

The regulation of commercial genetic testing services in the UK

A briefing for the Human Genetics Commission

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Foreword

This briefing has been prepared for the Genetic Services Sub-group of the Human Genetics Commission (HGC). Its main purpose is to assist members of the Sub-group as they reconvene after a period in which the group has been in abeyance. Its focus is the regulation of commercial genetic testing services, an area the Sub-group is expected to address as it reconvenes. It sets out the history of such activity from the formation of the ACGT in 1996 and outlines the complications which arose when this body was absorbed within the newly established HGC in 1999. It briefly outlines the recommendations of *Genes Direct*, the HGC's report on the regulation of direct-to-public testing and highlights some of the main developments in the period since the report was issued, both in the regulatory arena and in the development of commercial testing services. Annex 1 analyses the recommendations made in the *Genes Direct* report pertaining to the IVD Directive and identifies areas which may be worthy of further investigation. The briefing also encourages the HGC to clarify its use of the term 'predictive' in the *Genes Direct* report and Annex 2 seeks to assist in this by listing all the uses of the term in the report.

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Brief chronology

- 1995 – University Diagnostics offers CF testing – first commercial genetic testing service in UK
- 1996 – establishment of Advisory Committee on Genetic Testing (ACGT)
- 1997 – Publication of ACGT’s code of practice on genetic testing services supplied direct to public
- 1999 – ACGT’s work subsumed within the newly established Human Genetics Commission (HGC)
- 2001 – Sciona launch a genetic testing service providing ‘personalised’ dietary/lifestyle advice
- 2001/2 - HGC review the Sciona service against ACGT code of practice
- 2002 - HGC begins public consultation on future of regulation
- 2003 – publication of *Genes Direct*, the HGC’s report on the future of regulation
- 2003 – EU IVD Directive regulating diagnostic tests comes into force in UK, enforced by the MHRA
- 2004 – launch of NicoTest, a genetic testing service aimed at smokers wishing to quit
- 2005 – HGC reconvene the Genetic Services Subgroup

1) Introduction

Perhaps the primary issue to bear in mind when considering the regulation of commercial genetic testing services in the UK is that there has been to date very little to regulate. All but a tiny number of genetic tests carried out in the UK are delivered through the NHS’s network of clinical genetics labs. For a variety of reasons attempts to introduce commercial testing services have so far proved unsuccessful. The situation is quite different in the United States where there are a wide range of commercial testing services, but public sector testing dominates Europe with the notable exception of Germany, where a thriving commercial sector exists. Attempts to introduce commercial genetic testing services in the UK have met with expressions of concern and criticism from a number of actors ranging from members of the clinical genetics community to consumer organisations like Which? and campaigning groups like GeneWatch UK. Perhaps in large part as a result of this criticism, the nascent commercial sector has been subject to a series of regulatory initiatives.

Before outlining these initiatives, it may be useful to clarify what we mean by regulation. Historically much discussion of regulation has focussed on the regulation of business activities through what is termed ‘command and control’ regulation: that is “regulation by the state through the use of legal rules backed by (often criminal) sanctions.”¹ But there is now a greater focus on what is termed de-centred regulation – the use of (often non-statutory) instruments by a range of public and private actors from trade associations to public interest groups.

Within the context of genetic testing, this wider definition of regulation might be seen as operating at three levels: statutory controls, resource allocation and clinical governance.² So the use of a genetic test might be regulated at the first level by standards set by a statutory licensing body; at the second level by the requirements established by a purchaser - whether the NHS or, in the case of direct-to-consumer, a pharmacy chain – and, at the third level by the rules and guidelines set by professional

¹ Black, J ‘Critical reflections on regulation’ CARR discussion paper 4, LSE, January 2002

² Burke W. and Zimmern R.L. (2004) ‘Ensuring the appropriate use of genetic tests’ *Nat Rev Genet.* Dec;5(12):955-9

bodies, healthcare organisations and other groups, which control the practice of medicine. The *Genes Direct* report, which we shall consider later, took just such a broad view of regulation.

Finally, we might think of regulation as encompassing three broad tasks: information gathering, standard setting and behaviour modification (we will refer to this third task as enforcement/compliance).³ This functional definition will be important as we consider the historical development of regulation of commercial genetic testing services and identify who has been responsible for what.

2) From ACGT to HGC

a) Advisory Committee on Genetic Testing

The regulation of commercial genetic testing began with the establishment of the Advisory Committee on Genetic Testing (ACGT) in 1996. The Advisory Committee on Genetic Testing (ACGT) was established by the government in 1996 in response to the 1995 Science and Technology Select Committee report on human genetics.⁴ It was to consider public health and consumer protection issues around genetic testing in both the public and private sectors. They were interested in a range of issues such as assessment of test validity and utility and the services around testing such as counseling. Its terms of reference were to advise the government on developments in genetic testing, on ELSI issues around testing and “to establish requirements, especially in respect of efficacy and product information, to be met by manufacturers and suppliers of genetic tests”. In this respect we might say that the ACGT had responsibility for two key regulatory functions - information gathering and standard setting.

ACGT produced a code of practice for genetic testing services supplied direct to the public which emphasised the need for informed consent; the provision of data on the validity and utility of tests to patients in a easily understood format and the importance of counselling. The code established a voluntary system of compliance and monitoring, whereby suppliers planning to offer a genetic testing service direct to the public (or proposing an amendment to an existing service) should present their proposal to them prior to the its introduction. This was a significant step because the ACGT had thus extended its remit from information gathering and standard setting to also take in the third major regulatory task of compliance or enforcement (albeit without any statutory powers). The code was non-statutory but offered the threat of statute in the case of non-compliance. Two testing services submitted proposals to the ACGT – University Diagnostics and the Manchester Children’s Hospital NHS Trust.

The ACGT developed two further guidance documents, one for research ethics committees and another on the provision of tests for later onset disorders.⁵ In its work it consistently emphasised the importance of gathering and disseminating data on the accuracy and predictive value of tests, for instance, in its report on late onset disorders it recommended that the clinical validity of a test must be established before it enters clinical practice.

b) Human Genetics Commission

In May 1999 the government completed a review of the advisory and regulatory framework for biotechnology. The concluding report recommended a new structure which separated strategic

³ Hood, C et al *The government of risk – understanding risk regulation regimes* (Oxford, 2001) pp24-7

⁴ House of Commons Science and Technology Select Committee *Human Genetics: the science and its consequences* (London: HMSO, 1995)

⁵ All these can be found in the ACGT’s *Third Annual Report and Compendium of Guidance* (London, 1999)

advice work from the day-to-day business of implementing regulation and placed a new emphasis on consultation and transparency.⁶ Two new bodies were to be established: the Human Genetics Commission (HGC) and the Agriculture and Environment Biotechnology Commission, which would take on the role of strategic advisers. This strategic role would include oversight of the regulatory frameworks; examining how they worked in practice and advising the government on any changes which might be needed, thus they would be involved in information gathering and standard setting but not enforcement/compliance on a case-by-case basis which would be carried out by existing bodies. In effect their role would be to act as the watchmen watching the watchmen.

In accordance with this new framework it was decided that the HGC would take on the work of the existing advisory bodies - the Advisory Group on Scientific Advances in Genetics and the Human Genetic Advisory Commission - and would monitor and report on the work of three regulatory bodies - the Genetic Therapy Advisory Committee, the Genetics and Insurance Committee, and the Human Fertilisation and Embryology Authority. In this division of labour the ACGT was deemed to be an advisory body rather than a regulatory body and its work was also subsumed within the HGC's remit.

