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Assessment*

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**DIRECT TO CONSUMER GENETIC
TESTING**

STUDY

(IP/A/STOA/FWC/2005-28/SC32 & 39)



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SCIENCE AND TECHNOLOGY OPTIONS ASSESSMENT

DIRECT TO CONSUMER GENETIC TESTING

STUDY

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CONTENTS

CONTENTS	3
LIST OF TABLES	5
LIST OF FIGURES	6
EXECUTIVE SUMMARY	7
1. INTRODUCTION	10
2. GENETIC COUNSELLING AND GENETIC TESTING	13
2.1 Recent Trends in Genetic Testing and Counselling	13
2.2 Ethical, Legal and Social Aspects of Genetic Testing	21
2.3 Guidelines for Testing and Counselling	26
3. DIRECT-TO-CONSUMER GENETIC TESTING (DCGT)	28
3.1 Advertising Genetic Testing Directly to the Public	30
3.1 Direct-to-Consumer Sales of Genetic Testing	31
4. THE MARKET FOR DCGT	34
4.1 Supply - DCGT Offers via the Internet	35
4.2 Demand - Public Attitude towards DCGT	37
5. ASSESSMENT OF WEBSITES OF COMPANIES OFFERING DCGT	39
5.1 Companies and Tests Offered	39
5.2 Scope and Kind of Information Available on the Websites	44
5.3 Quality Assessment of the Information Available on the Websites	47
6. REGULATION OF DCGT	52
6.1 Problems and Concerns Regarding DCGT	52
6.1 Restriction of Genetic Testing to Referral by a Medical Doctor	57
6.3 The Approval of Tests and Offers – Pre-market evaluation	60
6.4 Quality Control and Evaluation	61

6.5 Regulation at the European Level - IVD Directive and Council of Europe	62
7. CONCLUSIONS - POLICY OPTIONS	67
REFERENCES	71
ANNEX	76
1. Assessment form for the evaluation of websites offering DCGT	76
2. Overview of testing services offered via internet	81

LIST OF TABLES

TABLE 1	DCGT Companies evaluated in the period 15/06/08 until 15/07/08 (if based on outside the USA, contry given in parentheses)	43
TABLE 2	Number of criteria met by company	53

LIST OF FIGURES

FIGURE 1	Types of tests offered	45
FIGURE 2	Number of companies meeting quality criteria	52
FIGURE 3	Percentage of websites complying with X or less quality criteria	54

EXECUTIVE SUMMARY

At the end of the 1990s, genetic testing offered directly to consumers came onto the market as a new "business model". Up until then, genetic testing had been carried out by specialised institutes in the medical sector upon referral by a medical doctor. In recent years, new companies offering direct-to-consumer genetic testing (DCGT) via the internet alone are emerging constantly.

This method of "bypassing" the medical sector with its established ethical and quality standards has given rise to concerns regarding an uncontrolled growth of the market for genetic testing. Tests are offered whose clinical validity and utility is doubtful and thus could do harm to consumers who might be misled and insufficiently informed by the DCGT companies' advertisements.

The present report provides an overview of the current discussion on DCGT among experts and public authorities and on the current status of DCGT offers on the internet. Guided by an analysis of the market development and the pros and cons of DCGT, the report discusses possible options and needs for political intervention.

The increasing number of DCGT offers can be regarded as being driven by the following trends that currently characterise genetic testing in general:

- The availability of genetic tests for common diseases and susceptibilities to common diseases represents a promising economic option for companies developing genetic testing assays or kits as well as for companies offering services on a private basis directly to customers.
- Technical achievements such as the development of DNA microarrays reduce the technical and financial barriers to a private market for genetic testing.
- Genetic testing is on its way to becoming an option for preventive medicine in general. It is discussed as a new important public health option, and the perspectives of new applications such as pharmacogenetics and nutrigenomics indicate new business opportunities.

The central difference between DCGT and the standard genetic testing situation in the context of the established system of genetic counselling is the way informational support is (or rather is not) provided in internet offers of testing. It may well be that there is no provision for counselling at all except for the written advice on the webpage. Counselling may be offered as an additional special service at extra costs and at the customer's request. It may also be that a recommendation or at least an offer is given for the customer to contact a doctor or health practitioner from the company via phone for counselling. In other cases, the customer may be recommended to consult his own doctor on the test results. It may also be the case that the entire process follows a standardised non-personal web-exchange procedure. Even the report containing the results of the diagnosis and their interpretation as well as recommendations to the client can be produced by software that automatically combines information from the DNA diagnosis with information read from a questionnaire on the customer's lifestyle.

The most obvious problem of DCGT is that - as is supported by an assessment of 38 DCGT websites carried out in the context of the project - the majority of tests offered to consumers directly are tests for susceptibilities for disease based on so-called SNPs (single nucleotide polymorphisms). These tests are most interesting from a commercial point of view since they are related to widespread common diseases (such as cancer). Experts regard most offers of testing based on SNPs to be meaningless from a scientific point of view, since the clinical validity of most of the tests has not (yet) been sufficiently proven. However, since recommendations that can be drawn (and are drawn by providers) from positive test results usually do not go beyond what a doctor would recommend to any patient as being good for his/her health (e.g. practise sports, avoid fatty foods), some consider offering this directly to consumers to be harmless. Others, however, opine that this kind of testing may harm clients. If results are negative, the client may gain the false impression of being safe with regard to developing a certain disease and might not see the need for adopting a healthy lifestyle; this would be totally misleading, as the absence of "negative" SNPs tested does not imply an absence of the risk of developing e.g. high blood pressure from bad dietary habits, other behavioural and environmental factors or other (so far unknown) genetic traits (that were not tested).

The internet survey supported the notion that,

- many DCGT offers do not meet a minimum set of quality criteria that can be regarded to be necessary for ensuring adequate information and protection of customers against misleading interpretation of the need for as well as the possible consequences of genetic testing,
- most DCGT offers fail to provide proper information on the scientific evidence behind genetic testing services offered to customers (clinical validity and utility),
- many of the companies offering genetic testing services via internet do not include genetic counselling at all in their services. Only a few urge customers to involve an expert before purchasing a gene test, and "counselling" in most cases only is provided as written information via mail or via web-log.

Due to the complexity of genetic information that could well mislead consumers or be used to mislead them, and due to the likely serious health and psychological consequences of this, there is a consensus that principles such as informed consent and quality standards of testing and counselling must be ensured since DCGT offers via the internet can obviously be associated with consumer protection problems. Thus it is widely regarded to be legitimate to regulate the market for DCGT. It is, however, a matter of discussion to what extent governmental intervention is needed, and whether regulations should apply in the same way to all different types or purposes of DCGT services.

At the centre of discussions on possible regulatory interventions, there are two options:

- Statutory restriction of genetic testing to the medical context (e.g. by making the referral by a medical doctor mandatory) could ensure a minimum standard of quality of testing and counselling. This is for instance suggested by the Council of Europe's recently released "Additional Protocol on Genetic Testing" which stipulates that "a genetic test for health purposes may only be performed under individualized medical supervision". It is, however, discussed to what extent all types of genetic testing should be covered by such a regulation or whether "non-risk" tests should be openly available commercially.
- As companies offering DCGT so far are not obliged to provide any scientific evidence regarding the clinical validity and utility of tests offered and as the evidence for many tests is regarded to be doubtful by experts, a system of pre-marketing approval of genetic tests is argued for. The European In-Vitro-Diagnostics Devices Directive which stipulates the marketing of in-vitro diagnostic does not cover genetic testing so far or treats gene tests as "low-risk" devices for which no pre-marketing approval is provided.

At the European level, the following options for policy interventions are conceivable in order to ensure high standards of genetic testing services and to hinder misuse and uncontrolled growth:

- The IVD Directive is currently undergoing a process of amendment. To provide for a broad scope of gene tests being covered by the directive would allow the establishment of a European system of pre-market approval of gene tests which might drastically restrict the leeway for DCGT.
- At the national level, there are discussions of setting up a code of practice for DCGT to ensure minimum quality standards. It must be considered whether such a code could be established on the European level, and could be enforced by monitoring by a European public authority.
- In order to ensure the "technical" quality of testing services, it could be envisaged to establish a European system of control and accreditation of laboratories carrying out molecular testing, as is demanded by guidelines recently published by the OECD.

1. INTRODUCTION

Genetic testing has been the subject of public and political debate for almost two decades now. The enormous and continuous pace of scientific and technological development in this field of biomedical research and healthcare drives the ongoing discussions of the pros and cons of genetic testing. Genetic testing makes it possible to detect at a very early point in time the genetic traits of an individual that cause serious disease or disabilities for the individual himself or for his offspring, or to detect genetically based susceptibilities which indicates an increased risk of a person for developing a serious disease such as cancer. The new diagnostic options made available by genetic testing can without a doubt be helpful for detecting health risks early in order to initiate medical treatment in a timely manner. With regard to monogenetic inherited diseases, for instance, genetic testing can provide individuals with certainty as to their genetic status and thus about any increased likelihood for them to develop a disease or to pass a genetic predisposition for a disease on to their children. Without testing, persons at risk have to live with an uncertainty of a 25% or 50% risk of being a carrier.

The basic feature that genetic testing adds to medical practice for good (and at times for bad) is its "predictive" character. We gain the ability to know about our (or our offspring's) genetic status and thus should be able to better predict our health status in the near or distant future.

Diagnostic and predictive options made available by genetic testing - despite their medical benefits - have caused debates about possible negative effects of genetic testing, among which are:

- a) The possible misuse of genetic information by third parties: Cases have been reported about employers and insurance companies discriminating against individuals on the basis of genetic testing.
- b) Information about a person's genetic status can imply knowledge about the risks of a person's relatives to carry the same genetic "burden". This together with information about a person's future (particularly in cases where no therapy is at hand), which is often sensitive and psychologically problematic, has led to demands for a person's "right not to know" about his or her own genetic make-up.
- c) Testing for complex (common) diseases can only provide information about the probability (higher than average risk) of a person with a susceptibility gene to actually develop the disease. The clinical usefulness of testing is therefore considered in some cases doubtful. The only consequence of diagnosis might be to cause psychological damage.

- d) There has been criticism that the availability of more and more genetic testing options in medical practice and the high-flying visions associated with the complete identification of the human genome in 2001 could provide credence to a wrong view of “genetic determinism”, suggesting that most diseases are caused by a person's genetic makeup (and thus neglecting detrimental environmental factors) and possibly leading to a decreased social acceptance of people with disabilities or handicaps, since the availability of genetic diagnostics might make disabilities come to be regarded as avoidable.

