to accept this pluralism. But with enlightened debate and discussion I hope that it may be possible to arrive at a single set of definitions that would be acceptable to most.

Genetics and genomics

The terms *genetics* and *genomics* have been used interchangeably by many commentators. I believe this to be a fundamental mistake. *Genetics* is the branch of biology dealing with heredity and variation of individual members of a species. *Clinical genetics* or *medical genetics* is that branch of medicine that studies inherited or heritable disorders. William Bateson was the first to suggest the word *genetics* (from the Greek *gennō*, γεννώ; to give birth) to describe the study of inheritance in a personal letter to Adam

Sedgwick, dated April 18, 1905, then publicly at the Third International Conference on Plant Hybridization in London in 1906. Wilhelm Johannsen used the word *gene* to describe the units of hereditary information three years later in 1909.

But the word *genetics* has also been used more broadly to embrace the science of DNA, the study of genes and their function and how they contribute to disease. This may be more accurately conceptualised as the science of *genomics*, the use of information and technologies derived from the entire genome (as distinct from individual genes) to determine disease risk and predisposition, diagnosis and prognosis, and the selection and prioritization of therapeutic options. *Genomics* is therefore a body of knowledge and set of technologies that can be used by all specialties in medicine, including the specialty of *clinical genetics*. The cardiologist will use it in the context of heart disease; the dermatologist in the context of skin disease; and the clinical geneticist in the context of inherited and heritable disease. To the extent that there will develop a specialty of *genomic medicine*, it will be a cross cutting specialty, using such knowledge and technologies across the entire range of medical specialties and the practice of public health.

Genetic tests and genetic diseases

The use of the term *genetic* to cover both the narrower concept of inheritance and the broader role of genes and the genome in human biology has been responsible for much misunderstanding, especially when applied to the terms *genetic tests* and *genetic information*. Figure 1 shows this as a two by two matrix on which one axis sets out the distinction between inherited diseases and common complex diseases, and the other axis the distinction between using DNA (or other nucleic acids) as the test analyte and

Table 1 Definitions of genetic testing

ACGT Sep 97	Tests Supplied Directly to the Public	...the presence or absence of, or change in a particular gene or chromosome
NIH Sep 97	US Task Force on Genetic Testing	...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
HGAC Dec 97	Genetic Testing and Insurance	...based on DNA research that can be used for diagnostic or pro-symptomatic testing
ACGT Sep 98	Late Onset Genetic Disorder	...the presence of or alteration in a particular gene, protein or a gene product In relation to a genetic disorder
HGAC Jul 99	Genetic Testing and Employment	...based on analysis of DNA or chromosomes, or on biochemical or haematological screening
GAIC Jun 00	Guidance	...the presence or absence of, or change in a particular gene or chromosome

Fig. 1 Genetic tests and genetic diseases

using other non nucleic acid based technologies for that purpose. The separation of the two categories of assays is categorical and distinct; assays are either nucleic acid based or not. By contrast, there is no categorical distinction between inherited disorders and complex disorders; there is in effect a continuum, a function of the penetrance of the genetic variants involved. Genetic variants responsible for inherited disease (or the inherited subtypes of common diseases) have high penetrance whereas those that together with environmental factors have an influence on the risk of common complex diseases are of significantly lower penetrance.

The definitions of genetic testing in Table 1 emphasise the use of DNA as the main component of a genetic test; but in two of the definitions, the requirement for there to be a *heritable disease* or *genetic disorder* is also stated. So, from a formal perspective, the question arises: what exactly is a *genetic test*? Is it that represented by boxes A and B (red frame), or by Boxes A and C (blue frame), or is it represented by the Boolean AND (box A) or the Boolean OR (boxes A, B and C) of the red and blue frames? These distinctions have not been addressed in any formal policy document. Indeed, even in a clinical context, experts do not appear to have agreed whether the formal definition of hereditary non-polypoid colon cancer is to be defined by virtue of phenotypic characteristics using the Amsterdam or Bethesda criteria, by the presence of the relevant mismatch repair genes, or as a Boolean AND or a Boolean OR subtending these two sets of criteria (Zimmern and Kroese 2006). Dr Jorge Sequeiros, for Eurogentest, has done a great deal of work on definitions (Sequeiros et al. 2012). His conceptualisation is slightly different from that which I

show in Table 1, but the principles behind the need to define precisely are exactly the same.

