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Federation of European
Academies of Medicine

Direct-to-consumer genetic testing for health-related purposes in the European Union



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building science into EU policy

EASAC

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European Academies



Science Advisory Council



FEAM

Federation of European
Academies of Medicine

Direct-to-consumer genetic testing for health-related purposes in the European Union: the view from EASAC and FEAM

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Foreword

Until recently, human genetic testing was mainly confined to specialist medical genetic services, traditionally focusing on the relatively rare inherited disorders. However, the rapid pace of advance in DNA analysis has led to increasing interest in the development of genetic tests for determining susceptibility to the more common, complex disorders. Such tests are increasingly being offered by companies through the internet.

These consumer genetic services raise scientific, regulatory and ethical questions. Various concerns have been expressed about the quality and validity of the direct-to-consumer genetic testing offered, the clinical usefulness of the information supplied and the implications for the consumer, their family and the public health services. These issues affect all of us and are of sufficient importance and relevance to warrant attention by all the national academies in the European Union (EU). Our Report represents the first joint project between the academies of science in EASAC (the European Academies Science Advisory Council) and of medicine in FEAM (the Federation of European Academies of Medicine); we decided to collaborate on this occasion and in this way to draw upon the widest possible expertise in the scientific disciplines and experience in the Member States.

The Report has been prepared by consultation with a Working Group of academy-nominated experts, acting in an independent capacity, during the period May 2011 – May 2012. The topic is controversial but the project was very productive in identifying and addressing vital issues across a broad front relating to regulation, support for research and innovation, professional skills development and public engagement. Our report is timely in our collective objective of clarifying the evidence base to inform policy development in the EU: the reform of the Directive on In Vitro Diagnostic

Sir Brian Heap,
President of EASAC

Medical Devices is underway; there is commitment within both the scientific and policy communities to build an increasingly supportive environment for clinical research and development; and the research and innovation priorities for Horizon 2020 are being actively debated.

We address our recommendations to policy-makers at the EU level – in the European Commission, European Parliament and Council of Ministers – but also in the Member States where complementary action is necessary. Furthermore, we are sure that the issues are of interest worldwide; EASAC and FEAM will continue to stimulate discussion through other academy networks.

We thank Volker ter Meulen, the Chairman, and all the participants in the Working Group, for their considerable commitment, collegiality and hard work in delivering authoritative project conclusions based on extensive analysis and reflection. We also thank the independent reviewers of the Report, the Academy members of FEAM and EASAC for their advice and support, and the EASAC Biosciences Steering Panel for their guidance. In addition, we are grateful to the InterAcademy Panel for their support in funding this project. We should also like to take this opportunity to emphasise that the project had an additional objective: to build competence for joint work between EASAC and FEAM. In our view, this objective has been successfully and efficiently accomplished and we look forward to further collaboration on topics of mutual interest.

We believe that our joint Report will help to stimulate further debate as well as inform development of the strategic options for attaining the good balance between use of responsible testing and protection against unsound testing. We welcome discussion on any of the points we have raised.

Professor Jesus A.F. Tresguerres,
President of FEAM

Summary

Advances in genomics are leading to the discovery of new genes that cause disease or increase its risk. Traditionally, genetic testing was confined to specialist medical genetic services, focused on relatively rare, inherited diseases.

The common, complex disorders are usually the result of variation in many genes, each contributing a small amount of genetic susceptibility, acting in concert with environmental or other non-genetic factors. The interpretation of such information is complicated but private companies now offer genetic testing 'predictive' services through the internet directly to consumers (direct-to-consumer genetic testing, DTC GT).

Companies have claimed various putative advantages for their services in allowing increased personal choice and control. However, there are concerns about the accuracy and usefulness of such tests and their interpretation for providing health-related information, in the absence of individualised medical supervision and genetic counselling. DTC GT may create unrealistic expectations because of overstated claims, may induce confusion and anxiety, may harm privacy, and there may be implications for the established health services if inducing unnecessary follow-up assessment.

These issues were examined in a project initiated by the European Academies Science Advisory Council (EASAC) and the Federation of European Academies of Medicine (FEAM), with support from the InterAcademy Panel (IAP), which aimed to review the scientific evidence already available, to assess the regulatory developments underway and to ascertain the principles that should underpin the options for action by public policy-makers. In developing our recommendations in this report, we have attempted to avoid the over-regulation that impedes innovation while not wishing to relinquish strategy-setting to the private sector. Our conclusions are directed primarily to policy-makers at the EU level but we recognise that Member States may also wish to implement their own initiatives as part of the wider management of the opportunities and challenges for health services and consistent with their established national priorities for regulation.

We note first that there is controversy about whether using a nucleic-acid-based test is fundamentally different to using other types of biomarker as the predictor of risk, and whether concerns expressed about genetic testing are primarily related to the use of nucleic acids as the analyte or to the more general use of predictive risk information. In our view, efforts to devise recommendations relating specifically to genetic testing should be regarded as part of longer-term efforts to address all medical testing.

The scientific literature on potential benefits and harms of DTC GT is still rather limited and, because it is drawn from consumers who can be regarded as 'early adopters', it may not be entirely relevant to the broader population. Our first conclusion relates to the imperative to collect more evidence for the impact of testing on health outcomes and to share good practice in understanding, handling and communicating information about risk.

Varying views have been expressed by scientists, professional societies and others about what and how to regulate with regard to DTC GT. Procedural options encompass national legislation, adoption of international guidelines and standards, accreditation of tests, laboratories and companies, and voluntary codes of practice based on greater transparency of information provision. In the EU, the regulatory environment for novel tests is governed by Directive 98/79/EC on In Vitro Diagnostic Medical Devices, which is currently being revised. Several Member States have more stringent legislation on DTC GT services.

What are the particular concerns about the scope of DTC GT?

Based on our Working Group discussion, it seems to EASAC–FEAM that all kinds of genetic testing require an appropriate and relevant level of professional advice. On the whole, DTC GT has little clinical value at present and, on occasion, has potential to be harmful. We would not wish to encourage EU citizens to use DTC GT at present. We suggest especial caution about DTC GT in several specific respects, as follows.

- (1) Individuals should not seek DTC GT services if they have symptoms or are at known increased risk.
- (2) Testing for monogenic, high-penetrance, serious disorders should be presently excluded from the services offered by DTC GT companies.
- (3) Prenatal screening and carrier testing in children should also be excluded.
- (4) Nutrigenomic testing should be discouraged because of its association with the sale of nutrient products of little or no proven value.
- (5) Pharmacogenetic testing for prediction of drug response requires further discussion, but should not be offered unless necessary safeguards are in place.
- (6) Testing of samples from minors and third parties should not be permitted.

Principles for the management of DTC GT

Taking into account the particular exclusions and cautions listed above and acknowledging that the boundaries between categories of test may be imprecise, the broader governance of DTC GT should create the strategic coherence that tackles the concerns expressed about the validity and completeness of information supplied before testing, consent, test data management, and access to advice and counselling. Key points to note in developing the general principles for governance include the following.

- Susceptibility testing for complex disorders should be regulated on the basis that claims about the link between genetic marker and disease are scientifically valid.
- Test quality assurance must cover not only laboratory analytical quality but also the professional interpretation of results and the provision of counselling that is appropriate to the disease risk and burden.
- Information supplied by the DTC GT company should be controlled by the enforcement of advertising standards (truth in labelling), and must emphasise who is advised not to use DTC GT services.
- Implications for the established health services and others need to be assessed, for example in terms of the potential waste of scarce resources in unnecessary follow-up to test results.
- Companies should include proper, additional, consent-seeking (specifying the handling of samples and information) when desiring to use data for research.

Informing policy development

These principles have consequences: for EU policy-makers, for informed consideration of the regulatory alternatives; for the research community in developing an accessible evidence base; and for health professionals in translating research into practice. There will need to be flexibility to enable future innovation, and among the major implications are the following.

- Directive 98/79/EC. The scope of the Directive on In Vitro Diagnostic Medical Devices should be clarified to ensure that it covers all genetic information that is used to make medical claims. The European Commission will need to explore the options for introducing independent review of the claims made for a test, based on some form of risk stratification but independent of the nature of the analyte. The evidence base for all information provided must be accessible and verifiable.

- Other EU legislation. The wider implications for the reform of the other Directives on Medical Devices (for example, if a clinical efficacy requirement were to be introduced) and the Data Protection Directive (ascertaining its scope to cover genetic information accessed by a consumer within the EU) need to be addressed.
- Professional and technical competences. Whatever can be achieved by reform of the In Vitro Diagnostic Medical Devices Directive to require demonstration of scientific validity of claims will need to be accompanied by appropriate mechanisms for ensuring professional and clinical good governance according to standard procedures.
- Industry code of practice. While awaiting public policy development, it would be highly desirable for DTC GT companies to work together to develop and implement industry-wide quality standards, including those relating to the labelling of advertising claims and additional consent-taking for research purposes.
- Public databases of information. There is great potential value for an international registry of information on the availability, validity and usefulness of genetic tests so that physicians and consumers can judge for themselves whether to avail themselves of a particular test or service. The European Commission with its international partners should consider what is needed to collect and validate the evidence on gene-disease associations – establishing the relative roles of research funders, academia and industry – particularly in generating data on lower-penetrance genes.
- Professional education. It is vital for Europe to do better in educating medical and other health professionals about genetics, for example to improve the confidence of primary care physicians to interpret and explain risk and benefit based on genetic information.
- Public engagement. It is also critically important to address common public misconceptions about what genetic tests can offer in terms of medically relevant information so as to inform and empower the consumer to decide for themselves when faced with offers of DTC GT.
- Whole-genome sequencing. Very soon, it will be easier and cheaper to sequence an entire genome than to genotype a series of known mutations. Such sequencing and analysis currently represents a very small proportion of the DTC genomics market but it can be expected to grow rapidly. The challenges of consenting, communicating and acting on data will be accentuated by whole-genome sequencing, which has considerable potential to reveal incidental information that was not anticipated or requested

by the consumer. Regulatory authorities and other policy-makers need to prepare for the translation of the technology from the research setting to routine testing.

- Global implications. EU reform of Medical Devices legislation must be well integrated with global harmonisation efforts and this requires further work to develop shared understanding of diagnostic/predictive test clinical performance. The situation is complicated by differences in the relevance of genetic information for different populations. There are major implications for a global DTC GT industry such that there must be a global priority to build global databases containing the clinical information on DNA variants of specific genes.

In conclusion, although some of these issues are controversial, there are opportunities to improve the regulatory and innovation framework for genetic testing in the EU, which is a collective responsibility for the European Commission, European Parliament and Council of Ministers. However, legislative reform will take time and can only be successful if there is also action to improve clinical governance and professional and public education, to facilitate translation of the available evidence base into practice and to support research to collect new evidence and to ensure the widespread availability of accurate information. Action in the short term will be particularly valuable if it helps to build international standards and validated repositories of test information, and clarifies options for mandating good practice by, and accreditation of, DTC GT companies.

1 Introduction

1.1 The changing landscape of genetic testing

Since the completion of the Human Genome Project a decade ago, many genes have been identified that cause disease or increase its risk. These discoveries have led to the development of molecular diagnostic tests of considerable importance in the prevention or early management of disease, for example of hereditary breast cancer. Advances in genetic sequencing and related technologies have meant that DNA analysis has become progressively cheaper and faster (National Human Genomes Research Institute, 2011), promising an increasing pace of discovery, but clinical information on the phenotypic consequences is always slower to acquire.