When genetic testing first entered medical practice during the mid 1980s, it was restricted to a few inherited diseases, such as cystic fibrosis. Genetic testing and counselling were only offered by experts working at university hospitals and institutes and by a limited number of doctors who specialised in human genetics. The limited number of persons seeking genetic testing and counselling, the quite complex and expensive technical procedure of testing as well as the limited number of well-educated experts who can offer genetic testing and counselling are all factors that have contained the problematic potential of genetic testing. Many of the negative expectations connected with genetic testing were based on the assumption of an uncontrolled growth of genetic testing for a great number of common diseases, which might open the door for misuse and clinically non-indicated applications of testing. Apart from the limited number of tests available, the fact that a small group of medical practitioners and genetic counsellors has controlled the practice of testing has been regarded as guaranteeing a knowledgeable, cautious and responsible application of genetic testing, which contrasted with the negative scenarios of its widespread and clinically doubtful use. In recent years, however, some of the barriers to a growth of genetic testing beyond the “protected” realm of genetic counselling carried out in hospitals for a restricted number of persons who might be carriers of rare inherited genetic diseases have vanished or are losing strength. New technological options are available that make it both technically easier and cheaper for a genetic test to be carried out. Connected with the lowering of the technical barriers to genetic testing is a tendency for new (private) suppliers to enter the market. And last but not least, genetic testing is being offered not only for some rare Mendelian diseases but increasing for common and widespread diseases such as cancer, diabetes or cardiovascular diseases. However doubtful the clinical validity and usefulness of these tests may be, such use has the potential of making genetic testing a part of everyday health care.

A related phenomenon has been the transition to a new “business model” or “practical setting” for genetic testing since the late 1990s, namely genetic testing and counselling services offered directly to consumers. Some regard this way of by-passing the medical or healthcare setting (with a specialised doctor and its client) that previously controlled access to these services as providing free access to genetic testing, letting consumers decide on their own whether to make use of these testing options. Others consider direct-to-consumer genetic testing (DCGT) to be a possibly dangerous marketing ploy that will lead to genetic testing that is uncontrolled, scientifically unjustified, qualitatively doubtful and often intentionally misleading.

In contrast to the established practice, medical benefits and ethical and social problems of genetic testing, which have been the subject of many studies and numerous inquiries by ethical committees and other non-governmental and governmental advisory boards during the past 10 to 15 years, the debate on DCGT has just begun. DCGT is a rather new phenomenon that is apparently driven by the use of the internet. Although it is a growing market, it is still a niche market; new companies offering genetic testing via the internet currently are showing up constantly. It is however too early to tell whether they in the long and medium term will succeed to establish themselves on the market. This makes it difficult to assess the actual relevance of DCGT, which might well develop into a serious competitor to the established forms of genetic counselling and require political or statutory regulation in order to protect consumers' rights and health.

It was the objective of the STOA project "Direct-to-Consumer Genetic Testing" to explore the current use of DCGT. Starting with a discussion of the status and perspectives of genetic testing in general (section 2), the present report discusses the development of DCGT, its possible advantages and disadvantages and the arguments used by different stakeholders (3 -4) in order to explore policy options for fostering an ethically and medically reasonable offer of genetic testing to consumers (6). The concluding section (7) provides a condensed overview of the policy options at hand and of actions that could be taken into consideration at the European level.

The discussion of the pros and cons of DCGT is based on the latest available scientific literature and policy documents dealing with DCGT as well as on a systematic scan of offers of genetic testing that can be found on the internet, which was carried out in the context of the project during June and July 2008. The results of the survey (see section 5) and their possible implications for policy intervention in the field were discussed with a group of experts at a meeting hosted by the Flemish Institute for Science and Technology Assessment (viWTA) in Brussels on 22 September 2008.

The following experts participated in the meeting:

Pascal Borry, University of Leuven
Stuart Hogarth, University of Loughborough
Heidi Howard, McGill University Montreal
Alastair Kent, Genetic Interest Group
Ulf Kristoffersson, Lund University Hospital
Peter Pohl, GATC Biotech
Helen Wallace, Gene Watch U.K.

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2. GENETIC COUNSELLING AND GENETIC TESTING

2.1 Recent Trends in Genetic Testing and Counselling

Genetic testing and counselling is a well-established form of medical practice that belongs to the standard provision of health care in most countries. The objective of genetic counselling is to educate persons at risk for a genetic disorder about their genetic status and about the possible implications and complications of their genetic condition. Genetic counselling helps people make decisions about their future lives with respect to diagnostic, therapeutic and ethical and practical factors. Genetic counselling is provided by medical geneticists and genetic counsellors trained to provide these services. Genetic counselling comprises:

- Counselling for individual adults about their own genetic condition mainly when inherited diseases are known to exist in an individual's family history.
- Genetic counselling for couples at risk of passing a genetic condition (for disease or disability) to their children.
- Prenatal counselling for pregnant women at risk of giving birth to a child with a birth defect or genetic disease.

Up to the 1970s, information about the genetic condition of a person asking for genetic counselling was primarily based on "phenotype" data, such as the appearance of the client, data from X-ray (later also ultrasound) diagnosis or information based on the family history and family pedigree. For some genetic conditions it was possible to gain information from blood or urine samples, giving hints about specific metabolic anomalies. In the 1970s, prenatal diagnosis based on microscopic analysis of amniotic fluid that permitted examination of the number and appearance of the chromosomes of the foetus (e.g. for Down syndrome) became an established medical standard.

As all of these procedures provide information about a person's genetic status, they can in a wider sense be regarded as genetic testing, yet they do not provide information at the DNA level or the genes themselves but only about the presence (or absence) of a genetic variation from the patient's phenotype (gained from metabolic products found in blood samples or from distinctive chromosomal features).

Genetic testing at the level of DNA - which henceforth is referred to with the term "genetic testing" - started to enter medical practice in the 1980s (e.g. for inherited diseases such as Huntington's disease or cystic fibrosis). The steady progress in molecular genetic research during the 1990s and the successful sequencing of the human genome in 2001 have led to a steady growth in the number of diseases or susceptibilities for which a specific genetic trait is known. This in turn has led to a steady growth in the number of genetic tests used in medical practice and genetic counselling. A report on genetic testing delivered to the German Parliament in 1993 found that the number had grown from around 80 tests in 1986 to more than 700 in 1993 (Hennen et al. 1996, 57). The availability of tests does not necessarily imply that they are widely used in medical practice.

Nevertheless, the NIH-funded genetic information internet platform "genetests" currently lists tests for more than 1200 diseases that are used in clinical practice and another several hundred that are applied in research (www.genetests.org, as accessed Feb. 14, 2008).

Testing and counselling for relatively rare monogenetic hereditary diseases still play a major role. This means that relatively small groups of the population affected by these genetic conditions demand for genetic counselling and testing. The most common hereditary disease among the population of European origin is cystic fibrosis, with one person in 3000 affected in the U.S. New tests, however, led nonetheless to a remarkable expansion in the practice of genetic testing and counselling during the 1990s. According to the EC-funded Eurogentest network, 700 000 genetic tests are currently performed in the EU every year in around 1500 laboratories (www.eurogentest.org, Lab Times 2007).

The increased practice of genetic testing in recent years is partly due to the growing number of tests available not only for rare, hereditary, monogenetic diseases but also for diseases or health conditions for which multiple genetic traits are deemed responsible in combination with environmental factors, e.g. cancer, diabetes, and cardiovascular disease. Due to the complex interaction between various genetic and environmental factors, the interpretation of test results is much more difficult here than it is for monogenetic diseases. Whereas in the latter case, the diagnosis can usually definitely exclude or confirm the presence or future onset of a disease for the patient, genetic testing for multifactorial genetic diseases only allow verification of one of the genetic factors, and thus can only indicate an increased (more than average) risk of disease for a person.

Genetic testing is currently undergoing rapid and fundamental changes and is about to become a medical service that is no longer restricted to the traditional context of genetic counselling and prenatal diagnosis. It may well develop from a specialised branch of health care that is mainly offered by university hospitals to small groups of the population to a diagnostic practice relevant to all branches of health care and medical treatment of common diseases, and thus become relevant for everybody. The recently revived debate on genetic testing (originating from the start of the new millennium) is due to some considerable new scientific insights and technological developments that confront patients, doctors and society with options (and hence problems) that were not present in the 1990s and thus may not been covered by the standards, guidelines and legal regulation set up during that period.

Increasing Number of Tests for Susceptibilities for Common Diseases

The 2001 headline event of the total sequencing of the human genome not only brought human genetics (research and practice) onto the public and political agenda but indicated a new push in the development of genetic testing. The total sequencing of a human genome provides a reference that makes it possible to search for statistical associations between genetic variants in a single nucleotide (not in an entire gene) and a certain health condition. With more and more so-called SNPs (single nucleotide polymorphisms, i.e. single allele mutations that occur in people suffering from a disease) being related to the occurrence of diseases, testing for widespread diseases for which genetic factors have been unknown so far injects a new quality into the practice of genetic testing.¹ The identification of SNPs associated with common diseases such as cancer or cardiovascular disease can be regarded as the first important step toward understanding the role of genetic factors involved in the development of these diseases. For the time being, however, genetic testing for such SNPs in most cases can only indicate unspecific susceptibilities for a disease, the practical meaning of which for a person is often doubtful.

Most of the many reports about a "new gene" found for diseases are based on association studies looking for statistical correlations between certain SNPs and the occurrence of a disease in (often small) populations and are thus based on insufficient data. Hence most of these studies could not be replicated by further independent studies with independent general population samples. A study carried out to check 85 gene variants which had been linked to acute coronary syndrome (ACS) in earlier research failed to replicate the clinical validity of any of the 85 variants; nevertheless, six of the variants are offered as clinical tests to assess the risk of cardiovascular disease (Morgan et al. 2007; acc. to Hogarth and Melzer 2007, 5). Apart from bad science underlying some of the reports on genetic associations, it has to be noted that those associations that proved to be replicable are mostly responsible only for small increases in the risk of developing a disease.

At least in the general public - partly due to premature reports on a "new gene found" promoted by scientists - there is a tendency to seriously overestimate the predictive power of genetic testing. The discovery of a gene variant associated with obesity has been publicly hyped as the discovery of the "fat gene", insinuating that the genetic variant found was - if not the only - the most important determinant for obesity. In fact, the study could only show that patients carrying two copies of the gene variant weighed about 3 kilos more than the average population and that they only had a 1.67-fold increased chance of obesity (Frayling et al. 2007, Hogarth and Melzer 2007, 5). Specifically, new sequencing technologies - DNA chips which allow parallel identification of 500 000 markers (see below) - have led to a rapid increase in the detection of SNPs. Due to the complexity of the aetiology of common diseases such as cancer, experts, however, assume it will still be a long time until the relevance of SNPs is clarified.

¹ At the same time, in a survey on genetic testing services in Europe, indicators were found that the supply of genetic testing for rare (hereditary) diseases is still insufficient in some countries due to the complexity of laboratory work that is needed for proper testing (Ibaretta et al. 2004, 1231)

Doubtful Clinical Validity of Susceptibility Testing

The detection of more SNP markers will without a doubt lead to knowledge about a growing number of risk factors for many diseases that are found in the genome of patients with particular symptoms more often than in healthy patients. Even a statistically significant correlation, however, does not necessarily indicate clinically relevant risk. Most of the "risk factors" identified do not have any influence on the risk of the same syndrome occurring in first-degree relatives ("Wiederholungsrisiko"). The validity and usefulness of genetic testing based on SNPs must currently be regarded to be low (Ropers, Ullmann 2007, 21, 29). With the growing number of tests available for susceptibilities that indicate a certain risk or increased risk for the onset of a disease in future life, it is becoming crucial that we deal with the general problem of probabilistic genetic testing in order to ensure quality assurance of genetic counselling.