Such distinction is necessary not just in a policy context, but also in epidemiological studies. These depend on the ability to count disease of interest ‘X’. Thus to distinguish ‘X’ from ‘not-X’ is not just a whim; the ability to define and to make the distinction goes to the heart of epidemiological investigation.

Policy documents have more recently attempted to define and differentiate. Thus in the Nuffield Council on Bioethics’ report on *Genetic Screening* in 2006, they define a *genetic disease* as a disease that develops as a result of alterations in the genetic makeup of an individual (Bioethics 2006). The Human Genetics Commission UK (<http://www.hgc.gov.uk>), in its report *Inside Information* defines genetic information to be information about the genetic makeup of an identifiable person. Both appear to characterize the disease or the information through the use of DNA sequences, or using data from which DNA sequence may be deduced (Human Genetics Commission 2002). It is essentially the same as the definition used in the German Genetic Diagnosis Act 2009 (See below). Yet, in the same Nuffield Council report, we see the following sentences:

In our view, the critical aspect to consider is the information that a test reveals, rather than whether or not it analyses genetic material. We have therefore included tests that use non-genetic technology for a disorder that is clearly heritable or genetic, such as lipid analysis to test for familial hypercholesterolemia, as well as tests that use DNA (Bioethics 2006, p. 3).

This conceptualisation is inconsistent with other statements earlier in the report. First, it does not appear necessarily to require the use of DNA based technologies to identify the responsible DNA sequence for it to be considered a *genetic test* or *genetic information*. The implication is that a test such as an ultrasound scan that can establish the presence of multiple renal cysts and hence the diagnosis of polycystic kidney disease is a *genetic test*, at least when used in relation to a disorder that is “clearly heritable or genetic”. Second, by using the term “clearly heritable or genetic” it is implied that the words *heritable* and *genetic* are synonymous and interchangeable. This implication is true if applied to genetic sequences. It is not true if applied to the disorder or disease. All diseases are *genetic* (meaning in part determined by genetic variants), but not all diseases are heritable. Heritable traits are always due to changes in DNA but not all changes in DNA lead to heritable traits.

The German Genetic Diagnosis Act (GenDG) 2009 uses the term *genetic examination* (GenDG 2009). It is defined to be any examination directed at (a) *genetic analysis* for the determination of *genetic characteristics* and (b) any prenatal risk assessment measures. *Genetic analysis* is in turn defined as analysis directed towards determining genetic characteristics such as (a) the number and structure of chromosomes (cytogenetic analysis), (b) the molecular structure of DNA or RNA (molecular genetic analysis), (c) the products of nucleic acids (gene product analysis) (Sec 3 (2) GenDG). The term *genetic characteristics* is defined as human genetic information inherited upon fertilisation or otherwise gained before birth (Sec 3 (4) GenDG). The terms here are clearly defined; it is unambiguous that *genetic characteristics* refers to genotypic information. So defined, *genotypic characteristics* are clearly inherited and heritable.

This use of the adjective *genetic* in the term *genetic characteristics* within the Act contrasts with how it is used in the terms *medical genetics* or *clinical genetics*, or to the words *genetic disease* meaning inherited or heritable disease. In these instances the *genetic* element of these terms refers to disease rather than genotype. The distinction is important. Whereas genetic sequences are all inherited and heritable (*genetic characteristics* as defined in the Genetic Diagnosis Act), it is only certain diseases or phenotypes that are inherited and heritable. Therein lies the confusion which I seek to expose by use of the 2 by 2 matrix in Table 1. The definition of *genetic characteristics* will cover boxes A and B, but by virtue of including within the definition gene product analysis, also a subset of boxes C and D.