Initial expectations of the outcomes from the Human Genome Project were high in assuming that predispositional genetic tests – that is tests for susceptibility for common, complex disorders – would rapidly become available (Collins and McKusick, 2001). However, whereas genetic testing for the highly penetrant mutations in the genome that lead to well-defined Mendelian disorders is now established in public health services, the anticipated contribution of genomic science in susceptibility testing for the common, complex disorders has not yet occurred to a significant degree (Borry et al., 2010), although services are being developed for some monogenic subtypes of complex disorders (for example in cardiology, oncology and diabetes). The common, complex disorders are usually the result of variation in many genes for each disease, each contributing a small amount of genetic susceptibility, that act in concert with environmental or other non-genetic factors. In complex disorders, the predictive importance of individual elements (genetic or environmental) will vary for different individuals and predictability may differ for different population (ethnic) groups.

Although the interpretation of such information in understanding multi-factorial disorders is complicated, private companies, mainly residing outside the European Union (EU), are taking a lead and offering a wide range of genetic testing (GT) including susceptibility tests and profiling through the internet, directly to consumers (direct-to-consumer, DTC).

The rise of DTC GT exemplifies some of the wider changes affecting healthcare and public health: growth of a globalised industry; less public deference to traditional, physician-led, professional forms of authority; familiarity with the internet; an increasing desire by the individual to have information; and various pressures to exercise personal choice and responsibility, the latter being among the objectives of the European Commission's current health strategy (European Commission, 2007).

The proponents for DTC GT view its development as part of the increasing tendency to individualised healthcare and online medicine, trends that also include body imaging, pharmaceutical purchase through the internet and new ways to access and share health information (Nuffield Council on Bioethics, 2010). Many view these developments as of questionable value: they may allow an individual increased choice and control, but they also may create unrealistic expectations by making overstated claims, may induce anxiety, confusion and harm privacy, and may have implications for the established public health services, as discussed in the following chapters.

1.2 The role of our report

The starting point for the present work was the output from a project co-organised by academies in Germany (Leopoldina, acatech and Berlin-Brandenburg Academy of Arts and Sciences, 2010) on 'Predictive Genetic Diagnostics as an Instrument of Disease Prevention'. The report from that project provides a comprehensive description of the technological advances underpinning the development of genetic diagnostics; this detailed characterisation will not be repeated in our report. The German academies' publication takes a critical view of DTC GT, which is prohibited in Germany according to the national Genetic Diagnostics Act that confines the responsibility of diagnosis to physicians and, in some instances, to specialist clinical geneticists.

The issues relating to DTC GT are sufficiently important for all of the EU to warrant attention by other Member State academies. Furthermore, many of the issues raised for DTC GT are also relevant more generally for genetic testing in other settings. Currently there is wide variation among Member States in their provision and regulation of genetic services. In consequence, the academies of science in EASAC (the European Academies Science Advisory Council) and of medicine in FEAM (the Federation of European Academies of Medicine) agreed to organise a joint project, taking account of developments across the EU and elsewhere. The academies judged that it was important to extend analysis and discussion beyond the professional genetics community, to clarify and communicate information about the opportunities, scientific uncertainties and societal implications of DTC GT. Our shared goal is to provide the evidence to inform policy development at the EU level; aiming to achieve a good balance between the increased use of responsible testing and protection against unsound testing. Market development is often faster than the ability of the legislator to regulate and, therefore, it is important to consider the additional ways whereby the quality of testing can be assured.

Before discussing genetic testing in detail and the implications for policy development, it is important to emphasise three points that are central to avoiding confusion in interpretation of trends and to resolving controversy.

- (1) The current distinction between high-penetrance genotypes, with high predictive value in testing, the traditional responsibility of health service clinical geneticists, and low-risk alleles contributing to the etiology in the common, complex disorders. For the latter, apart from a small monogenic fraction, only 'genetic susceptibility testing' is currently possible given the usual joint causation by multiple genetic and non-genetic factors. In the future, it is very likely that the genetic understanding of complex diseases will improve in consequence of the use of high-throughput methods and broader developments relating to the use of biomarkers in health (Organisation for Economic Co-operation and Development (OECD), 2011).
- (2) Whether using a nucleic-acid-based test is different in principle from using other types of biomarker as the risk predictor.
- (3) Whether concerns expressed about genetic testing are primarily related to the use of predictive risk information or to the use of nucleic acids as the analyte.

1.3 EASAC–FEAM objectives

This is the first collaboration between the academies' networks, EASAC and FEAM, instigated because of the need to draw on science across a broad range of disciplines. The project was part-funded by the InterAcademy Panel (IAP) with a particular remit to strengthen academy policy advisory capacities throughout

the EU. Our report draws on the expertise of a Working Group (Appendix 1).

The initial objectives of the project were the following.

- Discuss the current situation and expected developments regarding DTC GT in the EU.
- Consider the implications of advances in science and technology for consumer access to genetic testing.
- Review regulatory agency objectives, clarify the principles that need to be taken into account in regulating DTC GT and inform revision of the current Directive on In Vitro Diagnostic Medical Devices.
- Identify recommendations for policy-makers in the EU primarily in the Commission and Parliament, relating to the support of innovation as well as to the management of service provision, taking account of work already accomplished by other bodies and of the growing scientific literature.
- Advise on issues and mechanisms for communicating about DTC GT to the public.

We recognise that much has already been written on these subjects and we cross-refer to the scientific literature where appropriate rather than attempting another detailed analysis of all the issues. Our primary focus is to clarify what is needed in public policy – principles and their reduction to practice – for the development of DTC GT for health-related purposes¹. Our messages are directed to policy-makers, medical professionals and the public. We concentrate on relating principles to policy options at the EU level, but we recognise that Member States may also wish to take additional actions consistent with their previous national strategies for regulation.

¹ We exclude from our remit, for example, services for ancestry tracing, paternity testing and testing for personal traits (phenotype within the normal range, for example for height).

2 Issues for developing and managing DTC GT: what is already known?

2.1 Challenges for public provision of genetic testing

In many EU Member States, clinical genetics is highly developed and an integral part of health systems. The traditional focus of these genetics services has been chromosome abnormalities and rare inherited disorders, not the common complex disorders, although they now conventionally include also the high-penetrance subsets of common disorders such as cancer or heart disease. This situation is expected to change further once high-throughput sequencing methods have been applied to large patient samples with complex disorders. The tests currently provided by clinical genetics services and public health programmes are of proven efficacy for making the diagnosis of an inherited or heritable disorder, for analysing the risk of certain medical conditions and help to inform new possibilities for prevention or intervention to reduce disease severity. These tests can be broadly categorised as follows:

- (1) Diagnostic, when a particular condition is suspected clinically and a definitive diagnosis is needed.
- (2) Presymptomatic, when the patient is asymptomatic but known to be at personal risk for a dominant, late-onset disease.
- (3) Carrier testing, for reproductive counselling linked to recessive disease.
- (4) Prenatal and preimplantation genetic diagnosis in a foetus or embryo.
- (5) Susceptibility testing, for genetic predisposition to common diseases of multifactorial causation.
- (6) Pharmacogenetic testing, for prediction of drug response.
- (7) As part of a genetic screening programme targeted at a population group (for example, the newborn, pregnant women or a specific ethnic group).

Further information on definitions taken from previous work by Working Group members (and others) is provided in Box 1.

There is both public and private provision of testing services in many Member States but both these forms of provision, mediated through a health professional, can

Box 1 Terminology and definitions

- An assay is a method for determining the presence or quantity of a component whereas a test is a procedure that makes use of an assay for a particular purpose. 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. Each test is likely to need evaluation in its specific context, depending on disease, purpose and population².
- ‘Genetic testing’ in medical applications is a term used in different settings with different meanings (Pinto-Basto et al., 2010; Sequeiros, 2010) and there is a considerable range of definitions of genetic testing used in various national and international recommendations (Sequeiros et al., 2012; Varga et al., 2012). The European Commission has a long-standing interest in developing a consensus on an operational definition (European Commission, 2004).
- In clarifying the terminology for tests offered by the traditional clinical genetics services, it is crucial both (1) to differentiate between testing undertaken to confirm or exclude a medical diagnosis (diagnostic testing) and testing in healthy persons (screening) and (2) to appreciate that genetic information can sometimes be inferred by medical procedures that do not directly use DNA laboratory-based tests (Sequeiros, 2010; Sequeiros et al., 2012; see also Chapter 4).
- Genetic test validity also has different dimensions (Burke and Zimmern, 2007): analytical validity relates to the ability to measure accurately and reliably the component (analyte) of interest; clinical validity relates to the power to detect or predict the presence or absence of clinical disease or its predisposition; clinical utility relates to the likelihood that information from the test will lead to an improved outcome for the subject.
- There is also increasing interest by health services in pharmacogenetic tests – assessing variation in drug metabolising capacity or in target sensitivity – that introduce the possibility of

Box 1 (Continues)

² Zimmern, R, ‘The evaluation of genetic tests and direct consumer access to genetic testing’, FEAM meeting, Rome, May 2011.

Box 1 (Continued)

identifying and explaining individual variation in efficacy and safety responses to pharmaceuticals. Use of such tests could both help to select better novel pharmaceutical products during their research phase and help to target current treatments more effectively (Academy of Medical Sciences, 2007; Vijverberg et al., 2010).

- Tests that are both marketed and sold directly to the public, including over the internet, without the supervision of a healthcare professional, are classed as direct-to-consumer (DTC) tests.

be distinguished from DTC GT (Box 1). In some Member States, it is possible for the individual to ask the medical genetic laboratory for a genetic test at the individual's own expense, independent of a medical indication. Our report does not address the issues for this private laboratory testing, subject to standard professional guidance, but focuses on the distinction between DTC GT and other genetic testing.

Although Member States vary substantially in the types of testing programme offered, most are experiencing increasing pressure to expand programmes even when evidence of clinical validity and utility does not yet adequately support the integration of new discoveries from genetics and genomics into routine clinical practice (Andermann et al., 2011). Evidence obtained from large Genome Wide Association Studies (GWAS, for example the pioneering Wellcome Trust Case Control Consortium, 2007)³ identifies many genetic variants associated with major complex diseases and traits. However, the size of the genetic effect is usually small and, even if replicable, it is extremely unlikely that such information, used on its own, can be of value in the clinical setting as a predictor of individual risk in a given population. It remains to be seen whether when many such variants are combined with non-genetic data in a risk prediction algorithm, the resulting predictor has any clinical value.

Decision-makers in the health sector need to understand that there is often scope to do better in developing and using the evidence base to inform genetic diagnostic and screening services according to transparent, consensus criteria (Andermann et al., 2011). The present level of development of clinical genetics, genetic counselling and genetic services in general varies substantially between the Member States. One example of a public health approach in developing criteria for influencing

the commissioning decisions for clinical genetic tests is provided by Kroese and co-workers (2010). The challenges for organising public health services are discussed further in Chapter 4, against the background of the current status of the laws governing genetic testing in Member States, discussed in section 3.1.

2.2 The advent of DTC GT

Since 2007, many companies, mainly outside the EU, have been advertising and selling genetic tests directly to consumers (see Borry et al., 2010). In 2008, the retail DNA test kit was named invention of the year by Time magazine. The commercial tests are often offered in the form of multiplex genetic profiles, based on variation in many different DNA sequences (mainly single nucleotide polymorphisms, SNPs) at specific points in the genome. The types of test currently offered are varied in their claims (Janssens and van Duijn, 2010; Ducourneau et al., 2011), including monogenic disorders (Mendelian disorders), pharmacogenetic targets and susceptibility for common multifactorial diseases (such as cardiovascular disorders, depression, type 2 diabetes and osteoporosis), as well as putative tests for health enhancement (such as nutrigenomics).