On a strict reading of only the ACGT's terms of reference (see above) this move was compatible with the broad approach of the review – that is to say the HGC would advise on improvements to the regulatory framework in line with the ACGT's third term of reference. However, as has been noted, the ACGT had gone beyond a standard-setting role by making itself responsible for enforcement of its first code of practice. So in this regard the HGC's assumption of the work of the ACGT was in contradiction to one of the primary aims of the review - to separate strategic advisory work from the enforcement of regulations. This tension can be clearly seen in the general terms of reference for the HGC and in the terms of reference for the HGC's Genetic Testing sub-group, which took on much of the work of the ACGT. Thus the HGC's terms of reference delineated a standard setting and information gathering role, stating that it was:

- To co-ordinate and exchange information with relevant bodies in order to:
- identify and advise on the effectiveness of existing guidance and of the regulatory and advisory framework as a whole, taking account of European and global dimensions;
 - look at the lessons learnt from individual cases requiring regulatory decision to build up a wider picture;⁷

But the terms of reference for the HGC's Genetic Testing sub-group, went beyond that by taking up the enforcement/compliance work of the ACGT, stating that it was:

- 2) To prepare and maintain codes of practice and guidance material on human genetic testing services where needed.
- 3) To receive and consider the approval of applications for 'direct to the public' testing services.⁸

It seems likely that this tension was either considered unimportant or was overlooked because, in the absence of commercial testing services, there had been so little active compliance/enforcement activity by the ACGT. However, the sub-group's first activities were to work with the HFEA on

⁶ Cabinet Office, Office of Science and Technology *The Advisory and Regulatory Framework for Biotechnology: Report from the Government's Review* May 1999

⁷ First Annual Report of the Human Genetics Commission (London, 2001) p 50

⁸ Terms of Reference and Membership of the Genetic Services Subgroup from HGC website – http://www.hgc.gov.uk/subgroups/genetic_testing.htm Accessed on 30/09/04

guidelines for pre-implantation diagnosis and to take part in the development of an additional voluntary code of practice, focusing solely on private paternity testing services, this was published in 2001. The HGC's workplan for 2002 anticipated a review of the ACGT's existing compendium of guidance, but before that could be carried out a new commercial testing service was introduced, bringing to light the tensions and ambiguities in the HGC's multiple roles.

c) Sciona

In 2001 a biotech company called Sciona who were planning a new direct-to-consumer testing service, notified the Genetic Testing subgroup about this new service. The subgroup evaluated the tests against the ACGT's code of practice. They met with Sciona in 2002 and expressed a number of concerns, some of which Sciona responded to by modifying their service. The HGC's criticism of Sciona was focused on the clinical validity and utility of the test and the failure to inform customers about possible associations between the genes tested and serious diseases.⁹ However, these concerns were not initially published, as doubts had developed about whether the ACGT code applied to the tests under scrutiny.¹⁰ Thus the Sciona case led the HGC to consider its position as a regulator and they came to three conclusions:

1. The ACGT's existing code, designed with single gene disorders in mind, did not cover Sciona's type of test.
2. The HGC felt that the role they had inherited from the ACGT as regulatory enforcer was not compatible with their primary mission to offer independent strategic policy guidance to the government, (in line with the conclusions which the OST report had reached in May and thus a return to the original mission envisaged for the HGC). The HGC now wished to transfer their enforcement role to a more suitable body and concentrate on advisory work unencumbered by a potential conflict of interest.
3. In its advisory capacity the HGC was asked to look at the regulation of direct-to-consumer tests, it was hoped that this piece of work would help to resolve the question of who should have regulatory responsibility.

As to what should happen in the meantime, it was felt that taking a broad, long-term look at regulation could conflict with a more short-term review of the existing ACGT code – a dilemma neatly illustrating their fears of a potential conflict of interest. So the HGC decided that they would recommend to the government that if an alternative regulator could not be found immediately, then the manufacturer/laboratory's duty to notify should be withdrawn, but that they would continue to give informal advice on such services until the review was complete.¹¹

The HGC wrote to the Government outlining their position and Ministers responded by asking them to continue to consider new testing services and discuss them with those involved, but suggesting that any final conclusion about compliance with the Code should await the outcome of the regulatory review.¹² Thus, as that review began, the HGC's responsibility for the ACGT's codes of practice became one where they would "advise potential suppliers to try to ensure that sufficient and accurate information was given about any tests."¹³

⁹ Human Genetics Commission *Genes Direct - Ensuring the effective oversight of genetic tests supplied directly to the public* (London: 2003) p 18

¹⁰ HGC *Genes Direct* p 11

¹¹ Minutes of HGC plenary session, 14 May 2002 and HGC News, August 2002

¹² HGC News, August 2002 p.2

¹³ Minutes of HGC plenary session, 11 September 2002

d) Genes Direct – the HGC’s review of the regulation of the supply of genetic tests direct to the public

The review began in 2002 with a public consultation exercise which set out the issues and suggested different possible solutions and then asked interested parties for their views. After this very broad consultation, the HGC produced a final report in 2003 which set out its recommendations.¹⁴ The HGC’s proposals clarified in some detail the current regulatory patchwork governing commercial genetic testing in the UK, from consumer law to professional codes of conduct, and made recommendations about how these different mechanisms or points of control might be improved.

Probably the central conclusion of the review was “there needs to be some independent mechanism to consider the scientific and clinical validity and utility of any genetic testing service.”¹⁵ They noted that the UK Genetic Testing Network were beginning to undertake such work within the NHS and suggested that all commercial genetic testing services should be similarly scrutinised by a regulator prior to being allowed to enter the market. They suggested that the MHRA take the lead role in assessing such tests and deciding whether they can be offered direct-to-the-public. The recommendations focused heavily on *predictive* genetic tests and the report suggested that such genetic tests should generally be restricted to something akin to prescription drugs – only available via a consultation with a doctor. It was also suggested that, like prescription medicines, these tests would not be advertised direct-to-the public.¹⁶

The report suggested that new legislation would not be needed to empower the MHRA, despite the MHRA’s view that it lacked the authority to take on the role which was envisaged for it. Instead they suggested that the MHRA could oversee non-statutory codes of practice. Considerable emphasis was also placed on the importance of appropriate training for any healthcare professionals involved in the delivery of genetic tests to the public and on consumer education, with the suggestion that an independent consumer body should be funded to provide impartial information on direct genetic testing services.

What was to be the role of the HGC? The report included a diagram outlining a possible regulatory framework and the HGC did not appear in it.¹⁷ However, although the future role of the HGC was not explicitly set out in the report, they did state that they would “keep the situation under review”, probably by holding a workshop or conference to consider progress in the light of the government’s response to the report and that the development of review criteria for the assessment of tests is something which they would wish to monitor “in conjunction with the UK GTN Steering Group and other interested bodies”.¹⁸

3) Developments since publication of Genes Direct

The government has yet to provide a response to the report although the genetics White Paper promised to do so once the report had been given due consideration. The timing of the report was

¹⁴ HGC *Genes Direct*

¹⁵ HGC *Genes Direct* pp 57-58

¹⁶ In preparing this briefing we became aware that despite singling out predictive tests for more stringent regulation, the report did not explicitly define the term predictive. Much hangs on this definition because a broad definition would potentially encompass a far greater number of tests than a narrow one. One of the authors of this briefing felt that the report was using the term *predictive* to cover both tests which are highly predictive of a late onset Mendelian disorder, such as Huntington’s, and also those of less highly predictive value (what is sometimes referred to as susceptibility testing) but another author felt that the report’s recommendations did not apply to susceptibility testing. This is an important point and one which the Sub-group might wish to clarify. To assist in this matter an annex to this briefing lists every reference to the term predictive in the *Genes Direct* report.