The language of prediction

One other area where use of language is loose and often undefined is in relation to predictive tests. When is a test

predictive? When is it acceptable to use the term? The concept of predictability can be extremely narrow, implying that if what we are testing for is present then the disease will inevitably follow. The test is for what might be conceptualised as a sufficient cause of the disease of interest, which in some cases may also be a necessary cause. In this sense, and in the context of genetic variants, we mean a genetic variant of 100 % or near 100 % penetrance. We accept that in most instances of inherited disorders, the presence of the genetic variant almost always gives rise to the disease. The exact cut-off in quantitative terms has never been defined, but probably common usage would place variants with a penetrance of 70 % plus in such a category. In these instances, where the predictive test is for an inherited disorder, an asymptomatic person would, as a consequence of a positive test result have pre-test risks moved, for example, from a probability of 0.5 to near 1.0, or in the case of a negative test from 0.5 to near 0.0. This type of test is usually termed a *pre-symptomatic test*.

By contrast, the term predictive test has also been used in relation to tests whose results can be used to alter the risk of a disease, to change it from a pre-test value of one figure to a post-test value of another figure. But the context is very much in relation to lower values of pre-test risks, perhaps dealing with risks at around 1 in 10 or lower. Convention suggests that in these instances we should refer to such tests as *pre-dispositional* or *susceptibility* tests and that the word *predictive* should be used as a generic term to cover both *pre-symptomatic* and *susceptibility* tests (Becker et al. 2011).

As an aside, we can also make a comment on the precision of policy and normative statements when applied to such tests. Often we read papers that make normative statements about *predictive genetic tests*. However, in respect of each of those statements it is often unclear whether the writer intends the statement to be a statement that applies to or qualifies (a) all tests (b) genetic tests in general or (c) only predictive genetic tests. Because of this, there is little clarity, in relation to discussions about *predictive genetic tests*, about the sense in which the word *predictive* is being used (narrow or wide), or about whether the concerns expressed are about the use of DNA or the ability of such tests to make predictions that concern future health status.

Assays, tests and test evaluation

For some years now, we have tried to promulgate the view that policy makers must pay critical attention to the distinction between an *assay* and a *test*. We have defined an *assay* as a method for *determining the presence or quantity of a substance* or to *analyse or quantify a substance in a sample*. By contrast, we define a test as a procedure that makes use

of an assay for a particular purpose. The word *test*, in our terms, is a shorthand for referring to *an assay used in the context of a particular disease in a particular population for a particular purpose*. An alternative way of conceptualising the relationship between the two words is to treat the *assay* as the measurement and the *test* as the interpretation of that measurement (Burke and Zimmern 2007).

The practical implication of the distinction is that 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. In effect, it is only assays that can easily be subject to statutory regulation, even though regulators refer to their role as one of test regulation. Regulating tests, so defined, is almost an impossible task, since each test is likely to need evaluation in its individual context, depending on disease, purpose and population. Statutory regulators may determine that a new technology such as a PET scanner may be allowed in the marketplace for diagnostic use, in that it is both safe and effective as a device for producing the relevant images. However, it is not the place of the regulator to determine in what circumstances, for what group of patients or in what disease, a PET scan may or should be used; nor to make statements about whether it should be used in preference, for example, to a CT scan or a MRI scan. The same principle applies to the use of genetic tests.

But this does not mean that we advocate a free for all, that whether or not a test is used in a clinical situation should be left entirely to the whim or discretion of the physician. New genomic tests are being developed at an unprecedented rate and are now more complex than ever before, both in terms of the technologies used and in their interpretation. They are now more generally available, in some instances direct to the consumer. The assessment of predictive or susceptibility tests brings its own challenges; it is not entirely practical or feasible to wait many years before outcome is definitively known. Commissioners, funders or reimbursers of health services are all under extreme financial pressure and require evidence of effectiveness before they will consider investment in the test. The provision of basic information about test effectiveness and efficiency is needed more than ever before.