The range of services offered by companies is detailed in the analysis compiled by The Genetics and Public Policy Center at Johns Hopkins University, USA⁴, although there are probably more companies commercially active. The size of the current DTC GT market is unclear (Wright and Gregory-Jones, 2010), as is its geographical distribution and, indeed, the sustainability of the original DTC business model. Some of the DTC GT offered previously is no longer available (Borry et al., 2010), although it is not clear if withdrawal from the market denotes problems associated with scientific or financial issues or difficulties in the protection of Intellectual Property Rights⁵.

DTC GT companies may be developing new business models in response to concerns expressed about the credibility and privacy of the information that they collect and compile. There is evidence of a preference for consumers to involve health professionals in test procedures (Borry et al., 2010). In consequence, some companies are concentrating on DTC advertising, rather than DTC sales, and involve healthcare professionals to order the test for the patient and interpret the results (see footnote 4); in these cases the 'DTC' designation is beginning to acquire new meanings, becoming direct-to-physician rather than direct-to-consumer. However, plans

³ The US National Institutes of Health website provides updated information on the GWAS evidence base: <http://gwas.nih.gov/15listserv.html>.

⁴ http://www.dnapolicy.org/news.release.php?action=detail&pressrelease_id=145, August 2011. There are 20 DTC companies listed (of which 8 offer genetic counselling) and another 7 that market DTC but require the test to be ordered by a physician.

⁵ A potential negative impact of DNA patents on diagnostic innovation has implications both for the public and private sectors in genetic testing (Human Genetics Commission, 2011).

Table 2.1 Potential advantages and disadvantages of unrestricted DTC GT for health-related purposes⁶

Modified from Working Group discussion and Nuffield Council on Bioethics, 2010; Anon., 2011; McGuire and Burke, 2011; van El and Cornel, 2011.

Advantages	Disadvantages
<ul style="list-style-type: none"> Enables individual empowerment and a feeling of personal control to improve quality of life. 	<ul style="list-style-type: none"> Lack of preparation for results and their impact in the absence of individualised medical supervision and genetic counselling, if appropriate. Lack of transparency on quality control and validity of offered tests.
<ul style="list-style-type: none"> Permits rapid molecular diagnosis of disorders when public or other private healthcare resources not available. 	<ul style="list-style-type: none"> Financial cost to individual and exacerbation of social inequity. Further social cost if DTC GT undermines trust in medical science or consumes scarce public health services resource by a knock-on effect in stimulating unnecessary follow-up.
<ul style="list-style-type: none"> Delivers more information, allowing early intervention. 	<ul style="list-style-type: none"> Interpretation of information may be complicated and incidental, unanticipated, findings may be revealed. Information may have no utility or may induce anxiety or other psycho-social consequences, for example if no intervention is then possible. False reassurance may be imparted. 'Over-diagnosis' may lead to excess medical intervention.
<ul style="list-style-type: none"> Allegedly provides greater privacy for information supplied (at least with regard to insurers and employers). 	<ul style="list-style-type: none"> Privacy concerns arise relating to procedures for DTC GT company data storage and use (including consequences if company changes ownership).
<ul style="list-style-type: none"> Alerts relatives to important genetic conditions. 	<ul style="list-style-type: none"> Problematic if the relative does not wish to know. Harm to others, for example children, if tested without their consent.

to sell DTC GT through pharmacies in the USA have not yet come to fruition.

2.3 Controversial value of DTC GT

The perceived potential advantages and disadvantages of DTC GT are summarised in Table 1. These putative attributes will depend on the nature of the service offered and have been discussed in detail elsewhere in the published literature.

On the whole, there is little empirical evidence to support the advantages (or disadvantages) claimed.

It is worth noting that in some Member States there may be only very limited public genetic testing facilities available and little trust by citizens in these facilities, such that DTC GT might appear, to some, to fill a gap. Unfortunately, uncontrolled provision of DTC GT may risk exacerbating the situation to '*seriously undermine public trust in genetic testing for medical purposes*' (van El and Cornel, 2011). Private genetic services in general, including DTC GT in particular, may be more likely to emerge when public services are absent. For example,

in Greece, where public genetic services are sparse, there has been an increase in private genetic testing laboratories (Sagia et al., 2011), but the lack of a clear regulatory framework for these needs to be addressed in a consistent way. Furthermore, in Greece genetic tests can be sold over the counter in pharmacies (Sagia et al., 2011), even though the customer population would prefer referral from a physician rather than a pharmacist (Mai et al., 2011).

The value of DTC GT is controversial and there is a significant literature emerging on key issues. It has been suggested (for example by Frueh in Frueh et al., 2011; Caulfield, 2011) that the risk of providing genetic information to consumers is significantly less than had been anticipated. Furthermore, although the opinions of professional geneticists are, of course, of great relevance and significance, others are more wary of the potentially inhibiting effect of professional bodies on the wider implementation of innovation. From their (Brand and Brand, 2011) perspective, the advice that any genetic test should be requested and performed by a specialist '*... is more about keeping the shop closed than serving the public health*' and, in consequence of increasing public use of the internet '*... democratization of information*

⁶ While paternity testing is not usually considered to be a health-related test and, therefore, is beyond the scope of the present report, it should be noted that there is potential for psychological harm.

poses a threat to many health professionals by challenging their expertise. These issues are contentious and it is important to try to avoid excessive conjecture and polarised debate; rather, to use the evidence available to assess the claimed advantages and disadvantages. Some major criticisms and comments are presented in the following paragraphs, to supplement the points listed in Table 1.

Test information provided to the consumer will be based on average risk and does not necessarily apply to the individual (Hunter et al., 2008). However, this is a criticism that can be applied to any form of risk prediction derived from epidemiological studies. For example, predictors of heart disease using cholesterol, blood pressure and smoking history are in use across Europe as a standard intervention in primary care. Another critical appraisal of the scientific basis of commercial genetic testing judged that there was insufficient evidence to conclude that genomic profiles are useful in measuring genetic risks for common diseases or in developing personalised diet and lifestyle recommendations for disease prevention (Janssens et al., 2008).

Recent outputs from two studies, led by researchers at the universities of Leuven (Belgium) and Leiden (the Netherlands) (European Society of Human Genetics (ESHG), 2011), provide evidence that DTC GT gives a distorted impression of risk and summarise the views of many EU clinical geneticists, concerned that many consumers do not understand test results. Inherent in this critique is the assumption that physicians themselves have the expertise to interpret genetic tests. The ESHG in its policy statement on DTC GT (ESHG, 2010) emphasises that similar fundamental considerations must apply to DTC GT services as to any other test for which health claims are made. These include (1) proven clinical utility, supported by quality standards and qualified personnel; (2) medical supervision; (3) provision of appropriate information; (4) respect for privacy; (5) respect for minors; (6) respect for research ethics principles; and (vii) appropriate regulatory oversight.

One other issue for evaluating the quality of DTC GT services relates to sub-contracting. Some of the smaller companies sub-contract the analysis to other laboratories, with the selection of supplier influenced by price. There is lack of transparency relating to laboratory methodological procedures and their quality criteria and assurance.

2.4 Societal attitudes and expectations

At present, as noted in the preceding section, there are relatively few data on the effect of DTC GT on consumer attitudes and impact, for benefit or harm. Moreover, the current consumers can be regarded as 'early adopters', including scientists and journalists contributing anecdotal evidence (for example, Frank, 2011), whose expectations

and behaviour may not be the same as future consumers. Examples drawn from the available published evidence on public attitudes are provided in the following bullet points.

- As summarised in the report by the Nuffield Council on Bioethics (2010), survey evidence indicates that there is significant public interest in utilising genetic susceptibility testing technologies.
- For example, in an online survey of one thousand social network users (McGuire et al., 2009), who may well not be representative of the general public, 6% had already used, and 64% expressed an interest in using, DTC but would expect their physician to help interpret results. A similar conclusion can be drawn from a focus group-based study in Australia (Wilde et al., 2010): high initial interest was expressed in having a hypothetical genetic test for susceptibility to major depression but some participants lost interest after discussion of privacy issues and the remainder would only stay interested in testing if it involved a trusted medical professional.
- In a US comparison (Leighton et al., 2011), the general public interpreted results to be significantly more helpful than did genetic counsellors. In another small US study (Graves et al., 2011), women expressed interest in knowing about even modest risk (for breast cancer), which may emphasise the need for education about the benefits and risks of testing for mutations that convey modest changes in risk.
- There is some evidence to suggest that attitudes to DTC GT are more antagonistic in Europe than in the USA. For example, in Greece strong opposition has been recorded (Mai et al., 2011; Kricka et al., 2011), but there have been no comparable surveys of opinion across the EU.
- Research on the attitudes of the public has been augmented by limited collection of evidence on impact on consumers of DTC GT. For example, one study of staff in health and technology companies (Bloss et al., 2011) found no increase in generic measures of adverse outcomes such as anxiety, on short-term follow-up of DTC GT, although it has been noted that disease-specific distress should also be studied (Salz and Brewer, 2011). Equally, there was no significant beneficial impact – on fat intake or exercise – after testing.
- A survey of more than 1000 US customers of three major DTC GT companies in 2009–2010 (American Society of Human Genetics, 2010) found that these early adopters were generally satisfied with the services and the majority (88%) reported that their test results were easy to understand, although a significant number (38%) also felt

that the information received was too vague and a minority (4–7%) misinterpreted examples of model risk reports presented to them in the survey. Two-thirds of the participants felt that DTC GT should be available without government oversight, although consumer protection agencies should monitor claims for scientific accuracy. A relatively high proportion of participants (about one-third) discussed the test results with their own physician. The majority had undergone testing to improve their health (a motivation confirmed by other recent research on consumer expectations (Su et al., 2011)). As a result of testing, 34% said they were being more careful about their diet and 14% were exercising more (by contrast with the outcomes reported by Bloss et al., 2011). However, it would take many years to show improved health outcomes for tests intended to prevent or help treat chronic diseases (Anon., 2011).

- A study of genetic health professionals' experience (Brett et al., 2012), found that DTC GT is not a major reason for referral for follow-up with clinical genetics services in Australia and New Zealand, and that the majority of genetic health professionals lack confidence in being able to interpret and explain DTC GT results. This study also showed that clients typically undertook DTC GT to identify monogenic conditions, including carrier tests, as well as susceptibility or predisposition for complex conditions.

The current literature is rather mixed in its reported outcomes and, to an extent, conflates the issues for inherited disorder presymptomatic testing and common, complex disorder susceptibility testing. There is general agreement that more research will be needed to understand consumer expectations (Su et al., 2011) and responses in terms of both attitudes and behaviour, in both the short-term and long-term. Better evidence will also be conducive to public policy, to guide decision-making about DTC GT (McBride et al., 2010). Some such work is in progress in the EU, for example collaboration between the United Kingdom (UK) and the Netherlands to study the impact of access to DTC GT for psychiatric disorders⁷.