¹⁷ HGC *Genes Direct* p 56

¹⁸ HGC *Genes Direct* p 58

perhaps problematic, as the MHRA was being formed from the merger of the MDA and MCA and the IVD Directive was coming into force, a combination of developments which no doubt kept the regulator extremely busy without consideration of any additional responsibilities.

Government inaction has perhaps also been encouraged by the continued lack of activity in the commercial genetic testing market. Sciona, for instance, have moved their headquarters from the UK to the US, a country where there is apparently a far bigger market for direct-to-consumer testing. However, late last year a new direct-to-consumer testing service was launched – the NicoTest (produced by an Oxford University spin-out called G-Nostics) and this has prompted discussion of the current regulatory situation within the HGC. Recently it has also come to light that a company called MediChecks based near Nottingham offer a wide range of genetic tests on their website.¹⁹ The company are not themselves a laboratory but act as intermediaries, arranging the collection of samples etc.²⁰ The company state that their general policy is to advise members of the public to seek a referral via their GP or other physician, but that they are happy to provide a number of genetic tests direct-to-consumer, for instance Factor V Leiden, and that, in the case of more serious genetic tests, if a customer insisted they want to order test without physician referral, then they would seek to provide expert counseling as part of the service.

As noted earlier, when the *Genes Direct* review began the HGC's responsibility for the existing codes of practice had become one where they would "advise potential suppliers to try to ensure that sufficient and accurate information was given about any tests."²¹ The Genetic Services sub-group's current terms of reference state that they will "keep under review .. codes of practice and guidance on the ethical, social and scientific aspects of human genetic services and their effectiveness."²² However, the relevant sub-group has been in abeyance for some time. Furthermore, it would appear that the ACGT code of practice is no longer in operation. Eighteen months ago, some time after the publication of *Genes Direct*, G-Nostics wrote to the HGC regarding compliance with the code. The company were told by the HGC Secretariat that the code had been withdrawn and that they might use the recommendations in *Genes Direct* as a guide to how to proceed.²³

The NicoTest was discussed at the February 2005 plenary session of the HGC. That discussion confirmed that the HGC have now returned to the role originally set out for them as strategic advisers with an interest in regulation at the strategic level. The current situation is that the status of the ACGT's compendium of guidance is unclear and the vacuum created by the HGC's decision that it should relinquish its role as case-by-case enforcer of the codes has not been filled.

a) Advertising and consumer legislation

The *Genes Direct* report discusses the advertising of genetic tests supplied direct to the public but made no reference to the Medicines (Advertising) Regulations 1994 (SI 1932) which would appear at that time to have prohibited the advertising of such services.²⁴ However, in 2004 the Medicines (Advertising) Amendment Regulations 2004 (SI 1480) was amended in a move primarily designed to lift the restrictions on advertising OTC medicines, but which also removed the prohibition on

¹⁹ See <http://www.medichecks.com/>

²⁰ Much of their laboratory work is done by The Doctors Laboratory, a private lab company based in London who perform genetic (and other) tests for a variety of doctors/hospitals etc but who do not themselves accept test requests direct from consumers.

²¹ Minutes of HGC plenary session, 11 September 2002

²² HGC website: <http://www.hgc.gov.uk/Client/Content.asp?ContentId=260>

²³ Audio recording of HGC plenary session, January 2005

²⁴ Regulation 9 states: Subject to regulation 11, no person shall issue an advertisement relating to any relevant medicinal product which contains any material which - (a) gives the impression that a medical consultation or surgical operation is unnecessary, in particular by offering a diagnosis or by suggesting treatment by post, FAX or telephone

advertising over-the-counter medicinal products for the diagnosis of genetic disorders to the public.²⁵

The role of existing advertising and other consumer legislation as regulatory mechanisms has also been tested twice since publication of *Genes Direct*. First in 2003 by the HGC's Genetic Services sub-group when it complained to the Advertising Standards Authority (ASA) about a product called 'Genetic Hair' being sold by the Growth Hair Clinic. The ASA upheld the HGC's complaint that the advert implied that the product used genetic technology for hair restoration/grafting when in fact no such technology existed.

The second test of consumer legislation came in 2004 when GeneWatch UK used the Trades Description Act to complain to their local Trading Standards office about claims made by G-Nostics regarding the NicoTest. GeneWatch were told that the Act did apply and the complaint was passed to the Trading Standards office in Oxford (local to G-Nostics). It is not known what the outcome of the complaint was, as GeneWatch did not pursue it, because the claims being made on the NicoTest website were significantly modified.²⁶

b) UK Genetic Testing Network and NICE

Following the recommendations of a paper entitled *The evaluation of genetic tests for the NHS Service* the UKGTN Steering Group have developed new procedures and criteria for evaluating genetic tests.²⁷ Since 2003 new tests, and existing tests which are deemed worthy of investigation, are evaluated via a Gene Dossier which requires evidence on a range of issues from the seriousness and prevalence of the condition being tested for; the purpose of the test; its analytic and clinical validity, clinical utility, and ethical, legal and social considerations. Tests which meet the criteria are submitted to GenCAG for approval and are then added to the NHS Directory of Molecular Genetic Testing as Network services. Since its introduction in 2003 around 30 genetic tests have been formally evaluated through this process, with an emphasis on rare inherited disorders. The Gene Dossier process has attracted the interest and approval of geneticists in the US and Europe.

The remit of the UKGTN does not currently extend beyond single gene disorders, but NICE also has a remit to assess medical devices and diagnostic techniques. Its assessments include evaluation of analytical and clinical validity and clinical utility. In 2004 NICE issued its first guidance on the use of genetic tests, in this case for the BRCA1/BRCA2 breast cancer genes. It has so far carried out no other work in the area of genetic testing and is unlikely to assess all genetic tests.

c) International harmonisation

The *Genes Direct* report emphasised the importance of liaising with other countries in order to "achieve effective and harmonised national and international controls."²⁸ In the EU there have been considerable efforts to harmonise non-statutory oversight of laboratory quality assurance systems. This has been developed through a number of national, regional and international schemes which cover both genotype evaluation and interpretation of the genetic data. Early efforts at joint action began with testing for Cystic Fibrosis but has been expanded to include other genetic diseases under the European Molecular Genetics Quality Network (EMQN) which started in October 1998. Participants in such schemes include 34 European countries and labs from Australia and the USA.

²⁵ See MHRA press release - <http://www.mhra.gov.uk/news/2004/otcadvertisingrestrictions.htm>

²⁶ Private communication with Helen Wallace, Deputy Director, GeneWatch UK.