What do risk factors mean for the patient or client? The problem behind testing for risk factors can be made evident from the well-established practice of prenatal diagnosis: A 40-year-old woman has a 30 times higher risk of giving birth to a child with a genetically caused disorder or disease than has a woman aged 20. This, however, does not mean anything without knowing the average general risk of a genetic disorder at birth, which is around 3%: In 3% of all children born there is a genetic disorder, some of which are harmless, and some can be easily cured. The risk for a 40-year-old woman compared to that number then is 4% (Lab Times 2007).

In expert communities the problem of evaluating the clinical validity (accuracy of detection or prediction of a phenotype, clinical disease or predisposition to disease) and the clinical utility (likelihood of improved outcome from use of the test) of predictive genetic tests is considered serious. At an EC conference on genetic testing, Segolène Ayme (previous Chair of the Professional and Public Policy Committee of the European Society of Human Genetics) demanded the establishment of an independent European agency to evaluate technology in health care by examining and approving genetic tests before they are accepted for public use. Currently, many tests for common polygenetic diseases have no clinical value for the patient (EC 2004, conference on May 6/7, 2007).

An international expert workshop, organised by the OECD, about evaluating the clinical validity and utility of genetic tests identified a profound "lack of evidence and data for clinical validity and clinical utility" which is due to "limited information on clinical outcomes of testing" (Kroese et al. 2007, 33). Problems include the facts that not all genetic variants are known and that the prevalence of variants differs depending on the population tested. Also standard definitions of phenotypic features of the diseases tested are missing, and often there is no information about possible false-positive or false-negative test results. The problems are illustrated by a statement on the clinical validity of currently widely applied BRCA testing for a predisposition to develop mammalian cancer: "Genetic heterogeneity and genotype/phenotype correlation are key characteristics for any genetic test, as they will directly influence clinical validity. There are no studies that have been developed specifically to assess the clinical validity of BRCA testing and, as a result, epidemiologic quality requirements are rarely met. For the hereditary breast and ovarian cancer syndrome, there is no consensus on a phenotypic definition which could serve as reference or gold-standard to assess clinical validity. Failure in study designs to include controls means clinical specificity (i.e. avoidance of false positive results) is usually not measured.

A range of different molecular techniques are used for testing and these have evolved over time. The lack of standardised protocols and the variability in selection criteria and testing indications hamper comparisons across studies and prevent pooling of results into summary measures of clinical validity" (Blancquaert, in: Kroese et al. 2007, 24)

Reduced Costs and New Technical Options (DNA Chips)

Genetic testing for both research and health care purposes has been a time-consuming procedure which requires specific laboratory equipment and specialised personnel. This long functioned as a barrier to further expansion of testing practice outside specialist laboratories and university institutes. Genetic testing for rare hereditary diseases was carried out on the basis of "home brew tests" developed by laboratories supplying a testing service, and only few standardised testing kits were available.

This situation has now changed with tests becoming cheaper and much easier to carry out (which often does not mean, however, that the interpretation of results has become easier too). The technical possibilities of sequencing the entire genome have developed such that nowadays the cost of complete sequencing of the non-repetitive parts (i.e. those possibly connected to phenotypic features) of the human genome is in the range of 100 000 €; in comparison, the first genome sequence in 2000 required a budget of 1 billion €. It is expected that delivery of a full sequence of a single human genome will be possible for 1000 € in the near future (Ropers, Ullmann 2007, 27), which would make it affordable for an average Western citizen to have his own individual genome sequenced.

It is currently difficult to assess whether there will be a considerable demand for personal genome sequencing and whether this will have any serious impact on the market for genetic testing. It is, however, noticeable that genetic testing has become cheaper and technically standardised. The costs of a genetic test vary between 200 € and 2000 € (Cassiman 2007). And with the so-called DNA chip, which is already widely used by laboratories, the cost of testing one single genetic variation of SNP may further decrease.

The DNA chip (or DNA microarray) is an easy-to-handle technology for processing DNA samples which may lead to "high-throughput laboratories" for genetic testing (or might even be a suitable tool for doctors to easily check the genetic make-up of their patients). A DNA chip consists of a set of microscopic DNA probes arrayed on a solid surface by covalent attachment to a chemical matrix. With a DNA chip, it is possible to automatically check a specimen (from blood or other cell material) for a series of genetic markers in one sequence of operation. DNA chips are widely used in genome research and for monitoring the effects of medical treatments and diseases on gene expression, but are also available for use in medical laboratories cooperating with medical doctors and medical geneticists and counsellors. Companies such as Affymetrix offer several sets of DNA microarrays that are tailored to a broad scope of research as well as clinical testing purposes (www.affymetrix.com). Microarray providers are focusing on the development of more user-friendly and cheaper technology for a broad range of applications and genes or SNPs (Flanagan 2007).

Emerging New Fields of Application

Pharmacogenetics

One of the most important problems (in medical as well as economic terms) in health care is patients' adverse reactions to drugs. With the emerging new field of pharmacogenetics, it is expected that genetic testing will become an important instrument of clinical and medical practice for solving this problem. Since the different reactions shown by patients to medical drugs are due to variations in their DNA sequence, responsible for the activity of enzymes involved in the uptake of drugs, research on such genetic variants is expected to permit the development of drugs tailored to the needs of specific patient groups or may help vary the dosage of drugs according to the patient's ability to take up the active pharmaceutical component. So far only few pharmacogenetic tests are being used in medical practice, and the clinical validity of some still is in doubt (Kollek et al. 2006, TAB 2004). Although a large number of genes are under discussion as potentially significant for the development of medicines, their clinical importance has as yet only been proven in a few cases. This is due to the fact that the effects and side effects of medicines are not influenced solely by genetic, but rather by other factors.

Nevertheless, in both public and scientific discourse, pharmacogenetics is currently perceived to be one of the most promising perspectives of genetic testing, and pharmacogenetics is a growing research field with specialised journals and industry support. Should research on genetic conditions for the uptake of medical drugs succeed in the future in providing more clinically valid pharmacogenetic testing kits suitable for preventing a significant number of adverse drug reactions, this would clearly open the door for a widespread use of genetic testing in medical practice (even by family doctors).

Nutrigenomics

With new insights into the genetic basis of widespread common diseases, another field of genetic research and genetic testing is emerging. "Nutrigenomics" is the diagnosis of genetically based susceptibilities for developing diet-related diseases (such as cancer, heart diseases or obesity) and research into the development of diets and food tailored to particular genetic dispositions. Under the umbrella of nutrigenomics, recent trends in food industry and food supply converge with genetic diagnostics. The diagnosis of genetic conditions that indicate the need for a particular diet can be connected with the development and marketing of so-called functional foods (Chadwick et al. 2004; Meyer 2003) or dietary supplements containing particular nutrients.

The idea of nutrigenomics is sometimes connected with the objective of tailoring an individual's diet to his or her genetic make-up. The growing number of diseases associated with SNPs (see above) can be used to associate them with particular dietary recommendations. For instance, to date more than 600 genes and DNA regions have been associated with human obesity. However, scientific evidence for the clinical validity of tests supplied as well as of dietary recommendations derived from these for the general population is so far relatively weak. The use of genetic testing for individualised nutrition or lifestyle recommendations is generally regarded as premature and misleading (Wallace 2006; Government Accountability Office 2006, Janssens et al. 2008).

The complex interactions between multiple genetic and non-genetic causes of common diseases often renders the predictive value of genetic profiling for e.g. cardiovascular disease insufficient for lifestyle or nutrition recommendations. The actual difference in disease risk between those designated high or low risk on the basis of the presence or absence of genetic variants statistically associated with a disease may be quite small, so that it can be expected "that both groups do benefit fairly equally from interventions" (Janssens et al. 2008, 593).

Nevertheless food manufacturers such as Nestlé, Kraft and Unilever are investing considerably in nutrigenomics research, and attempts to market tests and related dietary products direct to consumers can be observed (see below). Wallace (2006, 44f.) identified 15 major research projects or research networks with international partnerships currently dealing with "diet and genes".

Public Health Genetics

The new field of "Public Health Genetics" promotes genetic testing as a powerful tool for the prevention of common diseases that should be adopted and supported by public health authorities. With a growing number of genetic tests available, human genetics is expected to develop from a specialist medical field pertaining mainly to those small groups of patients with a risk of developing an inherited (and mainly monogenetic) disease into a significant area of mainstream medicine. Predictive testing for susceptibilities to develop common diseases such as diabetes mellitus and cancer is regarded to have potential importance for public health medicine. This, then, possibly would imply the development of public screening programmes using predictive genetic tests going beyond the scope of currently used programmes for newborn screening. A discussion on "Public Health Genetics" has started in many European Countries.

The expansion of the reach of human genetics is promoted by some human geneticists and public health authority representatives (e.g. the Public Health Genetics Foundation, www.phgfoundation.org, also contributions in Brand et al. 2007). Critics argue that a public, preventive programme making use of predictive testing for population screening is doubtful in many cases with regard to its effectiveness and must be regarded as violating the guiding principle of genetic counselling to date, i.e. a deliberate individual decision to use genetic tests. For N. A. Holtzman, there is no need to expand genetic screening beyond the newborn screening currently used, and, according to Holtzman, the most important role for public health is the regulation of the private genetic testing market (Holtzman 2006, ref. also Schmidtke 2007, van den Daele 2007). Promotion of public health genetic programmes is held to be premature and to overestimate the current clinical relevance of probabilistic testing for susceptibilities; in addition, it distracts the health authorities' awareness away from improving bad environmental conditions as a salient cause of most common diseases. As such, public health genetics were in danger of supporting deterministic views of the relation between genetic status and disease (Holtzman 2006, Henn 2007).

Problems of Quality Control

With the expanding market for genetic testing, there is growing concern about lower quality in testing services. With new private suppliers entering the market and with expanding testing options that open up economically promising testing for widespread common diseases, the "market" might get out of control, and the quality of testing and counselling might no longer be guaranteed. In 2001, the European Parliament's "Temporal Committee on Human Genetics and Other Technologies in Modern Medicine" stated in its report to the Parliament: "... genetic testing procedures are becoming increasingly common, since tests are carried out not only in specialised hospitals, but also in testing laboratories and to some extent are offered directly to patients. In Europe the number of laboratories performing genetic testing services is rising: Although genetics specialists and professional organisations have made many moves to promote quality assessment, genetic testing services are provided under widely varying conditions and systems of rules" (Temporary Committee 2001, 58).

A study coordinated by the European Joint Research Center (Ibaretta et al. 2004) in 2002 identified 751 laboratories providing genetic testing services in 21 European countries (in addition, 936 centres or laboratories were identified that were thought to offer genetic tests, but for these, the information was incomplete). The study found the laboratories' participation in any quality assurance scheme to be insufficient. For around 46% of the 151 laboratories investigated for existing quality control systems, the study found no official quality inspection or control in place. In 27% of laboratories, genetic testing was carried out without participation in any (deliberate) external quality assurance scheme (EQA) (Ibaretta et al. 2004, 1231). The same study found "... that testing for genetic diseases has rapidly moved from the laboratory to the medical practice and, in this process, issues of quality require adequate attention". Although the study found established standards and many examples of good practice all over Europe, there was also clear evidence of deficiencies in the technical quality of testing services as well as in counselling and interpretation of results.