It is difficult to find information on the current volume of usage of DTC GT in EU Member States. There is potentially relevant information on the usage of the internet for accessing health information more generally. This evidence indicates that, although there are regional differences across the EU, use of the internet for health purposes is growing in all regions examined (Kummervold et al., 2008). Its use to access

Box 2 Communicating genetic risk information

There are some common challenges for communicating information derived from genetic testing: in particular, conveying the relative contribution by genetic and environmental factors to disease risk and taking account of individual variations in risk perception. There is a significant literature on the psychosocial effects of genetic testing by health services, both for presymptomatic individuals and for disease cohorts: with regard to how subjects understand their risk of disease after testing and after counselling, their emotional response to the information, the impact of the information on family dynamics and individual attitudes and behaviour, particularly risk-reducing behaviours (see, for example, Marteau, 2010).

However, most research so far has evaluated the effects of information related to rare genetic variants on behaviour. The limited research with common genetic variants suggests that information based on single gene variants with low risk probabilities has little impact on behaviour. The effect on behavioural outcomes when genetic risk is based on numerous genetic variants has been even less explored (McBride et al., 2010).

Analysing the broader literature on genetic testing, the Working Group deduced that lessons that can be learnt that are also relevant to DTC GT include the following:

- The difference between the use of relative risk and absolute risk is crucial in communicating risk information: it should be absolute risk that determines both management of the subject and policy development.
- A patient's estimate of risk is often different from what the clinician believes the patient has understood. This perception differs among patients, and genetic counselling may improve risk perception accuracy to an extent.
- Probabilities are interpreted differently in different contexts dependent, for example, on family history, environmental factors and stress.
- There is little evidence that information about genetic-test-based health risks will lead to changes in behaviour although there may be some effect on intentions to change behaviour.

health information appears to supplement rather than replace other health services and users reported feeling reassured twice as often as experiencing anxiety (Andreassen et al., 2007).

⁷ 'New project examines online psychiatric genetic tests', May 2010, on <http://www.genomicsnetwork.ac.uk/esrcgenomicsnetwork/news/title,23549,en.html>.

2.5 Communicating and understanding risk information

It is also important for the emerging literature on the impact of DTC GT to be considered in the broader context of what is already known about communicating genetic risk information in other settings (Box 2).

Although this ancillary information is valuable, it can be concluded that there is need to collect more evidence for the impact on health outcomes in both traditional clinical practice settings and after DTC GT (Botkin et al., 2010) and to share good practice on understanding, handling and communicating risk information, for example based on the lessons learned in public health programmes for hypercholesterolemia, cascade screening and newborn screening. There is some initial evidence, using Alzheimer's disease as a model for genetic risk disclosure (Robert et al., 2011), to suggest the potential to streamline the genetic counselling process without the likelihood of participant distress or misunderstanding. However, the challenges for genetic testing will increase in consequence of handling the much larger amounts of information that will be generated by whole-genome sequencing (see section 4.7).

2.6 A new research resource?

In addition to any potential value for the consumer (Table 1), it is conceivable that the data obtained from personal genomics testing can be used as a primary research discovery tool (Scudellari, 2010), perhaps also forming the basis for participant-driven research initiatives. Studies are beginning to be published of how DTC GT can generate data within a research framework, for example for investigating genetic associations with common physiological traits (Eriksson et al., 2010) and with Parkinson's disease (Do et al., 2011).

However, the DTC GT/consumer relationship risks circumventing the normal regulatory framework for research and there are contentious issues for obtaining consent specifically for the research application. Identifying the appropriate conditions for establishing informed consent for research participation in a market-driven setting must be informed by the lessons learnt and guidance developed from the conceptualisation and use of informed consent in different clinical and research settings (see, for example, Royal College of Physicians et al., 2011). Moreover, there may be a wider problem if inadequate consent for research in the DTC GT setting undermines public confidence in clinical research more generally: in this situation, rather than becoming a new research resource, DTC GT will weaken the research environment. It is vital, therefore, that the current concerns on research consent-taking are addressed. DTC GT companies also need to ensure that their research data are available to other researchers seeking to replicate conclusions, according to the customary scientific conventions.

In addition to research trials specifically instigated by DTC GT companies, various models⁸ indicate a potential for greater sharing of genomic and phenotypic data to address research questions, if concerns about consent and confidentiality and the handling of samples can be satisfied. Some suggest there is also potential (Tung et al., 2011) to combine genetic information from DTC GT with internet-based phenotyping as a research resource to assess the replicability of previously identified genetic associations, however many would be sceptical about the quality of self-reported phenotypic information. A framework of good practice needs to be developed within the DTC GT industry for the conduct of research according to conventional guidelines and the EU should discuss this requirement with other international policy-makers.

⁸ Various websites have been created to share DNA data, for example <http://DIYGenomics.org>, <http://genomera.com>, <http://personalgenomes.oeg>, or to provide more research-based information than is supplied by the DTC GT company, for example <http://snpedia.com>.

3 The emerging regulatory framework

The current management of genetic testing in all settings in the EU is subject to a complex mix of European-level normative frameworks (in particular the In Vitro Diagnostic Medical Devices Directive, 98/79/EC, which became operative in 2000), national laws and other influences including EU-level guidance and international standards, particularly those developed by the OECD (2007), the Council of Europe (2008, 2010) and professional societies like the European Society of Human Genetics (ESHG, 2010). In addition regulation is exerted at the level of resource provision, for example reimbursement by insurance company or other payers, and through mechanisms of clinical governance that regulate the interaction between doctor and patient. In considering the current framework and the opportunities for reform it is important to clarify the issues for distinguishing between (1) the regulation of individual tests as compared with the regulation of laboratories that provide them, and (2) the regulation of nucleic-acid-based tests as compared with predictive tests in general.

3.1 EU Member States

Probably the strictest current national legislation within the EU is in Germany where, as noted in Chapter 1, the Genetic Diagnostics Act regulates predictive and diagnostic genetic testing and requires physician involvement that precludes some DTC GT services. In revising the Bioethics Law (July 2011), France now also has legislation similar in effect to the German Genetic Diagnostics Act.

Other Member States, for example Belgium (Royal Decree 1987), Austria (the Gene Technology Act, 1995) and Portugal (Law 12/2005 on Health and Genetic Information), have also implemented general legislation on genetic testing, but in some cases this predates the emergence of DTC GT and it is not always clear in the material reviewed by the Working Group how such legislation will apply for what is essentially cross-border trade or whether DTC GT companies are currently complying with the statutory requirements. In the Netherlands, it has been observed that the Dutch Act on Population Screening offers inadequate protection against DTC GT (van Hellemond et al., 2011).

Various advisory bodies have helped to clarify the issues. Bioethics groups, for example in Portugal (National Council of Ethics for the Life Sciences, 2008), Austria (Austria Bioethics Commission, 2010), Italy (Comitato Nazionale per la Bioetica, 2010) and the UK (Nuffield Council on Bioethics, 2010), have provided opinions on DTC GT. An earlier report in the Netherlands discussing the broad range of new forms of screening (Health

Council of the Netherlands, 2008), predicted a growth in popularity of DTC GT and noted the current weakness in EU regulatory protection. A more active approach to quality control was recommended, possibly involving the creation of an independent institution to provide a 'quality mark' for validating providers, linked to standards of professional conduct. That is, the laboratory responsible for performing the assay should be working under an appropriate quality assurance scheme. Additional quality assurance issues are raised by the advent of whole-genome sequencing (section 4.7).

In the UK, the Human Genetics Commission, a government advisory body, launched its 'Common Framework of Principles for DTC Genetic Testing Services' (Human Genetic Commission, 2010, building on earlier work, Human Genetics Commission, 2007) with an intention not just to inform the UK but also to guide the development of other national codes of practice, to take account of different existing regulatory structures and sufficiently flexible to apply to internet-based services. This framework for voluntary regulation covers a broad range of issues for DTC GT (Box 3), embracing the basic elements of consent, data protection, truth in marketing, scientific rigour and balanced interpretation.

Box 3 Framework for the provision of genetic testing services directly to the consumer (Human Genetics Commission, 2010)

The Framework covers the following.

- Purpose and scope of testing
- Marketing and advertising tests
- Regulatory information
- Information for prospective consumers
- Counselling and support
- Obtaining consent
- Data protection
- Sample handling
- Laboratory processes
- Interpretation of test results
- Provision of results
- Continuing support for customer
- Handling complaints

An overarching goal for this Framework is to support the transparent provision of accurate, evidence-based, information so that a more confident consumer can make better-informed choices. Implementation of the Framework would require concomitant strengthening of regulatory mechanisms associated with laboratory accreditation and consumer trading standards. The Framework has not yet been implemented as a code of practice in the UK and, so, challenges for adherence by companies have yet to be tested.

3.2 EU-level policy development

The current regulatory environment of novel tests in the EU, governed by the European Commission's Directive 98/79/EC on In Vitro Diagnostic Medical Devices, requires a test provider only to show evidence of laboratory test performance, based on analytical validity, not on clinical validity or utility. Most diagnostic tests are classified as low risk and consequently exempt from independent pre-market review of the evidence. Moreover, this Directive has been interpreted to cover only genetic tests that have a medical purpose, so that some putative predictive, lifestyle or nutrigenomic tests might be interpreted as falling outside its present scope.

There have been many calls for the Directive to be revised (see, for example, Hogarth and Melzer, 2007). However, it must also be appreciated that there are other tools available to regulate those aspects of a DTC service that require regulation, for example to ensure that the laboratory providing the service undergoes appropriate quality assurance and quality control (such as within the Clinical Laboratory Improvement Amendments guidelines in the United States of America (USA) or that those interpreting the test are appropriately qualified with the necessary competences (Wright et al., 2011).

Consideration of the issues by other European policy bodies has identified possible options for reform by the European Commission (Box 4).

In June 2010 DG Sanco opened a public consultation on specific issues for reform of the Directive⁹, discussing (1) adoption of a new risk classification, (2) pre-market review of genetic tests, (3) revision of essential requirements, (4) clinical validity and clinical utility, (5) clarification of status of laboratory-developed tests and (6) special measures for DTC GT.

In a summary of the responses received to this consultation, published in February 2011¹⁰, most of the respondents (86% of 80) were found to agree that

Box 4 Genetic testing and DTC GT: other relevant policy developments at the European level

Council of Europe (2008)

An additional Protocol was prepared for the Convention on Human Rights and Biomedicine, concerning 'Genetic Testing for Health Purposes' (<http://conventions.coe.int/treaty/en/treatise/html/203.htm>). Although not specifying DTC GT, this Protocol stipulates that a genetic test for health purposes may only be performed under individualised medical supervision. Possible exceptions might be admitted if the genetic test does not have 'important implications' for health. Other key issues addressed in this Protocol cover quality of genetic services, consent, genetic counselling and clinical utility.

European Parliament: Science and Technology Options Assessment (STOA, 2008)

This advisory group published its report 'Direct to Consumer Genetic Testing' (http://www.europarl.europa.eu/stoa/publications/studies/stoa32and39_en.pdf) to identify the options for revising the In Vitro Diagnostic Medical Devices Directive. In particular, STOA focused on the options for creating a European system of control and accreditation of laboratories (consistent with OECD guidelines) and of creating and enforcing a code of practice (consistent with Human Genetics Commission guidelines), to ensure minimum quality standards and monitoring, and introduce the criterion of clinical validity. These objectives would probably require a new, independent, supervisory body in the EU.

additional restrictions for DTC GT should be created to ensure a better level of health protection. Among important features mentioned were appropriate medical intervention and counselling. Some respondents called for a ban on the direct sale of tests. Revision of the Directive is likely to have significant impact on the regulation of all genetic testing, not just DTC GT. One particular issue is how will laboratory-developed tests ('home-brew tests') be regulated? One possibility is that these tests could be exempted from pre-market review if the laboratory is accredited (a similar proposal is being made in the USA). In this eventuality, the European Commission could outsource accreditation, if appropriately harmonised to Member State Competent Authorities.