²⁷ See UKGTN website: <http://www.geneticstestingnetwork.org.uk/index.html>

²⁸ HGC *Genes Direct* p 9

These initiatives (combined with calls for action from a European Commission expert group and a recent IPTS report on lab standards²⁹) have now culminated in a new project – EuroGentest.³⁰ Funded under Framework 6, this five-year project is an ambitious attempt to move beyond the previous focus on laboratory quality assurance, to develop a series of discrete but linked programmes which deal with all aspects of genetic testing services, from evaluation of the clinical validity and utility of tests to counselling. It seeks to address all the issues raised by the recent EC Expert Group report and the IPTS lab survey in a move towards the harmonisation of the regulation of genetic testing within the EU.³¹

EuroGentest has attracted the interest of further afield, including the US and Australia, and members of the project are working as part of an OECD expert group on international standards. Last year they held a joint EC-OECD colloquium on genetic testing quality assurance bringing together experts from 20 countries. The first major work of this OECD expert group has now been completed - a survey of laboratory practices in OECD countries which was published earlier this year.³² This is to be followed by further work on the establishment of internationally agreed common standards for evaluating analytic and clinical validity.

d) Developments in the US – the legacy of SACGT

The *Genes Direct* report noted with interest the work of the Secretary's Advisory Committee on Genetic Testing in the United States, and in its recommendations on evaluation drew on the ACCE analytic framework developed by the SACGT, highlighting the importance of evaluation of analytic validity, clinical validity and clinical utility.³³ In the US a more evidence-based approach to evaluation is being spearheaded by the Centers for Disease Control through its Office of Genomics and Disease Prevention (OGDP). Following the recommendations of the SACGT, the OGDP are taking a lead role in the development of the ACCE framework. The OGDP have tested the ACCE framework over a 3-year period. Five tests for different disorders have been evaluated, with a goal of facilitating appropriate transition of genetic tests from investigational settings to use in clinical and public health practice.

This work by the OGDP probably represents the fullest working out of the agenda set by the SACGT and has already had beneficial effects in areas such as cystic fibrosis testing, but it has one major limitation – it is primarily concerned with analysing existing data; it does not solve one of the fundamental policy issues – how do you ensure that good primary data is generated? Who does this work and who pays for it? Also the ACCE project did not address the issue of implementation but this issue is now being taken forward in a new OGDP project (EGAPP) which is taking the process forward by looking at how the framework can be used in practice.

The SACGT also recommended that the regulation of laboratory testing should be enhanced to ensure that labs provide data on the clinical validity of their tests. In recent years CLIAC, the advisory committee which has oversight of the CLIA regulations which govern laboratories in the US,

²⁹ EC Expert Group *Ethical, legal and social aspects of genetic testing: research, development and clinical applications* (Brussels, 2004), Ibarretta, D et al *Towards quality assurance and harmonisation of genetic testing services in the EU* for the Institute for Prospective Technological Studies and European Commission Joint Research Centre (Brussels, 2003)

³⁰ <http://www.eurogentest.org/cocoon/egtorg/web/index.xhtml> - Alastair Kent, a member of the HGC is taking part in this project

³¹ An emerging regulatory trend within European state-based health care systems which is worth noting is the centralising of services, in part to try and ensure better quality control. This can be seen in a number of European countries like Belgium, Holland and the UK.

³² OECD *Quality assurance and proficiency testing for molecular genetic testing: survey of 18 OECD member countries* (OECD, 2005)

³³ HGC *Genes Direct* pp 43-44 The report did not emphasise evaluation of the fourth criteria identified by SACGT – the ethical, legal and social implications of the test.

has been working to introduce a genetic testing specialty under CLIA to develop new standards for genetic testing. It issued a Notice of Intent as a consultation document in 2000 which included proposals to extend test assessment to clinical validity, and oversight to areas such as informed consent. Both these proposals have been controversial attracting both considerable support and much opposition. CLIA are now close to completing a proposed rulemaking which will develop those proposals in the light of the comments they received in 2000. This in turn will be put out to consultation and after consideration of comments will result in a new rule. The timetable for this process is unclear.

As regards regulation by the FDA, the *Genes Direct* report noted that new tests can be used in labs without having to go through the more lengthy and complex FDA approval processes either because they have been developed in-house and/or constructed in-house from purchased ingredients (termed Analyte Specific Reagents by the FDA) which do not have to go through the full FDA approval. Indeed it has been suggested that some companies have sought to circumvent FDA regulation by operating labs rather than selling diagnostic kits – the most infamous example being Myriad Genetics.

There are two possible solutions to this highly uneven playing field – lower the standards for test kits or raise the regulatory standards for home-brew testing in labs. The latter was recommended by the SACGT and would in part be implemented by the amendments to the CLIA regulations described above but the FDA may also develop this further, modifying the ASR rule using a broadly applied risk-stratification approach.³⁴ This was reported in *Genes Direct* but there has been little progress since then - like the SACGT the FDA are struggling to devise an appropriate system for classifying which tests need the most stringent scrutiny. An alternative development is that more and more genetic tests will be deemed full-blown kits rather than ASRs – this is what has happened with the first two microarrays – the Roche Amplichip and Tm Biosciences' cystic fibrosis panel – which have both gained full FDA approval. It seems likely that as the market for genetic tests grows, the demand for such devices will increase and so there may be a shift away from ASRs, increasing the FDA's role in the regulation of genetic tests and ensuring that data is provided on clinical validity as recommended by the SACGT.

The SACGT itself has been replaced by a new body – the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS). The SACGHS is not actively pursuing the broad regulatory legacy of the SACGT although it has been updated on developments by CLIA, FDA and OGD. However, it has expressed an interest in the issue of direct-to-consumer testing and has called for better co-ordination of regulation of advertising of such tests and more research on the public health impact on advertising and direct access to such tests.³⁵

e) BIVDA code of practice

At the time of the *Genes Direct* consultation the industry body BIVDA had suggested that it would produce a voluntary code of practice on genetic tests for use by its members. In the event they decided against producing a code, but their genetics working group did produce a position paper. This addressed a number of issues including the need for counselling; the need for manufacturers to provide information on tests to users and the general public; and the importance of laboratory quality assurance and accreditation.³⁶

³⁴ Gutman, S quoted in Lusky, K 'FDA puts ASR rule back on the table' *CAP Today*, October 2003

³⁵ <http://www4.od.nih.gov/oba/sacghs/reports/DTCletter.pdf>

³⁶ BIVDA *Genetic testing – the difference diagnostics can make* (London, 2004)

Annex I

IVD Directive

This briefing will consider the HGC's recommendations made in respect of the MHRA and its responsibility for the IVD Directive. It is not intended as a general guide to the Directive but only to those aspects addressed in the *Genes Direct* report. It draws on analysis of the Directive and corresponding UK medical regulations; a range of literature analysing the Directive; discussions with the MHRA and advice from lawyers with an interest in the Directive.³⁷

At the time that the *Genes Direct* report was published the Directive was not yet in force, and it is to be expected that in the initial phase of any new piece of legislation there will be uncertainty about interpretation regarding some aspects. This briefing attempts to clarify where that is possible; identify other areas where further clarification might be sought and comments more generally on some of the HGC's recommendations regarding implementation of the Directive.

Genetic tests – a higher risk category?

The Directive operates on the principle of risk-based regulation, where the level of regulation applied is intended to be commensurate with the risk of harm posed by the test. The Directive has three higher risk categories. One relates to self-testing kits and the heightened risk is based on user ignorance/incompetence. The other high-risks tests are set out in Annex II of the Directive where they are split into two sub-categories - List A includes test kits for HIV, HTLV and hepatitis; List B, includes tests for rubella, toxoplasmosis and phenylketouria and self-test kits for blood glucose.