The ACCE framework developed in the USA provides a basis for such test evaluation. Initially directed to genetic tests, the scheme is applicable to all forms of molecular diagnostics and biomarkers (Zimmern and Kroese 2007). The analytical validity provides in effect the evaluation of the assay, the measurement. I here suggest that clinical validity should be partitioned into two components. The first, scientific validity, should comprise the evaluation of the relationship between biomarker and disease. This is essentially a matter for the academic community, and there

are standards that determine the extent to which any publication that purports to show such a relationship is adequate or otherwise (Bossuyet et al. 2003). The second, test performance, is the evaluation of the performance of the test in the clinical situation, through the empirical measurement of test parameters such as sensitivity, specificity, positive and negative predictive values and the area under the receiver-operator curve (ROC) (Wright et al. 2010).

I have argued elsewhere that scientific validity is crucial and a sine qua non of a test. A test without such validity is in effect a fraudulent test and should not be allowed into the marketplace, and as such could be subject to formal statutory evaluation. By contrast, test performance may or may not show the extent to which a test may or may be clinically valid, and depending on context clinical judgement must be brought to bear on the interpretation of any of the parameters measured in its evaluation (Wright et al. 2010). A particular, level of sensitivity may be deemed valid in one situation but not in another. The problem is that at present no formal processes exist to enable the systematic evaluation of either diagnostic or predictive biomarkers, and no agreement between governments and industry about how such evaluations should be funded. A diagnostic summit hosted by the PHG Foundation and the Royal College of Pathologists in the UK in January 2008 considered these issues and made a set of recommendations which we set out in Table 2 (Furness et al. 2008).

I should perhaps make two other points. First, that considerations of clinical utility are primarily subjective. Given the same set of facts, I may find a test incredibly important and useful, whereas you may take a different view. Where funding is provided by a third party, it is inevitable that a more objective evaluation of utility is required, but all things considered there will inevitably be a significant element of

Table 2 Conclusions from diagnostic summit (PHG Foundation and Royal College of Pathologists, Jan 2008)

1. A new body should be established to ensure the evaluation of diagnostic tests.
2. A publicly available database be created of new and existing laboratory tests—a diagnostics formulary—containing evidence for clinical performance, and explicitly stating where any evidence is lacking.
3. Policy makers and industry should be encouraged to address issues around gathering the necessary evidence for clinical evaluation.
4. An independent expert body should be responsible for evaluating the evidence for test performance and for making recommendations about appropriate clinical use.
5. Commissioners and health care professionals should be encouraged to use only those tests where appropriate evidence of clinical performance exists.
6. Statutory regulators should be empowered to require transparency relating to evidence of test performance, and ensure responsive and proportionate risk assessment to ensure patient safety.

judgement in making such decisions. One implication of such considerations is that two thresholds may have to be established for each test or intervention. The lower threshold being that which allows the test to be sold in the marketplace; and the higher threshold requiring much greater evidence, particularly of cost-effectiveness and of utility, before third party payers are willing to fund.

Second, it may prove to be of importance to distinguish between what I call pre-biomarkers and post-biomarkers. The former are in effect markers that predict the risk of future disease. The disease has not yet developed and the biomarker in effect is a risk factor for the disease. Genetic variants would be considered a pre-biomarker, as would cholesterol in relation to coronary artery disease; a raised level implies increased risk but says nothing about whether or not there are signs as yet of disease. By contrast, post-biomarkers are markers that are only present once disease has developed albeit at a pre-clinical stage. They are markers of disease as distinct from markers of disease risk.