The response by the ESHG to the consultation (ESHG, 2010) reiterated points made by them previously

⁹ European Commission, Public consultation on Revision of Directive 98/79/EC, 29 June 2010, available on http://ec.europa.eu/consumers/sectors/medical-devices/documents/revision/index_en.htm.

¹⁰ European Commission, summary of responses to the public consultation, 25 February 2011, available on http://ec.europa.eu/consumers/sectors/medical-devices/files/recast_docs_2008/ivd_pc_outcome_en.pdf.

(see Chapter 2) and cited studies that have identified problems with the quality of information provided by DTC GT companies. The ESHG also discussed the challenges inherent in regulation (and the implications, for example for product labelling), because complex supply chains may be involved in providing genetic testing services. In the view of the ESHG, even if the laboratory-developed test is located outside the EU, because it is an integral part of the whole service, it can be judged as part of the medical device product and, therefore, subject to the Directive. As the ESHG observes, if DTC GT was excluded from the remit of the Directive, not only might this be a failure to protect public health, but it also provides a perverse incentive for companies to be based outside the EU, incompatible with the objectives of the European Commission's Life Science and Biotechnology Policy Strategy and the 2020 Strategy.

The Foundation for Genomics and Public Health takes a somewhat different perspective in their response to the consultation (PHG Foundation, 2010), although also emphasising the importance of finding a balance – in a targeted, appropriate and proportionate regulatory regime – between protection of consumers and facilitation of innovation, and advising that the Directive is relevant for those consumer tests that make medical claims. The PHG Foundation reiterates two fundamental points for the attention of public policy-makers, as follows.

- (1) The importance of avoiding unwarranted genetic exceptionalism, that is the Directive should focus on evidence-based risk assessment as the means by which test regulation is categorised into different levels, rather than singling out a particular analyte and the placing of genetic testing into a single category irrespective of the risk posed by each particular test.
- (2) The importance of recognising that, besides the Directive, there are additional instruments for regulating the provision of genetic testing services (including DTC GT), for example by insisting on each DTC company having a named professional who takes responsibility for the advice and the service provided to the consumer.

3.3 Other international developments

In the USA, the Food and Drug Administration (FDA), the Federal Trade Commission and the Centers for Disease Control and Prevention (FDA, 2006) issued guidance for consumers recommending scepticism about DTC GT. The American College of Medical Geneticists (ACMG, 2008)

advised that a test should only be ordered and interpreted by a knowledgeable health professional.

The US Secretary's Advisory Committee on Genetics, Health and Society (SACGHS, 2008) issued a consumer's alert and has discussed the issues for US consumer genomics in some detail¹¹. Also in 2008, the California Department of Public Health issued a 'cease and desist' letter to 13 genetic testing laboratories, following a similar action by the New York State Department of Health.

In 2010, the House of Representatives' Committee on Energy and Commerce initiated an investigation on DTC GT and reviewed a report from the Government Accountability Office (GAO, 2006). This report concluded that the information provided by DTC GT was medically unproven and ambiguous and found that contradictory results were obtained from different DTC GT companies. There were concerns expressed about inappropriate marketing of tests and other questionable practices in securing samples from third parties, in the provision of results and in their follow up. However, it was not clear from the GAO report or the Committee hearing if poor practice was found consistently throughout the DTC GT industry sector (Vorhaus, 2010); there may well be significant variations in company attitudes and performance, in light of the evolving business model (Chapter 2 and footnote 4).

In June 2010, the FDA announced its intention to ensure analytical and clinical accuracy by regulating DTC GT (laboratory-developed tests) as medical devices requiring pre-market review and approval. In March 2011, the FDA Molecular and Clinical Genetics advisory committee recommended that DTC GT should be subject to medical supervision, consistent with evidence received from the American Medical Association (AMA, 2011) calling for strong regulatory oversight. The advisory committee's recommendation was welcomed by many (Anon., 2011) although some deemed it paternalistic (Patch and Prainsack, 2011). In view of the continuing controversy, the FDA agreed to collect further input on the scientific issues but, in the meantime, has continued to warn companies that their commercial tests or services might require regulatory approval as medical devices. The FDA's expressed intention to regulate the consumer genetics industry has wider implications for the entire laboratory-developed tests sector (see preceding section) and may come to represent a significant change in the FDA's general approach to regulation of diagnostics.

In Australia, the National Health and Medical Research Council published a report (NHMRC, 2010) acknowledging many problems with DTC GT, but also

¹¹ http://oba.od.nih.gov/SACGHS/sacghs_focus_marketing.html.

the difficulty of preventing access to internet-marketed products. Control on DTC GT will be attempted as part of the wider revision of medical devices regulation. A recent statement from the Canadian College of Medical Geneticists (2012) recommends that requests for medically significant indications should only be accepted from a medical professional on behalf of the individual to be tested.

In Japan, guidelines on protection of individual genetic information were produced by the Ministry of Economy, Trade and Industry (2005). In 2006, companies established a Consortium for the Protection of Individual Genetic Information, encouraging compliance with the 2005 Ministry guidelines. Genetic testing is currently subject to the national guidelines, variously covering research, clinical practice and industrial activity, which are also informed by the OECD (2007) best practice guidelines and by national guidelines agreed by Japanese societies involved in human genetics and medical sciences¹². However, as there is no legal regulation, there is no formal control on the introduction of DTC GT and, indeed, the current framework is generally viewed as insufficient to assure quality of genetic tests in

any setting. From this perspective, the accentuation of concerns following the emergence of DTC GT is providing a stimulus to implement current quality standards for laboratory genetic tests more broadly, to ensure that companies disclose their standards, to build consensus on specific new standards and to establish a regulatory body alongside self-regulation (Watanabe et al., 2010).

In summary, regulatory options for the EU reviewed by the Working Group encompass national legislation, adoption of international standards and guidelines (including those pertaining generally to clinical governance), accreditation, reform of the In Vitro Diagnostic Medical Devices Directive, the provision by third parties of a transparent evidence base and creation of codes of practice. These options are not, of course, mutually exclusive. The choices for Regulatory Agency statutory action on DTC GT range from severe restriction, tantamount to banning, through to more flexible control measures that can be augmented by other measures including the enforcement of consumer protection laws. Some possible workable and robust options that in the view of the Working Group have the flexibility to cope with future developments in science and technology are described in Chapter 4.

¹² Guidelines for Genetic Testing, http://jshg.jp/resources/data/10academies_e.pdf.

4 Principles, practicalities and potential for devising proportionate and flexible regulation

4.1 Defining the scope: what might be included in DTC GT?

Our report focuses on genetic testing that provides health-related information (see Chapter 1), which the Working Group defined as ‘any type of information directly or indirectly linked to the health status of a person, either diseased or healthy, that relates to processed clinical data’. Policy-makers must recognise that it would be inconsistent to introduce regulation of DNA-based testing, if other tests that yield information on inherited disorders are not regulated equivalently: the individual and societal consequences accrue from the diagnosis, not the modality used for diagnosis or the particular analyte. Genetic information can be inferred from other medical tests involving, for example, physical examination, imaging or the measurement of protein: in these cases the DNA sequence is probabilistically inferred from the phenotype assay. However, it has also to be acknowledged that (1) advances in DNA-based testing are proceeding particularly rapidly and these advances challenge traditional concepts in health services policy, and (2) some genetic information has attributes unlike most other information in some situations (most importantly in the context of inherited or heritable disorders) – it may have consequences for relatives and because a genetic test need only be performed once in a lifetime it must be of particularly high quality.

The Working Group assessed that, on the whole, at present DTC GT has little clinical value and may, on occasion, be harmful (Table 1). Drawing on the Working Group’s analysis, EASAC–FEAM would not wish to encourage EU citizens to use DTC GT at present. In particular, we suggest that individuals should not seek DTC GT services if they have symptoms or are at known increased risk. Based on the discussion of the Working Group, it seems to EASAC–FEAM that all kinds of genetic testing require an appropriate and relevant level of professional advice. However, within the broad portfolio of DTC GT, we suggest especial caution in several specific respects, as described in the following sections.

4.1.1 *Monogenic disorders merit particular caution*

In assessing the implications for considering how to regulate DTC GT, it is helpful to clarify the issues for distinguishing between testing for monogenic disorders (and other high-penetrance genotypes) in the individual

tested and testing for susceptibility genotypes that play a role in common complex disorders, where the contribution made by genetics may be significantly influenced by environmental determinants and each contributor (whether genetic or environmental) will most often have a small impact. It is important not to conflate discussion of the provision and regulation of tests in the two categories, although the boundary between them may sometimes be imprecise, artificial and controversial, and there is a continuum of variability in genetic and environmental influences. For example, there are an increasing number of examples where monogenic sub-entities exist within the spectrum of complex disorders (such as low-density lipoprotein (LDL) receptor defects leading to hypercholesterolemia; maturity-onset diabetes of the young (MODY) as part of diabetes; mutations to *BRCA1/2* genes as part of breast/ovary cancer within an otherwise polygenic background).

Based on the Working Group’s deliberations, recognising that the topic is controversial and that the state of knowledge is advancing rapidly, EASAC–FEAM recommend that testing individuals for high-penetrance genotypes associated with serious diseases, including monogenic disorders, should be currently excluded from the services offered by DTC GT companies. In practice, because of the difficulty that may be experienced in defining the boundary between high- and low-penetrance genotypes, it is recommended that DTC GT services are discouraged from including those tests that health services currently use for investigating serious (including monogenic) disorders. The reason for proposing to exclude these monogenic conditions from DTC GT services is not lack of clinical validation – they may usually be well-characterised tests – but rather their greater need for individualised medical supervision and genetic counselling (before and after the test). Where there is uncertainty about the serious nature of a specific disease tested for, this should be detailed by the DTC GT company to the consumer.

4.1.2 *Excluding prenatal testing*

Prenatal screening is a newly expanding area that in the view of EASAC–FEAM should only be offered in the context of clinical obstetric and genetic services and should not be allowed within DTC GT. Research advances have opened up new options for prenatal screening and diagnosis by analysing free foetal DNA and RNA, from transplacental passage, in maternal blood samples¹³.

¹³ General issues for implementing these research advances are discussed in the Sixth Framework Programme Network of Excellence SAFE, ‘Special non-invasive advances in foetal and neonatal evaluation network’ (details available on http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_RCN=7922154 and in Chitty et al., 2008).

Although there are increasing opportunities to broaden the scope of what might be tested in prenatal screening, there are some contentious societal issues relating to relevance of tests, access and equity, and implications for reproductive choice (de Jong et al., 2011). Because of significant potential consequences for the mother and foetus, such testing requires the highest quality information, appropriate genetic counselling and closest medical supervision.