The study found these deficiencies to be partly due to the expansion of testing practice beyond established communities of medical geneticists and genetic counsellors. As a future challenge to quality control, the study mentions reaching "out beyond the 'core' genetics community to related disciplines and laboratories, which are not involved in the existing networks" (Ibaretta et al., 1234). The current development of genetic practice thus gives rise to warnings that with new actors entering the market, the quality control so far provided for by professional and ethical standards - as stipulated in guidelines of professional associations or public authorities (comp. 2.3) - are no longer guiding genetic testing and counselling practice.

2.2 Ethical, Legal and Social Aspects of Genetic Testing

What are the main subjects of discussions on genetic testing? In other words, what are the main problems that are addressed when it comes to evaluating the pros and cons of genetic testing? There is a broad range of literature available on the ethical, social and legal aspects of human genome research and genetic testing (ESLA). Most national and international human genome research programmes are generally accompanied by research on the ethical aspects and possible social consequences of genetic testing (as well as human genetics research in general). The European Union has made a large contribution to promoting such research by reserving funding for social and ethical research in the Research Framework Programmes. Starting from FP3, a standard component of the Framework Programmes has been a programme dedicated to bioethical research. An overview on current research activities in the field of ESLA genomics is available from the ERASAGE consortium (2006, the European Research Area on Societal Aspects of Genomics), to which partners from eleven European countries contribute.

Aside from research activities, many international and national bodies have initiated deliberations and reports on the social implications of genome research and genetic counselling and have developed recommendations for the quality control of applying genetic testing in medical practice as well as for policy measures with respect to regulation and control. The European Parliament set up a "Temporary committee on human genetics and other new technologies in modern medicine" that, in 2001, provided a "Report on the ethical, legal, economic and social implications of human genetics".² In 2004, the report of an independent expert group set up by the European Commission on "Ethical, Legal and Social Aspects of Genetic Testing" was published (McNally et al. 2004a, 2004b). A document that is most likely to gain seminal attention in Europe is the "Additional protocol to the convention on human rights and biomedicine concerning genetic testing for health purposes", recently released by the Parliamentary Assembly of the Council of Europe (COE 2007, 2008).

The ethical, social and legal aspects of genetic testing have been the subject of many technology assessment studies carried out from the early 1990s in many European countries. An overview and synopsis of the issues and findings from 18 technology assessment studies was provided to the Eurogentest Network of Excellence (VIWTA/Eurogentest 2005) by the technology assessment institute of the Flemish Parliament (VIWTA). The Eurogentest network can be regarded as the most outstanding activity of European professionals in genetic counselling and in human genetics research, preparing the ground for a harmonised and high-quality supply of genetic testing in Europe. Work on the ethical and legal aspects is one of the focal activities of the network (www.eurogentest.org).

² The exchange of views on the report did, however, not lead to any decision or a formal common point of view of the European Parliament.

The following pages provide an overview of a set of issues and problems that after more than 15 years of discussion in science, in politics and in the general public can be regarded as forming the core of deliberations on social, legal and ethical aspects of genetic testing. This summary to a great part draws on the findings of the technology assessment synopsis provided by ViWTA and the results of an international workshop that was organised in the course of preparing the synopsis (VIWTA/Eurogentest 2005).

Concerns and demands for regulations on and ethical standards in the provision of genetic testing in general are based on the sensitivity of the personal data and information conveyed by genetic testing.

- Since genetic tests make it possible to predict the future health status of the person undergoing the tests (or of this person's offspring), their outcome can imply a prediction of a harmful fate to the patient or client without any possibility for the individual to obtain medical treatment or an effective therapeutic intervention.
- Information about a person's genetic status can lead to discrimination by excluding the person from particular jobs (for which a particular genetic trait might indicate a risk) or from health insurance (because of foreseeable increased health care costs that might be indicated by a person's genetic status).
- As discussed above, for the genetic testing for common diseases, the way in which a genetic trait contributes to the onset of a disease is complex and widely unknown. What a positive or negative result from a test that indicates a (often only slightly) increased risk of getting a disease means for a person is difficult to assess in terms of clinical validity as well as clinical utility.

These factors may lead to problems for individuals and society at large as well as to questions regarding the need and options for ethical and juridical principles and rules that have to be obeyed in order to guard against the misuse or detrimental practice of genetic testing.

Free Choice and Deliberate Use of Genetic Testing

In a liberal society the fundamental individual rights can be considered to include access to (and make one's own choice with regard to) medical treatment and diagnostics that may be helpful for improving one's health condition or that can help an individual make decisions regarding life style and health. Thus, a person has the right to make use of genetic testing just as of any other medical treatment or procedure. On the other hand, an individual may not be forced to seek genetic testing against his or her will. The principle of free choice and the possibly problematic character of information gained from genetic tests require that genetic testing may not be carried out without a person's explicit consent, i.e. that nobody should undergo a genetic test without his or her knowledge or against his or her explicit will. Whereas this principle in itself appears to be uncontested, it can be impeded by many factors.

An obvious problem exists in case of a person who due to intellectual impairment is unable to make an informed decision as well as in the case of minors. It can also be argued that individual choice is always affected by the social environment or culturally shared values and preferences. In the case of genetic testing, the social environment (family, friends) might, for example, influence a pregnant woman's decision in favour or against a prenatal test to avoid giving birth to a child with a genetic disorder. In the case of prenatal genetic testing, it has often been stated by women's organisations that the widely established practice of testing has now created a social expectation which compels women to undergo prenatal testing (as their "duty as a mother", so to speak). Organised groups of disabled people argue that the choice for or against genetic testing is guided by cultural prejudice regarding views on what is regarded as normal and abnormal. The possibility of tracking the genetic (biological) cause of disabilities might increase the tendency for disabilities not to be regarded as a variant of the human condition but as a disease that "should be avoided", particularly when the socioeconomic costs are taken into account.

The Right to Know and the Right Not to Know

Knowledge about one's own genetic condition must be regarded as an essential individual right, since this knowledge (in the case of predictive genetic testing) can inform important choices with regard to a person's future life. On the other hand, the character of genetic information may in some cases motivate a person to decide not to know about his own genetic condition, in order not to encumber his present life with the burden of the knowledge of the inevitable onset of a severe disease in the future. A right "not to know" is even more important since an individual's knowledge about his own genetic condition (and the possible future state of his health) in many cases implies knowledge about his relatives to be carriers of the very same genetic trait. It is therefore essential for the rights of relatives to be protected against unwilling disclosure of genetic information. In practice this may confront patients and doctors with a dilemma since they know about the genetic condition of relatives, yet do not have the possibility to decide whether these afflicted third persons want to know about the result or, on the contrary, would reject this opportunity to know about their own genetic status.

Informed Consent

Due both to the often complex nature of genetic information and to the serious consequences this might have for a patient, it is decisive for a patient to be able to provide their informed consent. To be able to give this, they need comprehensive and scientifically based information about the meaning and possible consequences of testing results. In order to empower a person to make a deliberate and free choice for or against genetic testing as well as to allow for an informed decision on the consequences to be drawn from the result, the person needs information and possibly psychological support. Consequences may have to be drawn with regard to the client's own life planning, with regard to third parties for which the result might be meaningful as well (right not to know for relatives) or in case of prenatal testing with regard to the continuation or interruption of pregnancy.

The principle of free choice and the frequently ethically sensitive character of the decisions to be made (e.g. in the case of abortion) necessitates that the client make his own decision and not be overruled by his doctor or genetic counsellor. As a result, professional associations have established the principle of non-directive counselling in their guidelines for counselling and genetic testing, which means that the counsellors part is to provide the best available information about the usefulness and possible consequences of a gene test to his patient, but not to lead him to a decision for or against the test, leaving this decision totally up to the patient himself (Council of Europe 2007, Eurogentest 2007). While there are no doubts about this principle, the question has been raised whether it is practicable in the patient-doctor setting where the patient asks for advice) It is well known and often criticised by human geneticists and genetic counsellors that in everyday practice neither proper information that would allow for informed consent nor non-directive counselling is provided for. Whereas most actors consider informed consent and non-directive, unbiased counselling to be a prerequisite for testing, most professionals themselves - as noted at an expert workshop and confirmed in a review of a set of recent technology assessment studies on genetic testing - "consider that even though the regulatory framework for pre-test counselling is available, the concrete implementation of counselling is still confronted with practical difficulties ... in many cases, resources are lacking to offer systematic and comprehensive pre-counselling services" (VIWTA/Eurogentest 2005, 22). Experts express their concern about the fact that a growing number of the tests are being carried out without any counselling at all. For Germany, statistics show that around 40% of such tests were done without genetic counselling at the end of the 1990s (Hennen et al. 2001, 53f.).

Genetic Data and Privacy

Genetic testing produces information and data on the current or future health or (more generally) physical status of a person. This information, like any other medical information, must be protected and not disclosed to other persons. It has, however, been debated whether genetic data are particularly sensitive (since they are predictive) and therefore require special privacy and data protection regulations or whether the principle of confidentiality that currently rules the medical sector is sufficient to prevent the misuse of genetic data.

There is a broad consensus that genetic information may not be revealed to third parties without the explicit consent of the patient. There is, however, constant debate about the use of genetic data for research purposes. Recently, the ongoing construction of biobanks has caused debate on whether these biobanks provide sufficient protection to anonymise the personal data used. Also discussed is whether researchers need the explicit consent of clients or patients to store their data and specimen, or whether the principle of explicit denial by the client would be sufficient with regard to data protection and confidentiality (Revermann/Sauter 2006). Also with respect to the emerging field of testing for genetic variants that are associated with drug metabolism (pharmacogenetics), it has been discussed whether testing can be used to gain knowledge about other genetic traits carried by the patient and whether strict privacy rules should therefore be provided for (Kollek et al. 2006).

Discrimination against Individuals and Groups

A permanent thread in the debate about the particular sensitivity of genetic data is the particular interest that insurance companies and employers might have in obtaining predictive genetic information about employees or about applicants for health or life insurance. Employers – whether to avoid the costs arising from a likely disease or to protect an employee's health – might be interested in knowing about the genetic status and any genetically induced susceptibilities to developing a disease in the future or susceptibilities to react to certain toxicants that the worker might have to deal with in the workplace. There are concerns that employers might use genetic tests, whether clinically valid or not, to select the “best” employees and discriminate against allegedly genetically less fit ones.

Insurance companies are suspected of being interested in genetic data about applicants for insurance in order to exclude so-called “bad risks”, i.e. to exclude carriers of certain genetic variants that imply a higher than average risk of developing a disease, or only to provide insurance at increased rates. Insurance companies in many countries have declared that they are not particularly interested in using these data, and in Europe up to now only a few cases have been documented of insurance companies' and employers' attempts to ask for a genetic profile. Concerns nonetheless remain that, with genetic testing becoming a part of standard health care, employers and insurance companies will make use of genetic data. Insurance companies have also stated that they might need to ask for a genetic profile of applicants in order to protect themselves against counter selection, i.e. customers asking for a high insurance sum because they know about their genetic risk.

The prohibition of the use of genetic data by insurance companies and employers is thus a major issue in debates about legal regulations for genetic testing. The UNESCO (2003) declaration on the protection of genetic data states in Article 14 that data which can be connected to an individual person should not be revealed to employers, insurance companies and educational institutions (or to families) without the explicit consent of the patient. The Austrian law on genetic testing explicitly prohibits the use of genetic data by employers and insurance companies. A similar stipulation can be found in the Council of Europe's draft additional protocol to the Convention on Human Rights and Biomedicine concerning genetic testing for health purposes (COE 2007).