Test regulation

Tests can be regulated in many different ways. Legislation and use of formal legal instruments are but just one of these. Informal codes of practice may be useful in certain circumstances and may be often as effective as formal statutory provision. In practice, one of the most effective forms of regulation is through control of resources. Those who commission and pay for health services, whether insurers, government commissioners or health maintenance organisations, have a hold on the purse strings and can easily affect whether or not they will pay for a particular test. Educational strategies and clinical governance mechanisms can also be considered a form of regulation (Burke and Zimmern 2004).

But perhaps one key question which as yet remains unanswered concerns the effectiveness of tests. It is universally accepted that the statutory regulator must be concerned with product safety. But is it the role of the state to ensure that the product is effective before allowing it into the market? Safe, effective products should obviously be allowed, and unsafe, ineffective products banned. Products that are effective but not entirely safe (most pharmaceutical agents) require tight regulation and a detailed understanding of both risk and benefit. But what of safe but ineffective products? As a society, we already allow such products to be sold: homeopathic remedies, vitamin pills, and anti-ageing creams. How should a free and liberal society regulate predictive biomarkers without any objective utility? Should they be allowed into the marketplace? Or should society be protected through statutory regulation? The question is about the placement of products in the marketplace. It is not about the funding of such products by third parties. In

this latter case, whether the third party is an insurer or a commissioner of services such as we have in the UK NHS, it is entirely right and proper that interventions are only funded if they reach a certain standard of cost-effectiveness (Zimmern 2009).

My own conclusion here is that information and education should provide the key to how we should regulate. I would not favour the banning of safe, ineffective products. However, I would most vigorously pursue a policy of making available, and in an accessible form, information concerning the value and effectiveness of such products to physician, patient and citizen alike. The provision of such information should be compulsory, and obligations should be placed on test providers to make available in the public domain the evidence that they have relating to the diagnostic or predictive tests or services that they seek to sell.

Device regulators have, through the Global Harmonisation Task Force, defined clinical evaluation as *the assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device* (Page 7) (Global Harmonization Task 2007). However, with regard to *safety*, there continues to be uncertainty as to how it should be interpreted in the context of tests. A device, such as an endoscope, can cause harm; and if there is the propensity to do so, may be said to be unsafe. But does the word *safety* only apply to harms directly caused by a device; or, in the case of tests, can it also be applied to consequential harms that come about as a result of reliance on information obtained through the performance of the test? Even greater uncertainty is provided by the term *clinical performance* in the definition. Does the performance only apply to the analytical validity of the test? Or does it extend to its scientific validity, evidence of test performance or even to its clinical utility? Where does the regulator's role end, and where does the role of the clinical professional at the interface with the patient begin?

Information

In the previous section, I alluded to the idea of information, and the extent to which information may be unsafe if reliance on such information results in consequential harms. But the situation is even more complex, as Onora O'Neill and Neil Manson have pointed out (Neil et al. 2007). They have drawn to our attention that the meaning of information is critically dependent on context, and in particular of the understanding of the person to whom the information is conveyed. Both the giver and the recipient of information play a role in the ascertainment of the meaning of any particular piece of information transmitted by one individual to another. They refer to this as the *inferential fecundity of information*. An X-ray provides a simple example of what

they mean. To most people, the patterns on the photographic plate will be just that, a set of black, grey and white patterns; yet to the informed radiologist, the information conveyed will be much more specific. The meaning of the information may specifically spell out the chances that the patient has a tumour in the lung. The context and the expertise of the recipient determine the information conveyed by the X-ray appearances.

Much more can be said about this issue. But perhaps, for our purposes, I need only point out that this insight raises the question of whether our regulatory response should be directed, as it is at present, at just the acquisition of data; or whether, because of its inferential fecundity, there might be merit in considering regulating data at the point of interpretation or at the point of use.