4.1.3 Concerns on preconception carrier screening

Although carrier status might not customarily be considered to fall within a serious category that precludes DTC GT, information obtained may have implications for testing the partner in a couple and other relatives (cascade family-based screening). In addition, the term carrier (heterozygote) of a mutation is often misunderstood by the lay person as 'carrier of a disease'; experience shows that without appropriate genetic counselling the individual may not understand their own risk of disease, or their children's and may not understand the need for testing their partner and other family members. It would be difficult for DTC GT services to meet the requirements for pre- and post-test information and counselling that should be part of preconception carrier testing (Borry et al., 2011). The individual should be advised to use the established genetic medical services rather than DTC services and such guidance should be part of the information provided by a DTC GT company to a prospective customer. Thus, carrier testing is preferably conducted in the public sector, but if the range of carrier tests available there is insufficient, then any DTC GT services should follow guidance on information to users and quality control that apply to healthcare services in general. Carrier testing in children should not be included in DTC GT services.

4.1.4 What else should be discouraged?

As discussed in Chapter 2, the DTC GT business model may evolve; one possibility is that an increasing proportion of companies will offer some level of counselling provided by those who may or may not be genetic specialists, will require physician involvement in ordering tests or will form other alliances with conventional medical services. However, until these developments become clearer, EASAC–FEAM advise there are several contentious areas that should be excluded from the scope of services routinely and unreservedly offered by DTC GT companies:

Nutrigenomics. Some of the concerns associated with DTC GT clinical validity and utility are accentuated in nutrigenomic testing (see, for example, Ries and Castle, 2008). Such tests should be considered as falling within

the category of providing health information, but are often poorly validated and, indeed, may be meaningless and misleading (Sterling, 2008). One particular concern that distinguishes nutrigenomic testing is the associated sale of nutrient products to tackle claimed deficiencies, of little or no proven value but high cost. Unless extensive additional validation of the test and its associated nutritional intervention can be documented, a nutrigenomic test should not be offered as part of DTC GT.

Pharmacogenetics. In 2008 the European Commission estimated¹⁴ that adverse drug reactions kill nearly 200,000 EU citizens annually, at a total cost to society of about 80 billion euros. It has frequently been postulated that pharmacogenetic testing to measure individual variability in drug metabolism would help to develop safer medicines and ensure greater safety in clinical practice. For example, many anti-depressants are metabolised by cyp450 enzymes; there has been much clinical interest in genotyping cyp450 genes as a measure to guide more precise anti-depressant dosing and, although there has been controversy about whether testing for cytochrome P450 (CYP 450) polymorphisms is useful in medical, personal or public health decision making (Agency for Healthcare Research and Quality, 2007), various companies are offering such testing services. The ethical and social issues associated with pharmacogenetic testing, and the current status of implementation in clinical practice, has been discussed in detail in the literature (for example, Vijverberg et al., 2010), and problems have been identified for the inclusion in DTC GT services. For example, there would be significant concern about the DTC provision of pharmacogenetic testing if it encouraged patients to adjust their dose of prescribed medicine without seeking medical supervision (Katsanis et al., 2008). The case can be made that pharmacogenetic tests should not be available through DTC GT (Hogarth in Frueh et al., 2011), unless necessary safeguards are in place.

4.2 Identifying principles for the management of DTC GT

Taking into account the particular exclusions and cautions listed above, the broader governance of DTC GT should be subject to certain general principles, tackling concerns expressed about the validity of information supplied before testing, consent, test data management, and access to advice and counselling. Key points to note include the following.

- (1) Tests for high-penetrance genotypes, including monogenic disorders, should generally be provided within the clinical genetic services.

¹⁴ European Commission Memo/08/782, 10 December 2008.

- (2) The regulation of DTC GT, as for genetic testing in other settings to deliver health information, should be covered by the Directive on In Vitro Diagnostic Medical Devices (see section 4.3) but the regulation of the service requires more than the revision of the Directive, as discussed elsewhere in these chapters.
- (3) Susceptibility testing for complex disorders should be regulated on the basis that the claims about the link between the genetic markers and the disease are scientifically valid, and based on evidence that meets the standards of STARD (Standards for the Reporting of Diagnostic Accuracy Studies).
- (4) Transparency in information provision to consumers (truth in labelling) is of fundamental importance because it enables easier distinction between claims that are justified and those that are not. The information should also emphasise who is advised not to use DTC GT services. Information supplied should be governed by enforcement of advertising standards for evidence-based claims and accurate information in consumer law protection (Box 5).
- (5) Test quality assurance must cover not only laboratory analytical quality but also the professional interpretation of results and the provision of counselling that is appropriate to the disease risk and burden. Appropriate professional advice is necessary for the common, complex disorders.
- (6) DTC GT companies should have a competent, named person who takes responsibility for the service, regulated by the appropriate professional body.
- (7) DTC testing of samples from minors, pregnant women and third parties should not be allowed.
- (8) The cost and other implications for the health system, public health, health insurers and health policy need to be assessed, for example (1) impact on use of resources in interpreting and following up test obtained by DTC GT; (2) issues for equity of access to health information; and (3) information for medical professionals, the public and the media.
- (9) International co-ordination. There is need for international discussion and collaboration as part of the processes of Health Technology Assessment to ensure that global internet provision can be regulated consistently and supported by cross-border co-operation.
- (10) Data for research. DTC GT companies should include proper, additional, consent-seeking when desiring to use data for research rather than blurring the original company-customer relationship. This separate consent should describe the particular

purpose and specify the duration for holding samples and for the genetic information derived. Companies should also describe what will happen to samples and information in the event that the company changes ownership.

Although Member States may well develop their own additional controls on DTC GT, harmonisation of EU practice will need to recognise the increasing flow of samples for testing across national borders. Thus,

Box 5 Provision of transparent information and advertising standards

- The obligation to provide adequate information about the health risks and benefits before obtaining consent is a well-established requirement under the European Court of Human Rights (van Hellemond et al., 2011). Moreover, the Council of Europe Protocol (Box 4) on genetic testing for health purposes covers genetic testing in all settings. If a country has ratified the Protocol, it is required to ensure that DTC GT meets generally accepted criteria of scientific and clinical validity.
- The EU Directive 2005/29/EC (Unfair Commercial Practices) is relevant in prohibiting misleading and aggressive marketing, including through the internet. Under this Directive, whenever an 'invitation to purchase' is made, traders must ensure that the consumer is not enticed to make a purchase on the basis of faulty, incomplete or misleading information.
- However, Annex I and Section 3.3 of the Directive, relating to health-related claims notes that many such claims are already covered at Community level by other, specific, legislation, for example on pharmaceuticals or food. In these cases, legislation on labelling prohibits such products from making unwarranted health claims and requires claims to be scientifically substantiated.
- Directive 2005/29/EC does cover other products or services whose marketing is not necessarily regulated by over-riding sector-specific legislation, for example cosmetic products, where 'traders must be able to substantiate any factual claims of this type with scientific evidence'. However, the protection available is subject to variable interpretation of the relevant Articles in the Directive.
- A US perspective on the issues for DTC GT advertising is provided by the National Human Genome Research Institute (2004).

harmonisation requires not just reform of the In Vitro Diagnostic Medical Devices Directive to incorporate the principles listed above but also attention to codes of conduct, clinical governance, professional and public education, and the provision of available information in a standardised format (Patch et al., 2009). The principles we described above have consequences: for EU policy-makers, for informed consideration of the regulatory alternatives; for the research community, in developing an accessible evidence base; and for health professionals in translating research into practice. These points are elaborated in the following sections.

4.3 Revising Directive 98/79/EC and related matters

There is need for a more responsive and proportionate assessment during pre-market test approval, to be applied to all diagnostics, that takes account of the nature of the evidence linking test with claims. Although it is possible to do more at the Member State level (see, for example, Furness et al., 2008) there is significant scope to improve the evidence-based benefit-risk assessment in the regulatory framework provided by the EU Directive on In Vitro Diagnostic Medical Devices and its consistent implementation at the national level. This is true for all genetic testing, not just DTC GT.

Based on consideration of the principles (section 4.2), EASAC–FEAM advise that policy-makers should take into account the following points in determining the options for reforming the Directive. These points were formulated from discussion about DTC GT, but much is also relevant to other genetic testing:

- The scope of the Directive should be clarified to ensure that it covers all genetic information that is used to make medical claims. The Directive has an important role in providing the framework for independent verification of quality and validity of test information.
- Although the degree of regulation may be adjusted according to the level of perceived risk, it should be realised that risk is subjective and that there should be minimum core standards in regulation (for example, as defined by the UK Human Genetics Commission, 2010). The Directive should take care not to place all nucleic-acid-based tests in a particular risk category merely because they are deemed to be ‘genetic tests’. Policy must be sufficiently flexible to cope with future developments in technology.
- The current operation of the In Vitro Diagnostic Medical Devices Directive varies from the general procedures of the General Medical Devices Directive (93/42/EC) and Active Implantable Medical Devices Directive (90/385/EC) in that it exempts genetic

diagnostics from pre-market review and requires little activity by the Member State Competent Authorities and their designated Notified Bodies. That is, the evidence provided for claims made is currently ‘self-certified’ and not subject to independent review. The European Commission should consider the options for introducing independent review of the claims made for tests based on some form of risk stratification, but independent of the nature of the analyte. Risk should determine whether a test requires independent review or not. Low risk predictive tests can be self-certified, whether based on DNA analysis or otherwise.

- It is important to retain self-certification in testing for rare diseases in the established clinical genetic services, because scientific expertise is then often limited to the centre offering the test.
- As part of its current plan to strengthen Notified Bodies and improve their consistency across the EU (Council of the European Union, 2011), the European Commission should also consider the options available for Notified Bodies to extend their worldwide operations of inspecting and auditing of diagnostic manufacturers (including collection of data on the device in routine use) to assure standards by DTC GT companies. The European Commission with the Competent Authorities should also consider the potential of the latter in contributing to strengthening the approval process, taking account of current good practice, for example as developed by EuroGentest (see section 4.5).
- Implementing the objective to augment the pre-marketing requirement to include data on clinical validity requires significant further discussion. The first step is to ensure that whatever information is provided is clear and verifiable, emphasising the importance of the principle of transparency, coupled with commitment to act on misleading advertising (Box 5). It should be appreciated that if a clinical efficacy requirement were to be introduced for Directive 98/79/EC, this would have implications for 93/42/EC and 90/385/EC, both of which also have no mandated clinical validity criterion
- Criteria relating to clinical validity and utility are more difficult to regulate than analytical validity (Wright et al., 2011) because interpretation of the test may depend on clinical context (that includes professional judgement). Clinical utility also has a subjective dimension: the view of a subject may be at odds with the view of a physician, and a consumer may find a result useful whereas a physician does not (Kopits et al., 2011). Whatever can be achieved by reform of the Directive to ensure scientific validity will need to be accompanied by appropriate mechanisms for professional and clinical governance. A strong case

can be made for requiring published evidence for the clinical validity of the claims asserted. A test with clinical validity might be permitted even if its use has not yet been shown to result in improved outcomes, i.e. clinical utility because of the length of time needed to demonstrate such utility.