In Germany, insurance companies have declared – for the time being – that they will abstain from asking for genetic testing results. In the U.K. the government and the Association of British Insurers have agreed on a moratorium on insurers' right to use genetic data for contracts until 2011 (Mitra 2006).

Social Stigmatisation

Genetic testing has also been the subject of long-standing debate about the stigmatisation of and discrimination against social groups that differ genetically from the culturally fixed “normal” genetic make-up. Groups of handicapped and disabled people (or their representatives and spokespersons, parents of disabled children) often complain that they feel stigmatised by the fact that genetic testing is used in prenatal diagnosis for the condition they have.

The issue of genetic stigmatisation alludes to the concept of eugenics that was widespread in many Western countries at the end of the nineteenth century and up to the middle of the twentieth century, influencing public health institutions and being used in Nazi Germany to legitimise programmes to systematically annihilate persons with “abnormal” genetic traits. Today, experts in human genetics and genetic counsellors do not regard themselves as pursuing a “public health” programme of improving the genetic pool of the population, as had been claimed by the eugenic movement. The aim of genetic counsellors is to support individuals when making decisions about the state of their own health. In this sense, the principle on non-directive counselling is regarded to be an essential feature that distinguishes current genetic counselling radically from any eugenic programme. It has been argued by some critical observers of current genetic testing practice, however, that a shift in what is now considered to be “normal” and “abnormal” might occur as more and more genetic tests enter medical practice. A “backdoor to eugenics” may be opened by an undercurrent consensus of rejection and stigmatisation of people with certain genetic variants, which for instance would make it culturally unacceptable for parents to decide to give birth to a child that is genetically handicapped following a positive prenatal diagnosis (Duster 1990, Nelkin/Tankredi 1991, Waldschmitt 1996).

2.3 Guidelines for Testing and Counselling

At the European level, there are no binding legal regulations that specifically apply for genetic testing. Nor, as confirmed by a survey conducted by Eurogentest among human genetic societies in 38 European countries, is there any legislation directly related to genetic counselling in the great majority of European countries. Only Austria and Switzerland have a specific genetic testing law dealing with and regulating some of the above-mentioned ethical and legal questions associated with genetic testing. In most countries, however, professional guidelines for genetic testing and counselling do exist. Eurogentest found only six countries with neither legislation nor professional guidelines (Eurogentest 2006; for an overview of guidelines for genetic testing in Europe: Borry et al. 2007).

In the following, we roughly summarize the stipulations found in the most recent documents on legal regulation for genetic testing and services such as the protocol of the COE (2007).

Principle of Non-Discrimination

Discrimination against a person, either as an individual or as a member of a group on grounds of his or her genetic heritage is prohibited, and measures to prevent discrimination or stigmatisation should be ensured. The principle of non-discrimination may be fostered by more concrete measures as e.g. in the Austrian Genetic Diagnostic Act which explicitly prohibits the use of genetic testing by insurance companies and employers.

Quality Assurance of Genetic Testing Services

The quality of genetic testing must be assured by qualified personnel carrying out testing in laboratories. This can be promoted by requiring laboratories to take part in a quality assurance programme or by obligatory accreditation or licensing of laboratories.

Principle of Clinical Validity and Utility of Genetic Testing

The clinical validity and utility of tests is regarded to be a self-evident prerequisite of good practice in genetic testing. How this can be put into practice is subject to discussion. Measures range from laboratories and clinics reporting their data on the clinical validity of tests to obligatory approval of new tests by a public authority before they are marketed.

Health Purposes

With regard to genetic testing carried out for health purposes and tests that have important implications for the person concerned or family members, it is required that the test be performed under individualised medical supervision by a doctor.

This may also include the performance of genetic testing being generally only permissible after referral from and under supervision of a medical doctor. In the Austrian and Swiss Genetic Diagnostic laws, genetic testing is not allowed for any other purposes than medical ones.

Genetic Counselling (Informed Consent)

Genetic counselling by a qualified person is regarded to be obligatory before and after a genetic test is carried out, in particular for predictive testing for a monogenetic disease. It can - as in the Council of Europe's draft protocol - also be regarded as obligatory for tests serving to detect a genetic predisposition or a susceptibility to a disease as well as for carrier testing.

Genetic counselling must be performed in a non-directive manner, providing the best information and knowledge to the client without directing him towards a particular decision.

Informed Consent

A genetic test may only be carried out after an individual has given his or her free and informed consent. The consent has to be documented.

Specific criteria have to be met before a test can be carried out on a person not able to consent, specifically when the test is for his or her direct benefit or (in exceptional situations) when family members might benefit from it. The opinion of minors is given more or less consideration depending on their age.

Privacy and the Right to Information

A person undergoing a genetic test is entitled to know any information collected about his or her health derived from a test. Any data obtained from such a genetic test may not be forwarded to third parties without the explicit allowance of the person concerned. These principles are most frequently relevant with regard to the submission of human DNA samples to Biobanks for research purposes.

Right Not to Know and Information of Relatives

When the result of a genetic test can be relevant to the health of relatives of the person tested, the person tested has to be informed. The right of family members not to know has to be protected. More detailed professional guidelines require in-depth counselling of the person tested on whether and under which conditions to inform relatives about the possible implications of the test for their health (e.g. Eurogentest 2007).

3. DIRECT-TO-CONSUMER GENETIC TESTING (DCGT)

The current testing practice is still dominated by genetic counselling centres situated at universities and a few doctors in private practice specialised in human genetics. No one institute or doctor can offer genetic testing as a laboratory service for all known genetic disorders. Genetic counsellors draw on several laboratories specialised in particular tests to which they send specimen from patients for analysis. The sequencing techniques necessary for tests require certain equipment and, above all, experienced and well qualified staff. Besides professional codes of ethics, the fact that genetic testing requires particular equipment, a trained staff and is time consuming has until now restricted the availability of genetic testing. As has been noted above, some developments indicate that this situation is changing. The classical model of genetic counselling was (and still is) meant to be a particular service for a particular segment of the population to whom diagnostics and advice was supplied with regard to a single genetic condition for which the patient has (due to family history or symptoms) reason to believe he is a carrier. Due to new technical developments it is today at least conceivable that a family doctor could offer routine testing for a series of genetic disorders that are associated with common diseases such as cancer, diabetes and heart disease.

An indication of a change that is probably even more problematic is that start-up firms, doctors and laboratories enter the market offering genetic testing directly to consumers and thus circumventing the established institutional setting of genetic testing. DCGT can be regarded as a phenomenon whose emergence is supported by several of the above-mentioned trends in genetic testing.

- The availability of genetic tests for common diseases and susceptibilities to common diseases opens an economic option for companies developing genetic testing assays or kits as well as for companies offering services on a private basis directly to customers. The market for Mendelian inherited diseases has not been attractive for private companies because of their low prevalence. It still is possible to doubt that there is much money to be earned from DCGT. Yet the perspectives for DCGT at least appear to be attractive enough as a consequence of susceptibility testing for more and more companies to position themselves on the market and explore their economic potential, particularly since more and more gene tests for common diseases are expected to become available in the near future.
- Technical achievements such as the development of DNA microarrays reduce the technical and financial barriers to a private market for genetic testing. Tests can be carried out with little investment in equipment and training of personnel, at a price that makes it attractive for private customers.

- Genetic testing is on its way to becoming an option for preventive medicine in general. It is discussed as a new important public health option, and the perspectives of pharmacogenetics and nutrigenomics make new attractive markets become visible. These perspectives meet with a general trend (both in the public's perception as well as in health care policy making) to give emphasis to individual prevention of disease by living up to certain lifestyle recommendations as well as by making use of diagnostic monitoring of one's health status. It can thus be expected that a bigger part of the general population will be inclined to make use of genetic testing services (even if the costs are not covered by the public health service or by health insurance).

From the first appearance of offers for genetic testing via the internet (in the U.S. and U.K.) some six years ago, DCGT has become the subject of discussion (so far among expert communities and advisory bodies merely) since it appears that with DCGT genetic testing as a health care service may get out of control. In the existing setting of university institutes, public insurance systems, specialised genetic counsellors etc., it appears to be feasible to restrict the application of testing to the "useful", to sort out what is sufficiently clinically valid to be used in medical practice and to provide for a high standard of support and counselling for clients according to established guidelines for good practice (see above). This quality of genetic testing is thought to be endangered when the system is circumvented by DCGT. Concerns are expressed mainly by doctors and experts in human genetics as well as by professional medical bodies and health authorities. Klaus Bartram, Director of the Institute for Human Genetics at the University of Heidelberg and former president of the German Human Genetic Society, said with regard to a growing and uncontrolled market for genetic testing: "We have to prevent the formation of a market of thousands of tests that do not come along with proper interpretation" (Lab-times, 1-2007, p. 16). Bartram: "The market for useless tests is steadily growing and operates according to the mantra: send us some saliva but don't forget the cheque" (p. 15). Whereas clear criticism of the misinformation of customers, and bad quality of testing is uttered, companies offering genetic testing directly to consumers claim to support the consumers' right of free access to new developments in health care as a means of deliberate and self-determined prevention of disease.

The U.K. Human Genetics Commission (2003, 7) defines DCGT as "...any test to detect differences in DNA, genes or a chromosome that is not provided as part of a medical consultation." This includes any genetic test available to the public outside the usual medical control system. The Belgian Advisory Committee for Bio-Ethics uses the term "home-sampling test". A sample of the material to be tested is taken at home and sent to a laboratory for analysis. The results from the laboratory tests are communicated to the user by telephone, mail, e-mail or secured internet access. The definition includes a broad spectrum of tests, from ancestry testing, paternity determination and prenatal sex determination to heritable breast cancer testing.

In the present report as well as in most of the documents dealing with DCGT, the term "direct-to-consumer genetic testing" is used for testing services offered for health-related genetic variants and polymorphisms. This includes offers for so-called lifestyle-related genetic testing that provides recommendations regarding diet or everyday life (sports etc.). Consumers are the target of a growing number of offers on the internet for paternity testing and for ancestry testing. Paternity testing is associated with serious problems for privacy and data protection. In most European countries, such tests are not legal without the explicit consent of the child and the mother concerned or the explicit request of a court. Paternal and ancestry testing do, however, not address health-related questions or involve problems of interpreting results and consulting (since the "genetic fingerprinting" process applied for paternity testing is based on non-coding traits of the genome, which do not – at least to our current knowledge – imply information about the health status of a person). Paternity testing thus has to be regarded as a special field of genetic testing and is usually not explicitly dealt with in debates about DCGT (e.g. HGC 2003, 51).

It is in fact the health-related purpose of the test and the fact the test is supplied outside of the established system of health services (without costs being covered by a public health service or by health insurance, the referral by a doctor, or the consultation of a medical genetics expert) that give reason to discuss DCGT in the context of the probable detrimental effects on consumers and of a possible need for new or additional regulatory arrangements.

With regard to health-related DCGT, there are mainly two ways of providing genetic testing to customers which are conceivable or can be found in practice and are thus discussed in literature: advertising gene tests to the public and direct sale to consumers.