The German genetic diagnosis act 2009

This paper finishes with some short remarks on the German Genetic Diagnosis Act 2009 (GenDG 2009). The first point to make is that definitions are in abundance in the Act. Terms such as *genetic characteristics*, *genetic data*, *genetic analysis*, *genetic examination* and many others are all carefully defined, and I have alluded to these earlier in the paper. The scope of the Act is extremely clear. It is also extremely wide. It applies to any examination directed at “genetic examinations and genetic analyses conducted within the framework of genetic examinations involving (a) born natural persons and embryos and fetuses during pregnancy AND (b) the handling of genetic data and genetic samples gained for medical purposes, for the purposes of determining descent, in insurance and in employment” (Sec 2 (1) GenDG).

Research and forensic purposes are excluded from the scope of the Act (Sec 2 (2) GenDG).

My second comment concerns the prohibition of discrimination set out in the Act which states that

no one may be discriminated against or disadvantaged on account of his or her genetic characteristics...in regard to the performance or non-performance of a genetic examination or genetic analysis (Sec 1).

This section raises fundamental issues about genetic discrimination. The prohibition of discrimination and disadvantage based on genetic characteristics is, in my view, fundamentally problematic unless those terms are appropriately qualified. The appropriate qualification in my view is that for discrimination to be the subject matter of legal attention it also has to be unfair. The prohibition should thus be on unfair discrimination and not on simple discrimination or disadvantage per se. In my talk I stated that “clarity demands that this be explicitly stated in legislation”. I did

so on the basis of the translation that was available to me at the time.

I am therefore indebted to Professor Jörg Schmidke, for pointing out that this is already the case, and that the German word “Diskriminierung” is always meant in the sense of “unfair discrimination”, not just discrimination per se; and to Dr Eva Fisher for telling me that the term used in the statute, “Benachteiligung”, means disadvantageous treatment, and thus expresses more clearly the element of unfairness intended by the legislation (Jörg 2012).

Notwithstanding this clarification, given my belief that all discrimination that is unfair should be prohibited by law, it is my view that unfair discrimination whose basis is genetic variation need not be protected in any different way from unfair discrimination based on any other characteristic. Society needs legislation to prevent unfair discrimination; not legislation to prevent genetic discrimination. To treat genetic discrimination as a legal issue that is to be dealt with separately from other forms of unfair discrimination is for me unsatisfactory and troublesome.

It is for me a truism that it is the genotype that is (at least in part) responsible for the differences between one individual and another, and that by virtue of that difference each individual will go through life with a set of biological advantages and disadvantages. These are biological facts. Every day we interact with each other and with society, in some instances with advantage because of our natural attributes, and in other instances with disadvantage. This is part of the human condition. Unfairness comes about by virtue of how society deals with and reacts to those differences. Unfairness is not per se to be found within the nature of genetic heterogeneity itself.

As some evidence for my stance, Article 1 of the Universal Declaration of the Human Genome and Human Rights states that the human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and *diversity* (my italics) (UNESCO 1997). This recognition of human diversity, in part a product of the human genome, as a fundamental aspect of humanity sits uneasily against regulations that prohibit discriminatory action purely by virtue of such diversity, and brings greater emphasis to the need to recognise that it is unfairness not genetic diversity that is unacceptable.

My third comment concerns the failure of the Act to distinguish between the use of genetic examination or analysis in inherited (or heritable) high penetrance disorders and common complex disorders, or, in the context of predictive analysis and examination, to distinguish between their use in presymptomatic testing and in susceptibility testing. The definition of *diagnostic genetic examination* includes, inter alia, any genetic examination which has as its goal assessing whether

any genetic characteristics are present which, together with external factors or foreign matter, could cause an illness or health problem (Sec 3 No 7b GenDG).

and of *predictive genetic examination*, any genetic examination with the goal of predicting or assessing

any future illness or health problem (Sec 3 No 8a GenDG).

These definitions are very wide, and my fear is that their applicability to the common complex disorders, for which a genetic variant is no more or less predictive than any other non-genetic based biomarker, may have in the future significant negative consequences for the practice of medicine and for health care in general.