- The use of the internet is often regarded as imposing significant practical difficulties in determining the geographical location of a particular act for purposes of jurisdiction (Nuffield Council on Bioethics, 2010). Nonetheless, regarding the challenge of regulating internet DTC GT provision – it does not matter where the laboratory test originates, if it is used in the EU it must conform to EU standards. If a company based abroad were to ignore EU standards as regulated by the Directive, then Member State authorities have the capability to seize test kit material at their borders. A case can be made (ESHG, 2010) that the European Commission has responsibility for applying its standards to the laboratory services located abroad as well as to the physical parts of the test actually delivered within the borders of the EU.
- In addition to the reform of the In Vitro Diagnostic Medical Devices Directive, the European Commission should consider if there are implications for the operation of the Data Protection Directive with regard to safeguarding confidentiality of the consumer's personal data¹⁵, for example if the administration of the DTC GT company were to change following acquisition by another company or upon its discontinuation. Procedures for handling of stored personal data if a company closes, merges or is acquired are little discussed on company websites but require further attention (Zawati et al., 2011). The Data Protection Directive covers the processing of data about an individual by an organisation outside the EU if it makes use of equipment for data processing located within a Member State. It would be helpful if the European Commission could clarify whether genetic information accessed by a consumer within the EU is covered by the Directive. The European Commission should also take account of this particular privacy concern in DTC GT when it addresses sustainable healthcare and security of personal health information as part of the digital agenda initiative¹⁶.

4.4 Creating an industry code of practice

While waiting for public policy development, it would be prudent for DTC GT companies to work together to develop and implement industry-wide quality standards. An industry code of conduct would also be valuable '*to develop a strong identity to promote clarity and trust among consumers*' (Grimaldi et al., 2011) and the principles espoused by the UK Human Genetics Commission provide a suitable broad base with which to construct this. This approach can be categorised as regulation based on transparency of the evidence base. In terms of specific criteria for clinical validation, one proposal for industry sector action sets objectives on quality standards (Ng et al., 2009). Complementary responsibilities are also set out for the wider research community: to monitor behavioural outcomes after DTC GT; to perform prospective studies of the predictive value of multivariate genetic tests; and to replicate data in other populations. It is equally important for companies to agree among themselves, and with professional bodies and regulators, on the nature of the information delivered to the consumer – some companies are suspected to label their tests as 'lifestyle' to evade more onerous regulatory restriction on medical information (Grimaldi et al., 2011)¹⁷.

4.5 Registry of information on genetic tests

The US National Institutes of Health (NIH) has created a Genetic Testing Registry¹⁸ which will provide information on the availability, validity and usefulness of genetic tests. Such information, placed in the public domain, will be important for all genetic testing, not just DTC GT. The registry is potentially valuable for consumers, as well as researchers, healthcare providers, DTC GT companies and policy-makers – if flexibility of access by the different stakeholders can be ensured. Thus, consumers and physicians may judge for themselves whether or not to avail themselves of a particular test or service. The NIH initiative is based on voluntary submission of data by companies – it is questionable whether this will be effective. EASAC–FEAM recommend that a corresponding EU initiative should be considered, perhaps involving the European Medicines Agency and other relevant bodies including the European Network for Health Technology Assessment (EUnetHTA)¹⁹ and ESHG, and funded by the European Commission. There would be added value in a

¹⁵ European Commission, Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

¹⁶ European Commission, A digital Agenda for Europe, COM (2010) 245, May 2010, available on http://ec.europa.eu/information_society/digital-agenda/documents/digital-agenda-communication-en.pdf.

¹⁷ See also <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2795579/>.

¹⁸ http://oba.od.nih.gov/GTR/gtr_intro.html. In the EU, data on genetic testing for rare diseases has been collated by the Orphanet portal, <http://www.orphanet/consor/cgi-bin/index.php>.

¹⁹ www.eunetha.eu, focusing on scientific co-operation in Health Technology assessment in Europe and involving 34 government-appointed organisations.

global registry if the information provided was relevant to EU citizens and their health systems. However, the Directive on In Vitro Diagnostic Medical Devices currently obliges all parties to observe confidentiality and this stipulation would need to be modified to require that evidence relating to test performance be placed in the public domain.

The UK Royal College of Pathologists and the PHG Foundation have also made the case for a repository of information (Furness et al., 2008) – a publicly available database would be valuable in explicitly stating where evidence is lacking, as well as in collating the evidence in a standardised format. Perhaps the design of such systems for public access can be informed by lessons learnt in the EU from creating, accrediting and deploying online health information systems²⁰. For credibility, an independent expert body would need to be responsible for evaluating and verifying the evidence and its implications for test provision, whether by public services or commercial companies.

Public policy-makers also need to realise their responsibility to support the collection of the evidence to validate clinical claims and to establish the relative roles of research funders, academia and industry in identifying priorities. Validating evidence on susceptibility testing also requires research to provide the appropriate tools (algorithms) for risk prediction and for setting thresholds at which preventive interventions might be undertaken (Field et al., 2011). In the view of EASAC–FEAM, policy-makers must commit to improve public health service translational activities: that is, to become faster in the routine implementation of innovation. Principles of validation and verification for molecular genetic testing and for the implementation process in clinical services have been developed by a group of experts for EuroGentest (Mattocks et al., 2010). Accumulating experience with the Clinical Utility Gene Cards²¹ developed by EuroGentest and the Gene Dossiers of the UK Genetic Testing Network, mostly relating to single gene disorders, helps to provide the evidence base for improving public health services. A similar approach was developed in the USA by the EGAPP working group²² that also investigated some tests for low-penetrance genes, such as testing for CYP 450 polymorphism in adults beginning selective serotonin reuptake inhibitor (SSRI) treatment for depression, where insufficient evidence was found to decide for or against use²³. For lower-penetrance genes, there have been very few studies so far for generating the data that can be analysed, but this will

change in consequence of high-throughput sequencing methods and the development of algorithms for diagnostic and screening purposes, together with other advances in the use of biomarkers in health (Organisation for Economic Co-operation and Development, 2011).

4.6 Professional and public education

Professional education. Working Group members confirmed that it is important to do better in educating medical and other health professionals about genetics (Anon., 2011). Many primary care physicians lack confidence in their ability to perform basic genetic health-related tasks and there is need for co-ordinated European effort to improve their education (Nippert et al., 2011). In addition, a survey across Europe of the national status regarding training programmes and numbers of genetic counsellors found very large variation between countries (Cordier et al., 2012). The ESHG has called for a coherent European approach to accreditation of genetic counsellors but with sufficient flexibility to enable adaptation for national requirements. Suggested core competences in genetics for health professionals in Europe, covering competences both for genetic specialists and for those who are not, are also available from EuroGentest²⁴. Further suggestions on the training of health professionals together with the organisation of healthcare services in Europe are discussed in the Council of Europe recommendations (2010).

Public engagement. Better health services should be accompanied by better public education: goals for education and dialogue on genetic testing broadly (European Commission, 2004; Leopoldina, acatech and Berlin-Brandenburg Academy of Arts and Sciences, 2010) and for health literacy relating to genomics (Brand and Brand, 2011) have been identified and there is much to be done to address common misconceptions about what genetic tests can offer in terms of medically relevant information. The issues for public engagement, taking account of the views of various stakeholder groups, are becoming widely discussed (for example, in the USA by the Center for Public Health and Community Genetics/ Genetic Alliance, 2011). There is a specific need to educate the public to understand what is offered in DTC systems (see also Chapter 2). In this regard, it is essential, for example, to explain clearly any distinction made between testing for monogenic disorders and complex disorders. A key objective for public education, given the practical challenges in reliably regulating the

²⁰ For example systems such as MedIEQ (www.medieq.org) and MedCIRCLE (www.medcircle.org). An international code of conduct for medical and health websites has been developed (www.hon.ch/HONCode/Conduct.html).

²¹ <http://www.nature.com/ejhg/journal/v18/n9/pdf/ejhg201085a.pdf> for the principle.

²² <http://www.egappreviews.org/>.

²³ <http://www.egappreviews.org/recommendations/depression.htm>.

²⁴ Eurogentest, available on http://www.eurogentest.org/students/documents/info/public/unit6/core_compentencies.xhtml. Further discussion is provided by Skirton et al. (2010).

internet supply of tests, is to inform and empower the consumer to decide for themselves. One such approach is exemplified by the recent Italian National Prevention Plan for Public Health Genomics, being developed by the Italian Network for Health Genomics working with the Centre for Disease Control (Ministry of Health), within the current National Prevention Plan²⁵. The Council of Europe is also intending to provide information on DTC GT to the public. As part of the contribution made by the academies to debate in the EU, a lay summary of the present report will be prepared and disseminated widely by the member academies of EASAC and FEAM.

4.7 Related issues for whole-genome sequencing

It may soon be easier and cheaper to sequence an entire genome than to genotype a series of known mutations and this is likely to facilitate more accurate, sophisticated and cost-effective genetic testing. The recent report from the PHG Foundation (2011) provides a comprehensive overview of the clinical implications of whole-genome sequencing and the emerging issues associated with the volume and complexity of the data generated. Most whole-genome sequencing so far has been performed in a research setting, but there are significant opportunities for introduction into the health services to improve patient diagnosis, clinical outcomes or disease prevention.

Some practical considerations for the future expansion of whole-genome sequencing were summarised by Ormond and co-workers (2010), who recommended that patients should be provided with detailed information before taking the decision to be tested. In addition, the proponents of whole-genome sequencing were advised to consider the limitations of the sequencing methods used; to create, maintain and update information about the links between genomic sequences and disease; to develop better ways to communicate information about the implications; and to provide specialist training. Further information on potential implications is also provided in the report from the University of Leuven²⁶.

Whole-genome sequencing currently represents a very small proportion of the DTC genomics market (Janssens and van Duijn, 2010; PHG Foundation, 2011) but dramatically reducing costs are leading to whole-genome sequencing and analysis becoming more common and such sequencing will, in all probability, be increasingly offered to consumers. To lower costs still further, companies may select parts of the genome for analysis, in particular the protein-coding regions, and this might

further lower the threshold for wider personal consumer adoption of genome sequencing.

The challenges for consenting, communicating and acting on data from the present DTC GT services will be shared by the outputs from whole-genome sequencing and analysis, and some will be accentuated. For example, the provision of accurate and transparent information – about whether to have a test and on how to interpret the results – will be even more problematic because of the increased likelihood of results from whole-genome sequencing containing clinically or personally significant findings (PHG Foundation, 2011). Whole-genome sequencing also has considerable potential to reveal incidental information that was not anticipated and not requested by the consumer. Thus among the most important general issues to resolve for whole-genome sequencing, whether offered DTC or in other settings, are the following:

- (1) Should whole-genome sequencing be provided as an open-ended test with feedback of information on all variants or should it be carried out in relation to specific clinical questions and only the variants relevant to those questions reported?
- (2) How to deal with incidental findings of significant medical and psycho-social impact, and with variants of unknown significance?
- (3) Should the sequence information be stored without prior interpretation?

There are many challenges for Member States and the European Commission to consider in preparing for the wider adoption of whole-genome sequencing, whatever the particular service setting, and the various regulatory options (PHG Foundation, 2011) will need to be clarified. We take the opportunity to advise regulatory authorities and other policy-makers to prepare for the technology, for it has potential for considerable impact.

4.8 Global implications for policy-makers

Our report focuses on the issues for policy-makers in the EU but it is also necessary for EU policy to be co-ordinated with other international developments (Council of the European Union, 2011). It will be important to use the model procedures available through the Global Harmonisation Task Force for Medical Devices (<http://www.ghmf.org>) to develop the appropriate convergence between medical device regulatory systems. Study Group 5 of the Global Harmonisation Task Force has defined clinical evaluation as the assessment and analysis of

²⁵ Current National Prevention Plan (2010–2012) is on http://www.ccm-network.it/Pnp_2010-2012. Italian Network for Public Health Genomics, GENISAP, is on http://isituti.unicatt.it/igiene_1830.html.