Other than the PKU test, all genetic tests are currently deemed low-risk and are subject to self-certification only. The *Genes Direct* report suggested that in the future genetic testing array kits will introduce a number of new IVDs that pose 'high risks' and thus would warrant addition to the list.

The foreseeable developments in commercial testing services, especially the production of genetic testing arrays (DNA testing chips) will undoubtedly introduce a number of new IVDs that pose equivalent 'risks' to those currently found in List B. We suggest that the MDA, as UK Competent Authority for the IVD Directive, should continue to seek to ensure that the European Commission works proactively to update the Annexes to IVD Directive in light of anticipated developments, rather than reactively in the light of potential problems with particular genetic tests.³⁸

As regards the actual process for adding new tests to Annex II – member states make a proposal to the European Commission and this is then submitted by the Commission to the Committee on Medical Devices. If the Committee cannot agree to the proposal, then the Commission is required to submit the proposal to the Council which will act by qualified majority. In deciding whether new tests might be added to List B, Article 14 (2) states that due consideration must be given to three criteria:

³⁷ We are grateful to Julian Hitchcock, Senior Solicitor at Mills & Reeve for his assistance in this matter.

³⁸ *Genes Direct* pp 41/2

- (i) whether total reliance has to be placed on the result obtained with a given device, this result having a direct impact on subsequent medical action, and
- (ii) whether action taken on the basis of an incorrect result obtained using a given device could prove to be hazardous to the patient, to a third party or to the public, in particular as a consequence of false positive or false negative results, and
- (iii) whether the involvement of a notified body would be conducive to establishing the conformity of the device.

As regards the likelihood of agreement to such a proposal amongst the Committee, this may not be straightforward – there was a great deal of disagreement on what should be included in this list initially. As can be seen above, Annex II List B is a hotchpotch of different tests with no overarching theme. Its heterogeneity is the consequence of political horse-trading after profound disagreement amongst the representatives of individual member states about what should be deemed high-risk – some wanted all cancer tests included, others all infectious diseases. Many member states would strongly resist reopening old arguments.

The *Genes Direct* report failed to note that Articles 10 and 11 of the Directive place a special obligation on manufacturers to inform competent authorities (MHRA in UK) when they are introducing “new products” i.e. products which are new with regard to “the technology used and the substances to be analysed or other parameters ... this is true in particular of high-density DNA probe devices (known as micro-chips) used in genetic screening”. Such new products are subject to special vigilance procedures “The competent authority so notified may at any time within the following two years and on justified grounds, require the manufacturer to submit a report relating to the experience gained with the device subsequent to its being placed on the market.”

In fact the first microarray test completed the CE marking process in Autumn 2004. The Roche Amplichip, a pharmacogenetic test for the CYP2D6 polymorphisms which influence drug metabolism, was classified as low-risk and CE marked through self-certification. It would be instructive to learn more about this process; who the relevant competent authority is (i.e. which member state) and how they intend to use the special vigilance procedures for new products. It might also be worth exploring how broad the definition of ‘new products’ might be, for instance since it refers to analytes as well as analytic technology, it presumably would cover all novel genetic markers. It should also be noted that the ‘low-risk’ classification was in stark contrast to the view taken by the FDA that both the clinical use of the test and the novelty of the technology meant that it was not a Class I or low-risk device.³⁹

³⁹ Letter from OIVD to Roche Molecular Diagnostics Re: AmpliChip, October 2003, see <http://www.fda.gov/cdrh/oivd/amplichip.html> - accessed 31 August 2005

Clinical validity and utility

As noted earlier the *Genes Direct* report set out an important role for the MHRA in the evaluation of genetic tests. The HGC were of the view that tests should be evaluated on three criteria: analytic validity, clinical validity and clinical utility (as well as wider aspects of testing services such as personnel, promotional claims etc). The HGC expressed concern that the IVD Directive would not cover all these points and urged the government and the MHRA to address this.

However, the emphasis of the IVD regulations is clearly on safety, quality and accuracy of the tests. It does not, and is not intended to, consider directly the wider questions of scientific validity or clinical utility. We feel that the MHRA should consider how to extend the regulatory system for in vitro diagnostic devices in order to address wider aspects such as scientific quality and clinical utility.⁴⁰

We would agree that the Directive does not really cover clinical utility, but there would seem to be considerable ambiguity, or interpretative flexibility, regarding the degree to which there is an obligation on manufacturers to provide data on clinical validity. The stated view of the MHRA (and the view of many commentators) is that there is no such obligation; manufacturers are *obliged* to provide data only on analytic validity but the MHRA also state that when a manufacturer makes clinical claims for a device, then they must provide the data to back it up.

The view that the Directive's obligations are limited to analytic validity has been challenged by some who suggest that it may place greater emphasis on clinical effectiveness and may, in practice, require performance data on each test apparatus 'in its intended use in patients'. GR Higson, a UK expert on device regulation closely involved in the development of the medical devices directives, commented on this issue, stating that:

final confirmation of the safety and performance of a medical device is normally provided by observation of the behaviour of the device in its intended use with patients ... Essential requirements 1 and 6, and in some cases 3, can only be satisfied by the evaluation of clinical data relating to the use of the device.⁴¹

The most relevant part of the Directive would be the third essential requirement. The IVD Directive sets out a series of six essential requirements concerning safety, quality and performance which all IVDs must comply with before being CE marked and placed on the market. Requirement three states that devices must meet the manufacturer's specifications, taking into account "the generally acknowledged state of the art". Performance criteria that may be appropriate include "**analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity**". Common usage of these terms would lead one to understand analytical sensitivity and specificity as referring to analytic validity and diagnostic sensitivity and diagnostic specificity as referring to clinical validity. The Directive does not define the terms analytical and diagnostic, however, in the common technical specifications for Annex II List A devices published in 2002, the terms diagnostic sensitivity and analytic sensitivity are defined thus:

(Diagnostic) sensitivity - The probability that the device gives a positive result in the presence of the target marker.

⁴⁰ *Genes Direct* p 41

⁴¹ Higson, G *Medical device safety – the regulation of medical devices for public health and safety* (Bristol, Institute of Physics, 2002) p49

Analytical sensitivity - In the context of the CTS it may be expressed as the limit of detection: i.e. the smallest amount of the target marker that can be precisely detected.

It would seem that diagnostic sensitivity has been defined as what would normally be considered analytic sensitivity. It should be noted that these common technical specifications only relate to Annex II List A devices and are not part of the Directive.

Even if this definitional problem were to be addressed there is still the question of when the essential requirements for data on diagnostic sensitivity and specificity are “appropriate” i.e. is this apparent requirement for clinical validity data limited, as suggested above, to where clinical claims are made for the device? Can manufacturers who do not make clinical claims for a device i.e. specify a clinical use, avoid giving data on clinical validity? There is a question mark over the degree to which the clinical uses of a device are the responsibility of the purchaser of the device, rather than the manufacturer.

As Higson suggests, a further area of ambiguity is raised by the first essential requirement which states that the test must not “**compromise, directly or indirectly, the clinical condition or the safety of the patients, the safety or health of users or, where applicable, other persons**”. Any risks conferred by the test must be outweighed by the benefits to the patient. It is unclear how a requirement only to produce data on analytic validity is compatible with the first essential requirement. If manufacturers must assess “**any indirect risks which may be associated with their use**”, and since false positive and false negative results are indirect risks, then given that such false results might arise from either poor analytic validity or poor clinical validity, it would follow that risk assessment must take into account the clinical validity of the test in its likely uses.