3.1 Advertising Genetic Testing Directly to the Public

The standard means to forward genetic testing to customers is for customers to purchase them at their own initiative. Furthermore, advertising directed at customers is a means to gain the attention and interest of a potential customer and thus to increase the rate at which a test is purchased. It is common practice for new diagnostics (such as genetic tests) to be advertised in medical journals by companies producing such tests or by laboratories offering diagnostic services to medical doctors. It is, however, new for genetic testing that can be accessed via medical practitioners to be advertised directly to the public. A case in point here is an advertising campaign started by the American genomics company Myriad Genetics in 2002. Myriad launched a pilot campaign in two cities for its BRCA test predicting predispositions for hereditary breast and ovarian cancer. The aim of the campaign (via printed media, TV and radio) was to make women aware of this new option for preventing cancer and to motivate them to ask their doctors for referral for a test. Studies carried out on the effect of this campaign indicate that it led to an increased awareness of the test among doctors as well as patients. An increased referral rate for genetic counselling and testing services among women with relatively low risk (no family history of breast cancer) was reported (Mouchawar 2005, Williams-Jones 2006). A second advertising campaign was launched by Myriad in 2007, which announced a toll-free number that women could call in order to obtain information about whether or not they should have a breast cancer predisposition test (personal information from Stuart Hogarth).

The literature cites other examples for propagating and advertising DCGT. The British Human Genetics Commission reports that Great Smokies Diagnostic Laboratories in the U.S offered training courses in genetic testing for health practitioners and used these courses to market their genetic testing products to support their advertising of genetic testing to patients via the internet (HGC 2003, 17). Sciona Ltd. and Great Smokies Laboratories launched an advertisement campaign for a variety of nutritional and health-related genetic tests. In the UK, University Diagnostics Ltd. launched a commercial campaign for a cystic fibrosis test (Williams-Jones 2006).

The problems associated with advertising medical products directly to the general public have been discussed for many years. Direct advertisements for prescription pharmaceuticals are not allowed in Europe, while they are in the US. Advertising for prescription drugs is critically discussed by consumer organisations, because it may push the demand for drugs from lay people.

Most lay people do not have the knowledge required to understand the clinical validity and utility of pharmaceuticals offered. Advertising for genetic testing directed to consumers can be regarded as a new (and in some respects) specific variant of the general problem of advertising for pharmaceuticals.³ Advertising for genetic testing on TV, in print, on the radio or via the internet is criticized for providing simplistic explanations of genetics and exploiting existing anxieties and widespread misinformation about genetic determinism that can make lay people demand genetic testing from their physicians. In the case of Myriad Genetics' campaign, it was shown that the information given to consumers was seriously biased by - on the one hand - overestimating the risk of getting breast cancer and - on the other hand - giving incomplete information about the meaning of test results: "Myriads advertising acknowledges that only 5-10% of breast cancers will be hereditary but what is not mentioned is that the BRCA test will, ..., detect positive mutations in only 17-25% of patients with a strong family history (i.e., early age of onset, multiple affected family members, multiple cancers, etc.). Despite being an accurate test, it will still not provide any useful information for 75-83% of women with strong family histories - the heritable component of their cancer risk remains unknown and they continue to be at high risk. Further, given Myriads less stringent access criteria - one affected relative, which does not constitute a strong family history - most people purchasing testing will be found not to carry a mutation, which would have been predicted by the person's lack of significant family history." (Williams-Jones 2006, 95)

3.1 Direct-to-Consumer Sales of Genetic Testing

A laboratory developing and selling genetic testing devices normally uses several channels to market its products. The test provider Sciona markets its test kits via direct sales agents, health care practitioners, pharmacies and the internet (Statement of Sciona, US Senate 2006). The possibility of directly contacting consumers opened up by the internet has obviously given a particular impetus to DCGT.

³ Since genetic testing is not a prescription drug, advertising direct to consumers is not legally banned.

Marketing genetic testing directly to consumers can be organised by over-the-counter sales in pharmacies or drugstores. In fact, one of the first documented cases of DCGT was the case of Sciona Ltd contacting the Genetic Services Subgroup of the British Human Genetics Commission (HGC) because the company intended to market a service called "You and your Genes" via internet and via the cosmetics retailer "Body Shop"⁴. The genetic testing offered was for natural variations in genes that are linked to the way vitamins are absorbed and harmful components of diet processed in the body. Despite the fact that the genes for which testing was offered have long been known and there was a consensus among experts that the genes play an important role in the metabolism, the Subgroup of the HGC concluded "... that there was not yet sufficient understanding of the interactions between genetic, diet and lifestyle factors in determining future health". The Subgroup stated that testing for these genes was not appropriate to be offered directly to consumers (HGC 2003, 18). Sciona has now abandoned business in the U.K. and moved to the U.S. (US Senate 2006). The possibility of purchasing tests over the counter in pharmacies has been discussed as a possible option of DCGT that should be taken into account for further observation by the Human Genetics Commission. The fact that in a country like the United Kingdom about 6 million customers visit a pharmacy every day indicates that it could be an interesting business model for commercial offers of genetic testing.

The main channel for DCGT - and obviously the one regarded as most promising by providers of gene tests and related services - is the internet. One way of providing genetic testing via the internet is sketched in the following description of an offer for direct genetic testing of predisposition to breast cancer (BRCA1 and BRCA2 gene mutation) from the company DNA-Direct:

"At www.dnadirect.com consumers interested in BRCA testing complete a short online questionnaire that elicits their personal and family medical history and information about their ethnic background; the sites algorithm uses this information to recommend a specific test. After paying with a credit card (DNA direct does not accept health insurance) and speaking with a counsellor on the telephone, customers receive a requisition signed by the company's medical director and a test kit to take to a phlebotomist, who will draw their blood and send it to Myriad Genetics, the only U.S. company currently performing commercial BRCA testing. Results are provided to DNA Direct, which makes them available to the customer through a secure log-in on the Web site." (Wolfberg 2006)

⁴ "The Body Shop International plc. is a global manufacturer and retailer of naturally inspired, ethically produced beauty and cosmetics products. Founded in the UK in 1976 by Dame Anita Roddick, we now have over 2,100 stores in 55 countries, with a range of over 1,200 products, all animal cruelty free, and many with fairly traded natural ingredients." (drawn from the webpage: www.bodyshop.com)

In the example given above, the testing procedure involves some form of counselling and the service of a specialist for obtaining the blood sample. In many other cases, the procedure often totally excludes direct intervention by a specialist or medical doctor. In such cases, a kit is sent to the consumer who collects a specimen himself (normally via cheek swab). The specimen is sent back to the supplier, who usually runs laboratory facilities or cooperates with specialised laboratories where the swabs are sent for analysis. The test result then is conveyed to the customer via a log-in at the website or directly via mail.

The central difference to the standard genetic testing situation in the context of the established system of genetic counselling is the way informational support is (or rather is not) provided in offers of testing via the internet. It may well be that there is no provision for counselling at all except the written advice on the webpage. Counselling may be offered as an additional special service at extra costs and at the customer's request. It may be - as in the example above - that a recommendation or at least an offer is given that the customer contacts a doctor or health practitioner from the company via phone for counselling. In other cases, the customer may be recommended to consult his own doctor on the test results. In the case of an internet offer on nutrigenomic testing with dietary recommendations that was offered by Sciona Ltd. in the US the entire process apparently follows a standardised non-personal web-exchange procedure. Even the report containing the results of the diagnosis and their interpretation as well as recommendations to the client is produced by a software system (a so-called "rules engine") that automatically combines information from the DNA diagnosis with information read from a questionnaire on the customers lifestyle (US Senate 2006).

One form of supplying DCGT that is under discussion as being particularly problematic is the supply of complete self-testing kits that allow the customer to directly read the positive or negative result of the test from the kit at home, comparable to a common pregnancy testing kit. As the U.K. Human Genetics Commission reports, this kind of consumer "do-it-yourself" genetic testing is at least being discussed by some as a viable and appropriate option for lifestyle and other less serious conditions or for some pharmacogenetic tests. It is argued that it might be sufficient in these cases to provide written advice or offer contact via a telephone hotline (HGC 2003, 43).

4. THE MARKET FOR DCGT

The possibility of commercialising genetic testing and counselling as an increasing number of tests become available for common diseases was already the object of discussion and concern in the 1990s. It was probably in 1997 that DCGT became the object of a public advisory body for the first time. In 1997 in the U.K., a "Code of Practice and Guidance on Human Genetic Testing Services Supplied Directly to the Public" was published by the Advisory Committee on Genetic Testing (ACGT 1997), a public non-governmental advisory board, whose tasks were later taken over by the current Human Genetics Commission. The Code of Practice was induced by services offered for cystic fibrosis carrier testing direct to consumers.

During the following years, only individual cases of DCGT were reported from the U.S. In Europe, only a few activities on the part of laboratories and biomedical companies to explore the market opportunities of commercially offering genetic testing had been observed (Hennen et. al 2001, 60) when in 2001/2002 the (above-mentioned) testing offer for diet and lifestyle related genetic traits by Sciona Ltd. prompted the Human Genetics Commission in the U.K. to set up a working group on the issue and publish a report in 2003 (HGC 2003). It appears that in the following years, there has been rapid growth in DCGT offers via the internet. In the U.S., the growing number of DCGT offers and concerns about their doubtful clinical validity and about the quality of counselling services urged the Senate Special Committee on Aging to hold a hearing on "At Home DNA tests: Marketing Scam or medical Breakthrough" (US Senate 2006). In 2007, in the context of the preparation of an additional protocol on genetic testing for the Bioethics Convention, the Council of Europe supported an expert seminar on DCGT held in Paris (COE 2007a, 2007b). The HGC continuously observed the development of the market for DCGT and published a follow-up report on DCGT in 2007. In the foreword of this report, the HGC states:

"Almost every time the HGC meets, we hear about a new test becoming available and, simultaneously, about concerns regarding the test's efficacy, utility or its implications for individuals and their families. It is not yet possible to say whether we are on the verge of an explosion in direct-to-public genetic testing or whether we should expect merely a steady increase. [...] In particular, we are now seeing a burgeoning cottage industry in so-called 'lifestyle' tests together with the regimens, dietary supplements and self-administered medications that they are claimed to indicate." (HGC 2007, 3)

4.1 Supply - DCGT Offers via the Internet

It is obviously difficult to provide a complete overview of genetic testing offers currently available on the internet. In a systematic scan of English-language DCGT sites on the internet; we identified 38 companies active in offering DCGT (see section 5 and Annex 1). This is more or less in line with the findings of the UK Human Genetics Commission (HGC 2007, 31f.) and a list recently published by Hogarth et al. (2007).

Some of the web pages offering genetic testing are owned by large, established laboratories or pharmaceutical companies that provide genetic testing as one of their services (as far as this can be deduced from the web pages). There are also companies obviously founded for the purpose of selling one or a set of genetic testing services to consumers. These either market their own test kits or cooperate with laboratories for the technical part of testing. Many of the companies offering DCGT present evidence on their web page of a professional background and expertise in genetic testing. Some recommend consultation of a doctor before testing, others provide ample written information about the scientific and medical background of particular testing offers.