While I am sympathetic to the view that for inherited and heritable disorders, specialist knowledge and competence in genetic counselling is necessary, I do not believe this to be so for the use of genetic examinations (either predictive or diagnostic) in the common complex disorders.

My fourth comment is directed at the requirement for predictive genetic tests to be conducted only by medical doctors who are certified specialists in human genetics or “by other medical doctors who within the framework of their own area of expertise were also able to obtain certification, specialization or additional qualifications to conduct genetic examination” (Sec 7 (1)).

This comment is tied up with earlier points that I have made about failure to distinguish between presymptomatic and susceptibility testing. As we learn more and more about the human genome, the use of genetic variants in conjunction with other medical information to predict disease risk or prognosis, or to determine the likely efficacy of treatment will become common place. The correct response to this is not to prohibit other medical or even non-medical competent health professionals to carry out such tests, but to establish a far reaching set of educational activities to ensure competence in this type of testing.

The notion of genetic exceptionalism, the claim that genetic information is sufficiently different from other types of health information that it deserves special protection or other exceptional measures, lies behind my fifth concern. The fundamental notion behind the Act, namely that it is underpinned by genetic characteristics, gives it extremely wide scope, and my concern, perhaps not shared by everyone, is that these restrictions may in the future prevent the use of both diagnostic and predictive testing in medical practice, especially as it relates to common complex disorders.

My sixth, and final, comment is to suggest that perhaps legislators might consider the use of regulation at the point of data use rather than at the point of data acquisition. Thus, certain uses of genetic information, of data derived from

genetic analysis or genetic examination, should be prohibited and other uses allowed. At present, data protection legislation (as based on the European Directive) in most European countries is directed at the acquisition and the holding of data. If the aim is to prevent unfair discrimination or disadvantage the law should focus not on the technology of the analysis or examination or on the assay results, but on whether use is legitimate or illegitimate.

Conclusion

The conclusion of my discussions may perhaps be best summarised as a series of statements. They are set out below.

1. The precise use of language, taking care to define terms and understand concepts, is a necessary condition for the rational regulation of biomedical science.
2. The terms *genetic test* and *genetic information* need particular attention; to reflect the important distinction between inherited and heritable disorders on the one hand and the use of assays and technologies based on nucleic acids on the other.
3. The evaluation of genetic tests and other diagnostic and predictive biomarkers will become more important over time.
4. Policies, systems and funding mechanisms exist in most developed countries that allow data of biomarker-disease association to be generated. Such evidence is usually carried out by the scientific community and are funded through academic research grants
5. Policies, systems and funding mechanisms do not exist for the large scale generation of data to inform the assessment of test performance (sensitivity, specificity, positive and negative predictive values and the area under the ROC curve) of diagnostics. This is to be contrasted with therapeutic agents where clinical trials are mandatory. Such evidence is needed to determine the clinical validity of a biomarker.
6. Governments should be aware of this gap and the relevant parties (academics, research funders, the commercial sector) need to discuss their relative roles and responsibilities for funding and establishing such mechanisms.
7. The assessment of predictive or susceptibility (as distinct from diagnostic) tests is in its infancy and will require a reorientation of research effort to focus on (a) the establishment of risk prediction algorithms and (b) determination of the threshold at which preventive interventions should be undertaken.
8. The statutory regulation of the clinical performance (test measurement and evaluation) of a test should,

unless there is strong evidence to suggest otherwise, be by and large confined to:

- (a) the regulation of the safety, reliability and analytic performance of the assay
 - (b) the determination of scientific validity (production of evidence about the prima facie association between the test and the disorder) and
 - (c) the exact nature of the claims made in labelling the device or product
9. The regulation of a testing service is at present rudimentary and not well distinguished from the regulation of products and devices
 10. Systems for regulating services may need strengthening and should include consideration of how professional regulation should be used to ensure proper interpretation of results
 11. Regulation may be statutory or implemented through codes of practice. Will codes suffice or are statutory instruments needed ?

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