One could construct a narrower definition of “**use**” that limits it to the *analytic* use stated by the manufacturer, and on that basis only false positives and false negatives arising from poor analytic validity are the responsibility of the manufacturer. However, such a narrow definition does not seem compatible with the balancing of risks and benefits – the manufacturer is asked to balance risks against “the benefits to the patient” - as Higson clearly implies, since IVD devices are not universal panaceas, then to weigh up risks and the benefits it is necessary to consider the patients on whom it might be used, i.e. the likely clinical uses of the test and both the indirect risks posed by people acting or not acting on the information the test provides, and the benefit of acting on the information provided.

Furthermore, to return to the earlier issue of classifying a test as higher risk, we might ask how the criteria one and two in the list of criteria for inclusion in Annex II (see above) can be considered in the absence of a specific clinical use (for instance, criteria one refers to how dependent diagnosis is on the result of given by the device and how directly this result will affect medical action). Since as noted above, risk-based classification is central to the Directive’s approach to regulation, then any manufacturer who sets out to answer these questions can only do so in relation to a specific clinical use.

The *Guidelines for the classification of medical devices* issued in July 2001 (MEDDEV 2.4/1 Rev.8) asserts the idea that classification according to the risk posed by devices should be based on the intended purpose or use, not the device’s technical characteristics, and furthermore introduces the idea that where the manufacturer has not clearly indicated the device’s specific purpose, a device may be “deemed to be intended to be used principally for the purpose that is accepted in general medical practice.” It should be noted that these guidelines were drawn up for devices covered by the MDD,

the first of the three devices directives, and therefore do not apply to either active implantable devices or IVDs, however, if it is the case that for this type of device the regulations are interested in the intended clinical purpose, then why is that not the case with IVDs?

This is clearly an area which warrants further scrutiny. It may well be that at least in relation to clinical validity, the Directive offers more scope for consideration than the *Genes Direct* report suggested.

Purpose of the Directive

Discussion of possible limitations of the Directive often refer to the idea the purpose of the Directive was free trade, not public health. The *main* purpose is indeed the creation of a single market and the removal of barriers to trade (clearly expressed in the first paragraph of the preamble); however, the preamble also states that “maintenance or improvement of the level of health protection attained in the Member States is one of the main objectives of this Directive”. Thus, the Directive has a dual purpose – free trade and health protection – albeit the former may be considered its primary purpose. To put it another way: the Directive creates the structure within which free trade can take place and a central part of that structure is regulations designed to protect the health of patients.

This issue is discussed at some length by GR Higson, who disagrees with a number of commentators who have suggested that the Directives are simply trade measures, pointing out that the representatives of member states who took part in negotiations were from ministries of health and their chief concern was to ensure that the creation of a single market in devices satisfied “their responsibility for the health and safety of their citizens.”⁴² A similar point of view was expressed by John Sale, then Director General of the European IVD industry body EDMA, who complained in November 1998 (a month after the IVD Directive was agreed) that EDMA had asked for a harmonized regulation for free trade purposes and had ended up with increased regulation motivated by an over-estimation of the risks posed by IVDs.⁴³

Promotional materials, instructions for use and advertising claims

There seems to be some doubt as to whether the Directive covers claims made in advertising material. The *Genes Direct* report states:

The Medical Devices Regulations do not contain specific advertising controls and MDA has no statutory powers to regulate advertising of IVD test kits. However, if they become aware of misleading or inappropriate advertising or marketing they will hold discussions with the company concerned. They may refer the matter to the Advertising Standards Authority or where appropriate, the OFT who can take action where necessary.⁴⁴

Article one of the Directive states that the intended purpose of all medical devices is “the use for which the device is intended according to the data supplied by the manufacturer on the labelling, the instructions for use and/or the promotional materials”. Instructions for use of a test must be consistent with the manufacturer’s stated intended use and the manufacturer’s performance claims for the test. These issues are covered by the IVD Directive and the MHRA has authority to enforce.

⁴² Higson, G *Medical device safety – the regulation of medical devices for public health and safety* (Bristol, Institute of Physics, 2002) p31

⁴³ Sale, J *Industry point of view* Presentation at Advanstar Conference, Paris 1998

⁴⁴ *Genes Direct* p 42

Promotional materials are defined (at least by the MHRA) as those “coming within the packaging”, other promotional material e.g. advertising produced for marketing of the test, should also be consistent with the stated intended use and performance claims, but this is not covered by the IVD Directive; it is covered by a more general piece of consumer legislation - the General Product Safety Directive and in the UK the government department with authority to enforce this Directive is the DTI. Thus any complaints received by MHRA relating to promotional advertising would be handed to the DTI. However, the term ‘promotional material’ is not defined within the Directive and so a broader definition which encompasses advertising seems to be possible.

Transparency

Article 19 of the IVD Directive concerns confidentiality and states that: “Without prejudice to national law and practice on medical secrecy, Member States shall ensure that all the parties involved in the application of this Directive are bound to observe confidentiality with regard to information obtained in carrying out their tasks.” Notified Bodies and Competent Authorities are thus under an obligation not to reveal the evaluative data supplied to them. This can only be supplied with the agreement of the manufacturer.

The *Genes Direct* report places a heavy emphasis on the need for health professionals and consumers to be able to make informed decisions about the value and appropriateness of tests. The requirement that evaluative data be treated as confidential would seem to present a potentially serious obstacle to informed decision-making by anyone seeking to assess the claims made by manufacturers.

Homebrews and laboratory testing

Genetic testing is characterised by a high degree of dependence on homebrew tests developed in-house by laboratories. The regulatory status of such tests is ambiguous and has been the focus of much debate in the US (see above). Regarding the status of homebrew tests in the IVD Directive the *Genes Direct* report argued that “if a commercial company uses ‘in-house’ or purchased equipment or reagents to test human clinical samples as part of a commercial service, then it is considered to fall within the scope of the Regulations.”⁴⁵ But suggested that there was some ambiguity and that the MHRA should seek to clarify this area. The Directive exempts some tests developed by health institutions (Article 1, para 5). The nature of this exemption has been the subject of considerable debate but the MHRA’s current interpretation is that the exemption applies if device is:

1. made and used by a single health institution
2. used on the same premises as manufacture (or in the immediate vicinity)
3. legally owned (and probably controlled) by that health institution.

This may be understood more clearly according to the four following scenarios:

- Scenario A: health institution manufactures its own IVD in-house, uses it on premises of manufacture or in immediate vicinity - in-house exemption applies, regardless of whose patients are tested

⁴⁵ *Genes Direct* p 40

- Scenario B: health institution manufactures IVD, transfers it to different site of same HI, but not in the immediate vicinity - no in-house exemption
- Scenario C: health institution manufactures IVD, transfers it to a different legal entity, based on same premises - no in-house exemption UNLESS it can be treated as a single HI (e.g. manufacture of IVD by university research laboratory on trust hospital premises as part of joint health partnership)
- Scenario D: health institution manufactures IVD in-house, transfers it to a different legal entity, on different premises - no in-house exemption

The above scenarios may not entirely answer the question of how direct-to-consumer testing may be covered by the Directive. One central issue is what is a health institution? The MHRA's own guidance states it is:

6. ... a body whose primary purpose is the care and / or promotion of public health ... [such as] NHS trusts and bodies such as the National Blood Authority and the Health Protection Agency ... [and] private hospitals and bodies which provide private health care (for example, BUPA) ... provided that the primary purpose of those bodies is the care and / or promotion of public health.