Overviews of offers of DCGT on the internet (HGC 2003) have shown that the range almost covers the entire set of currently available gene tests. A few (often those from established laboratories) focus on well-known genetic disorders or testing for predispositions towards hereditary diseases such as carrier tests for cystic fibrosis, BRCA hereditary breast and ovarian cancer predisposition, haemochromatosis, glaucoma and others (e.g. Medi-checks). Some offer pharmacogenetic testing, such as asthma drug response (Consumer Genetics, Mygenome.com), or an entire test system for several SNPs associated with metabolism of drugs ("drug response panel", DNA-Direct). The majority of the offers comprise testing for susceptibilities to common diseases (cancer, diabetes, Alzheimer) and for so-called lifestyle or diet-related (nutrigenomic) purposes.

DCGT for so-called "lifestyle"-related genetic traits are based on SNPs for which a statistical correlation is associated with a more than average risk of developing common diseases such as high blood pressure, diabetes, or obesity. Depending on the test result, the company gives recommendations on how the client may reduce his/her risk by changes in lifestyle, such as dietary habits or sports. Companies offering this kind of testing usually (rightly) state on their websites, that their products would not test for disease or predisposition towards disease. The scope of offers includes athletic performance (Cygene Direct), alcohol and caffeine metabolism (Consumer Genetics), lipid and glucose metabolism (Genetic Health) and others. Tests for nutrigenomic or lifestyle testing is often connected with offers for purchasing particular dietary supplements that are recommended and (allegedly) tailored to the individual needs of the customer depending on test results (Salugen, Sciona, Holistic Heal).

A new trend is marked by recently founded companies ("deCodeMe, "23andMe", Navigenics, SeqWright) offering a general check of an individual's genome for all SNP gene variants that have been associated with any phenotypic features including increased or decreased risk of disease. A further step would be the total sequencing of an individual human genome, which would then convey information on any known genetic trait. Such an offer is made by GATC and Knome, but because of the high price (of 300.000 US\$) these offers are directed towards scientific institutions at the moment. How this information would be forwarded to an individual customer and with what kind of counselling is unclear. At present, apart from a set of specific susceptibility tests, the aforementioned suppliers offer an all-inclusive test for known genetic variants associated with susceptibilities for disease or behavioural traits and abilities (sports, intelligence). 23andMe and DeCodeMe offer regular updates of this information as research on the human genome proceeds. DeCodeMe offers to "scan over one million variants in your genome "with regular updates for new gene variants discovered, a "calculation of the risk for 26 diseases and traits" plus ancestor testing. The entire service costs \$985. In September 2008, 23andMe reduced its price for the genome-wide SNP scan from 1.000 US\$ to 400 US\$. Due to the poor evidence for the clinical validity of testing for most SNPs and owing to the complex and thus meaningless information forwarded to the customer, experts regard this service as useless for lay people. Nothing is known about the acceptance of this service so far, and it remains an open question whether this kind of offer will really be able to create an economically interesting market.

It is not impossible that we will be confronted with a completely new concept of genetic testing in general in the future, which is promoted with special emphasis by 23andMe. Genetic testing has been offered by 23andMe as a kind of "lifestyle" activity for people sharing and comparing their genetic make-up online or even at gene-test parties ("spit parties") in order to build communities according to their genetic particularities (Salkin 2008). If this kind of service is accepted by a relevant number of persons, including the voluntary posting of their genetic data in "genomic social network rooms" on the internet, then the hitherto ethical and legal considerations will be completely overrun. Taking into account the kind of personal information people are nowadays willing to present publicly on the web, the vision of every one's genome in a giant database still seems futuristic, but no longer phantasmagorical.

4.2 Demand - Public Attitude towards DCGT

Little is known about the public demand for genetic testing. In some general surveys (Hennen et al. 1996, Eurobarometer 2006) it appeared that the general public's knowledge about genetics in general and genetic testing in particular is quite limited, but despite (or perhaps due to) that lack of knowledge there is a tendency to easily accept genetic testing services since they appear to offer medical help for serious diseases. In an opinion poll and focus groups on genetic testing, the British Human Genetics Commission (HGC) found little awareness or interest in DCGT. Sixty percent of respondents in the UK-wide representative survey said they were "unlikely" or "very unlikely" to use "home genetic testing" whereas 81% were open to testing if it is offered by their doctor. The HGC took into consideration that this widespread reluctance toward using home test kits could dramatically decrease once tests were freely available on the market, as was the case with pregnancy home-test-kits (HGC 2003, p 19).

A study published by Goddard et al. in 2007 on consumers' and physicians' awareness of testing available for detecting genetic variants associated with physical digestion (nutrigenomics) in the U.S. found that 14% of the lay people answered that they had heard of such testing possibilities. Awareness of nutrigenomic testing among physicians (according to their answers) was 44%, and 11% of the physicians responded that they have been approached by patients asking about nutrigenomic testing. This might be remarkable as testing is a rather new option at the market. The results, however, do not give the impression that new forms of genetic testing (mainly offered or advertised by private companies) are already a major success. People still do not appear to be very aware of genetic testing for the average population (i.e., are not aware of carrying a particular genetic risk on the basis of family history). On the other hand, even taking into account that a large portion of the 14% claiming awareness of nutrigenomics may have given false answers (not willing to show their "lack of knowledge"), the fact that Goddard et al. found more young, well-educated and affluent persons among the 14% indicates that nutrigenomics might be attractive at least to a lifestyle oriented segment of the population. The success of the advertising campaign initiated by Myriad Genetics also shows that advertising might well easily lead to a shift in attitudes by appealing to widely shared anxieties about common diseases (like cancer).

There is no information available about sales rates of existing DCGT suppliers. According to the U.S. Government Accounting Office, a company in the U.S. in 2006 estimated that it has sold over 35 000 nutrigenomic tests to consumers after starting business in 2003 (GAO 2006, 2). Experts and practitioners in genetic testing and counselling, however, support the notion that DCGT is still a niche market. Some nevertheless report about patients asking for their advice concerning offers of genetic testing they have seen on the internet. The development of the market will depend on the general public's awareness of genetic testing available for common diseases. This awareness might increase from continuing media reports on new tests becoming available. These reports, just as advertising campaigns, normally do not care much about the details of the scientific discussion of the clinical validity and usefulness of particular testing options. Together with the increasing salience of "prevention" in public health systems this might push the demand for DCGT.

The decrease in costs for genetic testing could be an additional factor accounting for rising demand. Costs for genetic testing vary greatly depending on the gene variant tested. A study on nutrigenomic testing offered by four suppliers via the internet in the U.S. found that costs for testing range between \$89 and \$395 (GAO 2006, 2).

Some experts also see the future development of the DCGT market as dependent on the ability of policy makers and the public health care systems to convince the public that they will get what they need (in terms of genetic counselling and tests) from the publicly funded health care systems, and that options not covered by the public health care system are lacking in clinical usefulness.

A particular motivation to purchase DCGT – one that is often also portrayed by suppliers of DCGT, e.g. in the U.S. Senate hearing on DCGT (US Senate 2006) - is circumvention of the public health care system. Customers might fear having the results of testing on their personal health records, which might open up the option for third parties (insurances, employers) to get access to these data. This is supported by the observation of the U.K. Human Genetics Commission “ ... that one important reason why people would access direct genetic testing services was to ensure that the results were not present on their GP records and therefore not likely to be disclosed by the GP in preparing a health report for insurers and employers” (HGC 2003, 35)

5. ASSESSMENT OF WEBSITES OF COMPANIES OFFERING DCGT

A systematic scan of the internet was carried out in order to gain a deeper insight into the scope and quality of DCGT offers that are easily accessible for consumers. The focus was on companies offering DCGT for health purposes and for purposes linked to diet and lifestyle. Companies exclusively performing paternity and ancestry testing were not included, since the related issues and concerns are different.

Selection of Websites

The scan started from available listings of DCGT web pages (Hogarth et al 2007) which were used as reference to check comprehensiveness. A Google search was conducted using the key words "home test" + "genetic", "nutrigenetics", "genetic test" + "diet", "personalized nutrition" + "genetic", "genetic test" + "cancer". An initial list of 49 firms resulted, which was reduced to 38 (Table 1) according to our criteria for exclusion. As we were mainly interested in what kind of offers the end-consumer can access directly on the internet, we also ruled out firms which just advertised but did not sell directly to the consumer (which is the business model used e.g. by Myriad; see section 3.1).

We assume these 38 websites to be a representative sample of websites that the consumer would find on the internet when he/she is searching genetic tests for health- or diet-related purposes that can be ordered without contacting any medical personnel.

Carrying Out the Survey

The 38 websites were checked in the period between 15/06/08 and 15/07/08, following the assessment form documented as Annex 1. The goal of the survey was to collect some general company data, to check the type of offers and the testing procedure, and to assess the quality of information available on the websites. The results were discussed at an experts' workshop on September 22, 2008.

5.1 Companies and Tests Offered

Company Characteristics

Of the 38 firms, 32 are located in the USA, three in the UK and one each in Germany, in Iceland, and in the United Arab Emirates (Table 1). The dominance of US-based firms probably reflects the actual situation, but due to the restriction on English-language offers, websites offered solely in other languages were not accessed in any case. So the results of the survey cannot be regarded as being comprehensive on a global scale, but since the companies often have international markets and due to the technological leadership and the specific openness of the US scientific and economic system versus novel biomedical applications and enterprises, one can assume that the results show at least relevant trends and thus give important hints at recent developments.

Table 1: DCGT companies evaluated in the period 15/06/08 until 15/07/08 (if based outside the USA, country given in parentheses)

Company
23and Me
Acu-Gen Biolab Inc (BabyGenderMentor)
Carolyn Katzin's The DNA Diet
Consumer Genetics
Cygene Direct
deCODE (Iceland)
DNADirect
DNAPrint genomics
Eastern Biotech and Lifesciences (UAE)
GATC (Germany)
Genelex
Genova Diagnostics
G-nostics
GeneLink Biosciences/ Dermagenetics
Genetic Health UK (UK)
Graceful Earth
HairDX
HealthCheckUSA
Health Tests Direct
HIVGene
Holistic Health
Interleukin Genetics /Alticor /Quixtar
Kimball Genetics
Knome
Molecular Diagnostics Laboratories
Medi-Checks (UK)
Mygenome
Navigenics
NeuroMark
Proactive Genomics
Psynomics
Salugen
Sciona/Mycellf
SeqWright
HIVMirror/ Smart Genetics
Smart Genetics /ALZ Mirror
Suracell
SureGene

For 14 of the companies, offering DCGT is the only field of activity. For the other 24 companies, offering DCGT is just one of several different services. Their other activities cover research in the field of human genetics, the performance of non-genetic tests, or the offer of dietary supplements. Further activities (narrowly connected with DCGT) are the offering of genome-related social networking, diet advice, different services for industry and academia. In some cases, there is a link to health and wellness institutions.

Nearly half of the companies (17 of 38) carry out the laboratory work themselves, while one-third of them explicitly outsource the laboratory work. The remaining 20% of companies do not offer unambiguous information on this topic.

Type of Genetic Tests Offered

According to the categories of the assessment form used, the number of companies offering the different kind of tests are shown in Figure 1 (see Annex 2 for a complete list). Half of the firms offer testing for genetic variants (SNPs) for susceptibilities for multifactorial diseases (cancer, cardiovascular disease, diabetes, neurological disorders and others), while only 20% (8 companies) test for monogenetic Mendelian diseases (for example cystic fibrosis), and only one company tests for the fatal late-onset disease Chorea Huntington (Medi-Checks).