²⁶ Metaforum paper 6, University of Leuven, *Full sequencing of the human genome*, December 2011, http://www.kuleuven.be/metaforum/docs/pdf/wg_14_e.pdf

clinical data pertaining to a medical device to verify the clinical safety and performance of the device. However, there appears to be no firm understanding of what is meant by the term 'clinical performance', at least with regard to diagnostic and predictive tests. Along the continuum from analytical validity to clinical utility, there is no international consensus on whether the role of regulators should stop at analytical validity, scientific validity, clinical validity or clinical utility (see sections 4.2–4.3 for discussion in the EU context).

Implementing the results of policy co-ordination in the EU is already complicated by wide variation in the present quality and availability of public health services in Member States. However, considering the global context, application of the gene-disease association evidence base in genetic testing is further complicated by differences in the relevance of genetic information for different populations. For example, as noted in the US Congressional hearings (section 3.3), if results are based on studies in Caucasian populations, the relevance for African-Americans may be unclear. Differences found in the genomes of African and Chinese people may have implications for their disease susceptibility and drug responsiveness (Li et al., 2010) and hence for the value of their DTC GT information if calibrated from other populations. There are major implications for a global DTC GT industry and, in an era of whole-genome sequencing and analysis, building databases containing the clinical information on DNA variants of specific genes is a global priority.

We suggest that these issues be addressed in the current World Health Organization (WHO) work to prioritise research to harness genomics for tackling public health problems (WHO, 2011). EASAC and FEAM, in turn, will be considering the opportunities for extending the present work to a global scale by collaborating with other regional academy networks.

4.9 Translating principles into practice

The principles set out in this Chapter for regulating DTC GT and other genetic testing seek to build on shared interpretations and expectations in the work of many other groups that we have cited, even though those other groups may have construed their preferred options for reform in various ways. We reiterate that our purpose

is to set out the scientific evidence and to focus on the principles, not to prescribe specific regulatory solutions. However, our conclusions on what may be needed in practice for developing an appropriate regulatory environment are similar to ones elaborated in detail elsewhere (Wright et al., 2011, summarised in Box 6).

Box 6 Translating principles into practice in the EU

- Regulatory policy development for DTC GT can be viewed as needing to embody five steps in consumer protection (Wright et al., 2011), with the proviso that DTC GT must also ordinarily exclude certain designated services (serious inherited diseases and others specified in this chapter). These translational steps are compatible with the basic principles espoused, for example by the UK Human Genetics Commission (2010), relating to consent, data protection, scientific rigour, balanced interpretation and accuracy in marketing (see section 3.1 of the present report). The EASAC–FEAM Working Group summarised the necessary steps as follows.
 - (1) Information. Agreed guidelines on appropriate information provision (before, during and after the test) with proportionate consent as well as interpretation and follow-up.
 - (2) Analytical validity. Implementation of proper quality assurance and quality control programmes to ensure that the testing laboratory meets the required standards.
 - (3) Scientific and clinical validity. Establishing that the tests offered have genuine association with the claims made.
 - (4) Access to advice. Involvement of appropriately qualified, competent, responsible professional, subject to normal clinical governance procedures, including follow-up measures, management and treatment.
 - (5) Claims. Prevention of misleading assertions (publicity and promotion about meaning and usefulness of results)

5 Conclusions

Many of the issues discussed in previous chapters are relevant to the further consideration of genetic testing more generally, not just to DTC GT. In this final chapter we reiterate some of the specific points but also take this opportunity to note that there is need for continuing broader consideration of the issues for all genetic and all other testing. The regulation of DTC GT is already a much-discussed topic, as evidenced by the long list of representative literature cited in the previous chapters. Inter-sectoral initiatives involving public regulators, professional bodies and industry are important to inform policy development, facilitate development of standards and implement an appropriate practical framework to govern this rapidly developing technology (Caulfield et al., 2010). The European academies also have an important role – free of vested interests associated with the commercial and professional genetics communities – to provide an independent perspective on the fundamental principles. In constructing our recommendations, EASAC and FEAM have attempted to avoid both the over-regulation that impedes innovation and the relinquishing of health strategy-setting to the private market. We emphasise that there are common societal issues in all genetic testing, for example with regard to communicating risk and supporting physicians in their communication.

Our focus is on DNA tests but many of our conclusions also apply to other testing procedures, whether based on measurement of analytes or imaging. In our view, efforts to devise guidelines and recommendations relating specifically to genetic testing should be regarded as part of longer-term efforts to encompass all medical testing

We reiterate that, on the whole, DTC GT has little clinical use at present and we have no wish to encourage it. However, in considering regulatory options for all testing, it is important to ensure the flexibility to enable future innovation, building on the accumulating scientific evidence base, experience and ongoing debate. We recognise that Member States may wish to implement their own regulatory initiatives on DTC GT as part of the wider management of the opportunities and challenges for testing across the public and private sectors. Our conclusions are primarily directed to the policy-makers at the EU level and are based on developing principles for good practice informed by the available scientific evidence.

Regulation in this, as in other areas, should be responsive, appropriate and proportionate, targeted but flexible. Our recommendations have been described in detail in previous chapters and can be summarised as follows.

Scope of inclusion within DTC GT

We advise that the scope of DTC GT services should currently exclude the provision of diagnostic or presymptomatic genetic information for monogenic diseases (see section 4.1.1), prenatal testing (4.1.2, including foetal cells, DNA or RNA), carrier testing in children (4.1.3) and nutrigenomic tests (4.1.4). We recommend further discussion on whether pharmacogenetic testing could be included (4.1.4). Acquisition of samples from minors, pregnant women and third parties should also not be permitted. We recommend that policy-makers urgently consider the implications for the wider introduction of whole-genome sequencing (4.7).

Reform of EU In Vitro Diagnostic Medical Devices Directive and other regulatory procedures

We advise that this Directive should cover all tests for the purpose of collecting health-related information (4.2, 4.3). According to a risk-based, proportionate approach, genetic diagnostics should be included within the general requirement for independent review of pre-market evaluation and data should also be collected through post-marketing surveillance. For diagnostic tests for rare diseases, pre-market evaluation and post-marketing surveillance may demand novel approaches.

As discussed in Chapters 3 and 4, we also emphasise the importance of ensuring appropriate regulatory oversight of the other dimensions of test provision, in particular relating to laboratory quality performance, professional competences, and the other points covered in Box 6. There is need to pay attention to Quality Assurance and other procedures (4.2) and to consider options for accrediting/certifying quality standards to support international acceptance of tests. To be successful, reform of the Directive will require complementary activity to improve codes of conduct, clinical governance and information provision. Other issues for international co-ordination in regulation of DTC GT require further consideration (4.2, 4.3 and 4.8) and additional interaction between the EMA and other appropriate EU organisations, FDA and other agencies regulating medical devices would be helpful. The implications of reforming the In Vitro Diagnostic Medical Devices Directive on the other Medical Devices Directives (regarding proof of clinical efficacy) need to be examined with the objective of policy harmonisation (4.3). The options for increasing the roles of Competent Authorities and their Notified Bodies in the regulation and auditing of DTC GT also need to be explored. The relevance of the provisions of the Data Protection Directive regarding the storage and use of

personal health data in jurisdictions outside the EU should be confirmed (4.3).

Transparency of information

Transparency is fundamental to effective regulation (4.2). An EU/international registry of genetic tests with evidence-based claims, including those to be offered by DTC GT companies, would be very valuable for consumers, physicians, policy-makers, researchers and companies (4.5). It must be considered if such a registry will only be effective if mandatory, and what this entails in terms of independent verification and oversight. A role for EMA may be considered in supervising the database, with the previous work of EuroGentest incorporated, and a role for the European Commission in funding it. Consumer protection norms and the application of advertising and consumer trading standards to DTC GT (Box 5) must be reviewed by all Member States and, where necessary, enforced more vigorously.

Implications for research

Among the priorities for the research policy agenda are the following.

- (1) Consideration by research funding bodies of the resources needed to assess clinical validity of tests, including examination of potential differences between populations for relevance of test results (4.5). Analytical sensitivity and specificity, penetrance, positive and negative predictive values are items influencing analytical and clinical validity that may change in populations with different genetic background or with different stratification of genotypes. That is, in complex diseases, the same DNA sequence variant may have different clinical significance. In addition to building the evidence base using well-characterised clinical cohorts, it is highly desirable for the research community to devise tools and agree standards for reporting of genetic risk predictions (Janssens et al., 2011), to facilitate consistent evaluation of the evidence from different studies, and to improve algorithms for genetic risk prediction in complex disease (Jostins & Barrett, 2011).
- (2) Exploration of the impact of DTC GT results on individual attitudes and behaviour and assessment of other factors mediating that impact (2.3, 2.4).
- (3) Evaluation to improve understanding of variations in risk perception and how to improve risk communication in both traditional health service settings and DTC GT (2.5).
- (4) Considering potential for DTC GT itself to serve as a source of information for research and the issues

for securing appropriate consent for this purpose (2.6, 4.2): there is need for further exploration of the implications for privacy and confidentiality, in particular, relating to storage, use and re-use of samples and information.

Public health services

In addition to generating fundamental knowledge, it is vital to improve the translation between basic science and routine clinical practice, and the necessary steps in the implementation of translation need to be explicitly recognised and funded. In particular, the growing evidence base on gene-disease associations needs to be used more effectively to inform diagnostic and screening services (2.1). It is very important to educate health professionals to interpret and communicate the results of genetic testing (4.6). The implications of advances in genetic testing generally and DTC GT specifically need to be considered in terms of health service standards, priorities and training (4.2, 4.6).

Public education and communication

There is an important responsibility for DTC GT companies to provide high-quality information to their prospective customers (for example as detailed in the advice of the UK Human Genetics Commission, 2010), as a core part of their code of conduct (3.3, 4.4). This will include cautioning on when DTC GT would not be appropriate. The biomedical community, including academies of science and medicine, must also do more to provide accurate and accessible information to the public (4.6).

In conclusion, there are opportunities to improve the regulatory and innovation framework for genetic testing in the EU by reforming the Directive on In Vitro Diagnostic Medical Devices and this is a collective responsibility for the European Commission, European Parliament and Council of Ministers. However, such reform will take time and will only be successful if there is also action in the short-term across a broad front relating to clinical governance, development of evidence-based public health services, improved professional and public education, provision of information with greater transparency, and support for research. We consider early action particularly valuable if it helps to build international standardised repositories of test information, clarify proposals for accreditation of DTC GT companies and progress models to assess the validity of tests. This requires action by policy makers in Member States as well as in the EU Institutions, and the science and medical community has a vital role to play in informing and implementing these actions.

Appendix 1 Working Group

The report was prepared by consultation with a group of experts acting in an individual capacity and comprising expertise in clinical genetics, public health and ethics, brought together by EASAC and FEAM:

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List of abbreviations

CYP 450	Cytochrome P-450
DG Sanco	European Commission Directorate General for Health and Consumer Protection
DNA	Deoxyribonucleic acid
DTC GT	Direct-to-Consumer Genetic Testing
EASAC	European Academies Science Advisory Council
EMA	European Medicines Agency
ESHG	European Society of Human Genetics
FDA	Food and Drug Administration
FEAM	Federation of European Academies of Medicine
GAO	Government Accountability Office
GWAS	Genome Wide Association Studies
IAP	InterAcademy Panel
MODY	Maturity-onset diabetes of the young
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
PHG	Foundation for Genomics and Public Health
RNA	Ribonucleic acid
SNPs	Single nucleotide polymorphisms
WHO	World Health Organization

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