7. ... free-standing laboratories which provide diagnostic services, (which are not part of a body which has as its purpose the care and / or promotion of public health) do not ... qualify as health institutions. Similarly, were a clinic to be established purely to provide diagnostic services, which did not have as its overall purpose the provision of health care (i.e. care and treatment of patients) or the promotion of public health, MHRA would not consider such a clinic to be a "health institution." This means that the exemption will not apply to such bodies even if they would otherwise fall within the exemption.⁴⁶

It is worth noting that so far the in-house exemption has been the most contentious issue regarding the implementation of the Directive in the UK and the MHRA has revised its interpretation more than once as a result of lobbying. This reinforces the point made earlier that we are in the early developmental stages of this legislation and there is considerable scope for questioning current interpretations.

⁴⁶ MHRA Guidance In-house IVDs 2004

<http://devices.mhra.gov.uk/mda/mdawebsitev2.nsf/0/A93D14B5548D628E80256EE000534595?OPEN>

Annex 2

Use of the term ‘predictive’ in the *Genes Direct* report

As noted above, the Genes Direct report singled out predictive tests as requiring greater regulatory scrutiny but left the term predictive open to interpretation. In order to clarify this point it may be helpful to look at how the term has been used in the report. To assist in this process, we set out below every single instance of the term in the report. For those wishing to refer back to the original report, page numbers from the report are cited at the end of each paragraph, where we have quoted a continuous series of paragraphs, the page reference is listed on the concluding paragraph.

We identified two possible broad ‘harms’ from direct genetic testing (3.7):

- the impact on individuals of misinterpreted or erroneous **predictive** health information which overstates the role of genetics in developing common diseases. This may result in delays in seeking proper medical advice (or seeking unnecessary medical treatment) or making expensive and unproven dietary or lifestyle changes. [p.7]

We feel strongly that there should be a well-funded NHS genetics service supported by a genetically literate primary care work force, which can properly manage and allow access to new **predictive** genetic tests that are being developed (3.30). This could involve the NHS providing ready access to testing services provided by commercial testing laboratories. It would enable **predictive** genetic testing to be retained within a well-respected model of continuing healthcare.

In view of this, we conclude that most genetic tests that provide **predictive** health information should not be offered as direct genetic tests (3.32). We think that it is a helpful analogy to consider the restrictions on medicines. Medicines are often only available with a doctor’s prescription. But some may be provided via pharmacists and others, if they are low risk, can be bought in any shop. [p.8]

We have concerns about **predictive** genetic tests that are done at home (‘direct to the consumer’; paragraph 3.34). This is because of the problems of providing full information so that the implications of the test can be properly understood. There is also a danger that children may be tested without proper lawful consent on behalf of the child. We have recommended a new offence of the misuse of genetic information that we feel must be introduced before such testing is acceptable. [p.8]

We think that consumer education about genetic testing will play an important role in minimising the potential harms that may follow from direct genetic tests. We would like to see a broader Government effort to inform the public about all forms of **predictive** genetic testing and about which tests may be suitable for them. We would like funding to be made available to bodies like the Human Genetics Commission, NHS Direct or other independent and trusted bodies to provide impartial advice about direct genetic tests in order to empower consumers to make appropriate choices (3.62). [p.9]

HGC’s review of the ‘You and Your Genes’ genetic testing service

However, in this complex area of human genetics they felt that there was not yet sufficient understanding of the interactions between genetic, diet and life-style factors in determining future health. They were not convinced of the **predictive** value of any particular polymorphism nor of the

proven value of such genetic tests as indicators for dietary change in order to reduce the risk of ill health. Indeed, HGC noted that several important scientific reviews of original published reports concluded that there was little or no direct health benefit associated with screening for variations in some of the common genes. [p.18]

What to regulate and why

Our consultation sought views on the definition of genetic testing. We consulted on whether this term should be interpreted narrowly (i.e. just to tests on DNA) or more broadly. A broader definition would include tests that indirectly provided information about genes by detecting or measuring a gene product (such as a protein or other specific chemical in the body) that is associated with a genetic condition.

I.18 We received a number of interesting responses on this point, which we might loosely categorise as follows:

... [various definitions follow, including]

Purpose-specific – several responses qualified their comments about a definition by considering the purpose of a test. Some felt that any oversight should draw a distinction between **predicting** susceptibility to complex diseases and **predictive** testing for monogenic conditions or carrier status. Others felt that the penetrance of a genetic condition was relevant, others that the use of tests for the diagnosis of serious conditions or where there could be serious consequences for the consumer if a test was erroneous or the result misinterpreted, were relevant factors.

We have considered these points and have decided to retain the definition adopted by the ACGT, but noting the additions that were introduced by the Genetics and Insurance Committee in their criteria for genetic tests used by insurance companies.

Therefore for the purposes of our report we will define genetic tests as:

a test to detect the presence or absence of, or change in, a particular gene or chromosome, including an indirect test for a gene product or other specific metabolite that is primarily indicative of a specific genetic change

I.20 We conclude that this definition is simple and sufficiently broad to cover the majority of **predictive** and diagnostic tests that are likely to be considered as possible direct genetic tests. It also covers other activities such as DNA paternity testing, but these have not been addressed in our report. [p.21]

I.25 We also heard a range of views that were familiar from our previous work on personal genetic information. Several responses commented about the possibility of conducting DNA tests on small samples and without consent. Others felt that genetic tests could provide **predictive** information for individuals and their families. However, it was noted that other types of health-related test could equally provide sensitive and intrusive information to individuals and their family. [p.22]

I.64 Related to the provision of informed consent is the provision of adequate and appropriate information before and after tests. Most of the responses focused on the provision of extensive and non-directive pre- and post-test counselling which is considered good practice among the clinical genetics community. This was felt to be necessary for genetic tests that are **predictive** of serious conditions. Some felt that this would include **predictive** testing for single gene disorders and those that were predictive of a risk of cancer or other severe conditions. [p.30]

I.83 Some respondents to our consultation specifically endorsed the 1997 US National Institutes of Health task force recommendation that advertising or marketing of **predictive** genetic tests to the public should be discouraged. The SACGT similarly recommended that the Food and Drug

Administration (FDA) and the Federal Trade Commission should enforce the regulations in the area of genetic test promotion and marketing. [p.34]

3.9 We detected significant support for these views during our wider public consultation. There is strong public support for mechanisms to protect vulnerable individuals from misleading claims based on the widely held perception of the **predictiveness** of genetics. Some individuals and organisations who responded to our consultation argued that rapid advances in our knowledge of genetics, and the understandable public interest in these advances, could be misused as a powerful marketing tool by unscrupulous companies in support of misleading claims. [pp.48-9]

3.11 There have been several major research collaborations involving the sequencing of genes from many individuals. It has been possible to detect a large number of instances where the sequence in an individual differs from the 'consensus' human genome sequence at a single DNA base position. These are called single nucleotide polymorphisms (SNPs, pronounced 'snips') and have been extensively studied as a means of understanding the function of genes and of linking genes to the different features or disease patterns in individuals. Some SNPs are highly **predictive** of a certain feature (or phenotype), where for example they result in a different form of a protein or no protein at all. Others are simply markers for as yet undiscovered gene variants, but they allow some estimate to be made of the likelihood that an individual has a certain genetic makeup which might lead to disease. [p.49]

3.12 There are an enormous number of potential SNPs in the human genome – up to 10 million by some estimates – and this has been felt to limit the use of SNPs to map and predict disease. Developments in human genetics have brought an increased understanding of how genes are grouped and structured into larger blocks called haplotypes. We heard separately from Professor David Goldstein about the use of haplotype mapping to reduce the number of SNPs that are needed to characterize individuals for the purposes of genetic research. These techniques may also result in more sophisticated methods of screening an individual's genome for possible **predictive** health purposes.

3.13 Several of those we consulted pointed out that genes are poor **predictors** of complex diseases [p.49]

Future oversight of direct genetic testing

3.20 The developing scientific and clinical understanding of genetics illustrates why it is premature to consider genetic testing as part of the normal clinical care of most diseases. For the immediate future, it is likely that only a small number of genetic tests might be generally available for health screening purposes. In 5-10 years, however, this position may well change radically. It is anticipated that the costs of genetic testing will fall considerably, and as the market for genetic testing develops, economies of scale will lead to the development of high-throughput testing, either to screen multiple samples for a few conditions or to screen one sample for many different genetic markers. The clinical value of genetic testing will also radically increase, first in the diagnosis and classification of diseases. This may then be followed quickly by **predictive** testing in order to guide the prevention or treatment of disease or for more general 'well-being' screening purposes. Before these tests are introduced into the NHS, they must meet certain standards of accuracy, cost and clinical value. [p.51]

3.22 This inevitably raises the question of how to effectively regulate direct testing services relating to common gene variations that may have a greater or lesser predictive value. We have considered the wide range of relevant public and professional bodies that are relevant to some aspects of genetic testing services and given some consideration to the current range of applicable legislation, both in

our initial consultation and in subsequent discussions. There are a number of general consumer protection laws that will apply to aspects of genetic testing services. There are also some specific laws such as the 1939 Cancer Act and the 1992 HIV regulations. [p.52]

3.27 We found strong public support for the NHS and GPs in giving appropriate medical advice before and after test – providing continuity of care, appropriate treatment or referral, as well as keeping medical records to help manage the care of patients. In our view, most **predictive** genetic tests properly belong as part of a consultation with a registered medical practitioner, either at primary care level, or for complex and highly penetrant conditions, at consultant-led specialist clinics. We also consider that this should include established screening and testing procedures conducted under the overall supervision of a medical practitioner (for example the infant heel-prick (Guthrie) test conducted by midwives or nurses). In other words, and to extend our analogy, we conclude that there is support for considering most genetic tests as if they were ‘prescription-only’. [p.53]

3.29 The public also supports a major role for the NHS in providing genetic testing services and advice and treatment in the light of such tests. Our YouGov survey suggested that around two-thirds of people would like to discuss a test and to receive results face-to-face with their doctor. Only 7% would prefer to receive information from a doctor who works for the testing company. For genetic tests for serious disorders, over 80% would expect to involve a GP or NHS specialist. This contrasts with just 10% who would prefer to obtain a test through a private consultation with a health professional. We therefore sense support for the view that, at present, **predictive** genetic tests for health and other purposes properly belong as part of a consultation with a doctor. [p.53]

3.30 We feel strongly that there should be a well-funded NHS genetics service supported by a genetically literate primary care work force, which can properly manage and allow access to new **predictive** genetic tests that are being developed. Where genetic tests are clinically proven they should be potentially available on the NHS. Genetic services – clinicians, counsellors and laboratory support – need to be properly resourced and artificial access barriers (such as local variations in commissioning of services) removed so that patients can easily access genetic tests which have demonstrable benefit for purposes of health or reproductive choice. We look forward to the Government Green Paper on Genetics for reassurance that this is to be the case. [p.54]

3.32 In view of the above, we conclude that for the foreseeable future, most genetic test that provide **predictive** health information should not be offered as direct genetic tests. We think that the *presumption* should be that a genetic test that is **predictive** of a medical condition is generally unsuitable for supply ‘direct to the public’ via a non-medical health professional or other intermediary and unsuitable for a kit or services supplied directly to the consumer. [p.54]

3.34 We have concerns about **predictive** genetic tests that are done at home (kits or services that are supplied ‘direct to the consumer’). There are two broad types:

- home-test kits where the sample is taken by the customer and the results appear ‘before their eyes’ at home; or
- home sample collection where the sample is taken by the customer and sent to a laboratory for analysis. The results will generally be sent by letter, email or via the telephone.

[p.54]

3.41 In Part 2 we review the current requirements under the Medical Devices Regulations that affect genetic testing kits and commercial genetic testing companies. From December 2003 companies will need to CE mark in vitro diagnostic devices to show that they comply with the essential technical requirements in the relevant EU Directives. We believe that the regulatory system for marketing

some genetic test kits and, in turn, some aspects of commercial genetic testing services under the new Regulations should be clarified among the industry groups, as at present there appears to be some confusion. We concluded that any genetic testing for **predictive** health purposes, pharmacogenetics, lifestyle testing or carrier testing should be considered to be a measurement of a 'physiological function' and part of the 'diagnosis, prevention, monitoring, treatment or alleviation of disease'. It follows from this that such tests fall under the regulations and that kits and commercial testing laboratories must meet certain minimum standards. We would welcome assurances that the MDA (and MHRA) will continue to work on clarifying the interpretation of the EU directives in relation to commercial genetic testing and, where appropriate, promote the voluntary adoption by industry of more stringent arrangements for oversight and advice. [pp55-7]

3.43 We conclude that there is evidence to suggest that all sides, including the industry, would welcome clarity on the arrangements for considering the scientific and clinical value of **predictive** genetic testing. We feel that the MHRA should consider how to extend the regulatory system for in vitro diagnostic devices in order to address wider aspects such as scientific quality and clinical utility. We formed the impression that the MDA and MCA feel that they are not empowered to consider the wider aspects such as scientific or clinical validity of tests or their ethical implications. We do not believe that they are statutorily barred from such considerations, but if so, we would hope that the Government would address such restrictions in setting up the MHRA. [p.57]

3.55 We have some reservations at this stage about allowing other groups of health professional or therapists to provide **predictive** genetic tests. On the basis of the evidence we gathered, we feel that there needs to be additional work to improve training and accreditation in genetics before groups such as nutritional therapists should actively offer genetic testing services for diet and lifestyle. We conclude that, at this stage, diet and lifestyle genetic testing services should be restricted to qualified public health nutritionists or to State-registered dieticians who have adequate knowledge and accreditation in human genetics. [p.59]

3.62 In addition, we would like to see a broader Government effort to educate consumers about genetic testing and, in particular, **predictive** genetic testing. Such a campaign will be of wider value to ensure that any marketing or publicity around commercial genetic testing services, that is those that are available via referral by GPs or other health professionals, does not impose undue burdens on NHS resources. We look forward to seeing the proposed national strategy on patient information that is being developed by the Department of Health. We also suggest that advice and guidance material on direct genetic testing services is made available on established UK Internet sites, such as NHS Direct and the HGC website. [p.60]