Twelve companies each explicitly offer pharmacogenetic testing (specific response to medical treatment) and "nutrigenetic" testing (SNP testing on "risk factors" for genetic factors related to personal diet).

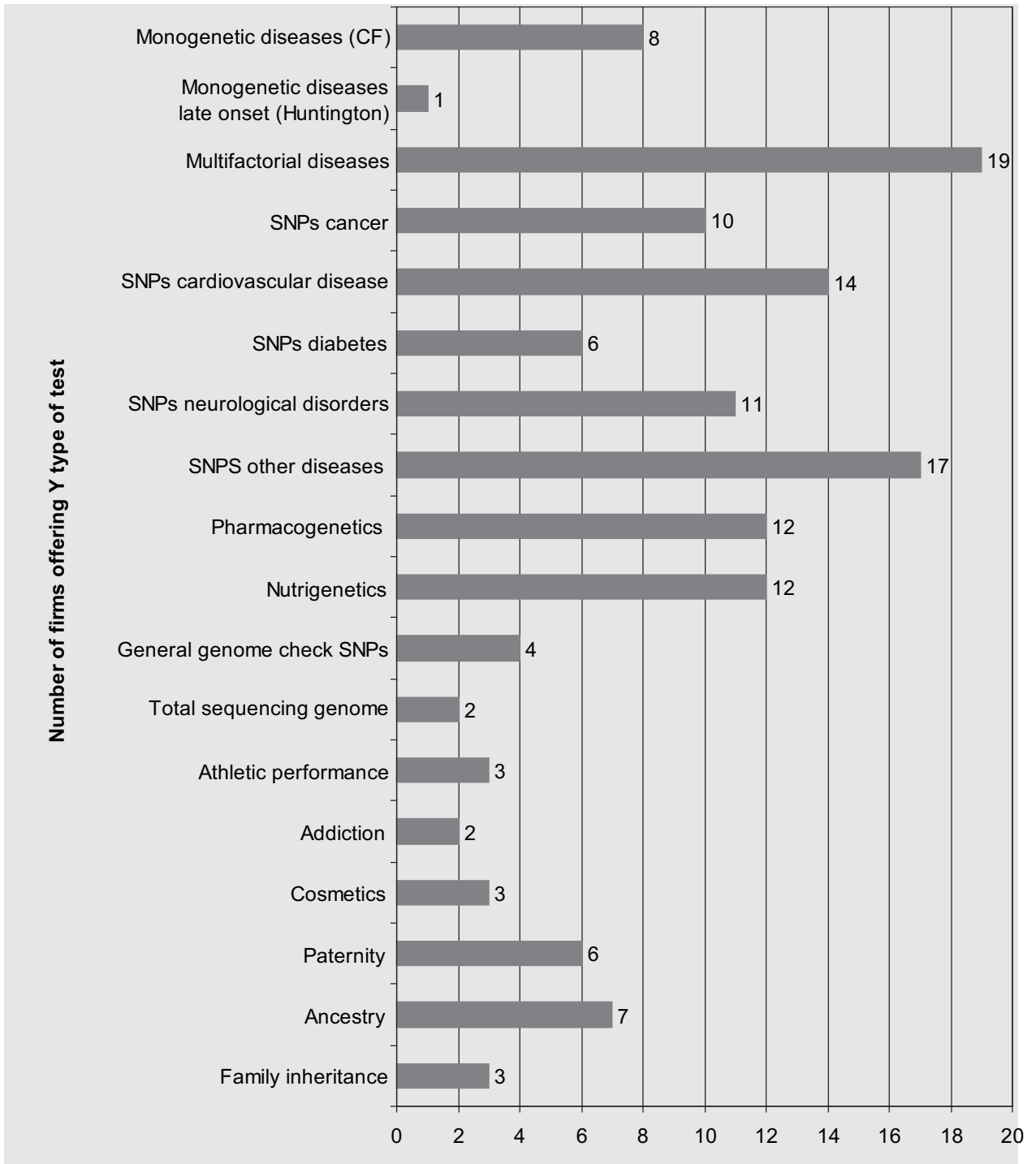
A "complete" check of all currently known SNPs was offered by four companies (23andMe, deCODE, Navigenics and SeqWright), while a total sequencing of the genome can be performed by GATC and Knome. Because of the high price (see below), these offers are aimed towards scientific institutions at the moment. But this is expected to change as soon as the announced \$1.000 or at least the \$5.000 genome (Hayden 2008) shows up.

Several companies offer genetic testing for other features, some of them only related in very general sense to medical aspects, such as genetic factors related to addiction (23andMe and G-nostics), athletic performance (23andMe, CygeneDirect and Sciona), or cosmetics (Genelink Biosciences, Hair DX, Suracell).

Non-health-related paternity and ancestry testing is offered by six and seven companies, respectively, in three cases in the broader context of "family inheritance" (23andMe, Eastern Biotech and Lifesciences, SeqWright), which aims to discover inheritance patterns and relations between relatives without a specific question or goal.

Other individual types of offers are tests for sex testing of fetuses (Acu-Gen Biolab), infertility testing (DNA Direct), premarital screening (Eastern Biotech and Lifesciences), or tests for mutations influencing HIV resistance (HIVGene and HIV Mirror).

Figure 1: Types of tests offered



Testing Procedure and Role of Health Care Professionals

Most of the companies (34 or 86%) offer a test kit for home use with the DNA probe (cheek swab or saliva/blood) to be sent to the provider for analysis. A total of 33% of the companies offer test kits to be used under the supervision of a doctor. Of these twelve companies, seven advise the patient to consult his/her doctor, and five advise the patient to contact the company's doctor.

Patients' doctor	Company's doctor
Consumer Genetics	DNADirect
Genova Diagnostics	Genetic Health UK
Kimball Genetics	Health Test Direct
Molecular Diagnostics Laboratories	Knome
NeuroMark	Suracell
Psynomics	
SureGene	

Results are never obtained directly at home. They are submitted to the client by letter (33%), on line/by e-mail (76%), by telephone (12%) and/or to the doctor stated (19%).

There is a wide variation in the mandatory or suggested consultation of health care professionals:

- In most cases, the results are submitted to the client without any option of consulting an expert⁵ (41%). Some companies, such as Health Check USA, urge the consumer to discuss the result with his/her physician.
- 27% of the companies submit the results to the client with the option of consulting an expert.
- 19% of the companies submit the results to the client with consultation as a mandatory part of the process. For the company Psynomics for example, which is specialised in testing for neurological and related disorders, the consumer needs to provide the licensing number of his/her psychiatrist, since the result must be interpreted by a psychiatrist. For the company Kimball Genetics "you need to provide your physician's details, NY residents need a signed authorisation form".
- For the other 14 % of the companies, the website gives no clear information on whether the submission of results is connected with consultation of an expert.

⁵ An expert is interpreted as a health care professional and not necessarily as a genetic counsellor.

Some companies have different procedures, depending on the residence of the consumer (in relation to state-specific regulations) or depending on the type of test (in relation to the gravity of the disease to be tested for). The company Consumer Genetics for example submits the results to the client without the option of consulting an expert, except for NY and CA residents, who need a prescription from a medical doctor.

On the UK website of the company Genova Diagnostics, the following information is provided: "The majority of our test kits can be used in your own home, but some kits requiring a blood sample will need the assistance of your GP/practice nurse, or could be taken from one of our Phlebotomy centres. Please note that in accordance with UK Laboratory regulations, results will be released to your referring practitioner where applicable. If you are not currently under the guidance of a practitioner, we are able to release the results to you; however these should be taken to a practitioner for interpretation and support." The US website makes clear that consulting an expert is a mandatory part of the process ("only available through licensed health care professional").

At the company DNA Direct, all tests are first authorised by a medical doctor on the basis of a pre-test questionnaire and consultation. For genetic tests for breast and ovarian cancer, infertility and recurrent pregnancy loss, a pre-test consultation is a mandatory part of the process. If the genetic testing is performed by DNA Direct's clinical services, post-test consultation is included in the service fees.

5.2 Scope and Kind of Information Available on the Websites

Information on Qualification of Institute and Personnel

Apart from a general assurance of good quality of the company's service (which was highlighted by 71% of the websites), more detailed information about the qualification (CVs) of the management team and the scientific staff was presented on 63% of the websites. Only two of the 38 companies' websites mention a membership of professional bodies (Smart Genetics/ALZ Mirror and Health Check USA) and only three mention that they are subject to control by public authorities (23andMe, SaluGen and SeqWright).

Two-thirds (26/38) of the companies highlight their scientific advisory board, while only seven (less than a fifth) mention an ethical advisory board as well on their website. A total of 39% of the companies mention privacy guidelines (data protection), 29% refer to the topic informed consent⁶, and 18% indicate other ethical guidelines.

Information on the Accuracy of Test Data

Overall, 63% of the companies mention that they are certified by the US Food and Drug Administration (FDA) according to CLIA (Clinical Laboratory Improvement Amendments) which defines quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patient test results (see <http://www.fda.gov/CDRH/clia/>).

⁶ Within the scope of this study, it was not examined to what exactly the consumer gives his/her informed consent.

Thirty-seven percent of the companies' websites give specific information on the analytical validity of the genetic tests offered (accuracy of the test identifying the biomarker), 24% give information on the clinical validity (relationship between the biomarker and the clinical status), and 16% give information on the clinical utility (likelihood that the test will lead to an improved outcome). In 47% of the scanned websites, reference is made to expert knowledge and/or scientific evidence.

Information on Genetic Testing in General and Test-Specific Information

On 61% of the assessed websites, information for lay people is given on the scientific basis of the genetic tests offered, whereas only 29% offer information on genetic testing in general. Thirty-two percent of the companies' websites contain information on the subgroups of population suitable for testing or information on the question of when a genetic test can be useful and when not. Fifty percent of the companies make reference to one or more scientific publications.

Of the 12 companies offering pharmacogenetic tests, four present general information on the topic of pharmacogenetics, the other eight do not explain what pharmacogenetics is. Of the twelve companies offering nutrigenetic tests, seven websites give general information on nutrigenetics.

A total of 53% of the websites give information on which SNPs are tested. Three of the four companies, which offer genome-wide SNP testing (23andMe, deCODE, Navigenics), deliver information on the algorithms used to predict risk.

Information on the Necessity and Possible Methods of Counselling

Ten of the 38 companies mention on their websites that they offer counselling (Carolyn Katzin's The DNA Diet, DNA Direct, Eastern Biotech Lifesciences, Genelex, Genetic Health UK, Health Check USA, Kimball Genetics, Navigenics, Smart Genetics HIV Mirror, Smart Genetics ALZ Mirror), but in completely different ways. Kimball Genetics, for example, delivers information on consequences in the form of a detailed report with genetic interpretation, recommendations and education, which is prepared by a board of certified genetic counsellors and geneticists. At Genelex, counselling is offered for physicians and patients. DNA Direct offers separate counselling for customers of 23andMe, before and after a genome-wide SNP scan, which is normally accompanied only by written information via internet access.

Of the ten companies that offer counselling, seven organise the genetic counselling within the company, and one explicitly outsources the counselling to another DCGT firm (HealthCheckUSA to Kimball Genetics). Two websites are not clear on how they organise the counselling (Eastern Biotech Lifesciences and Genetic Health UK).

Six of the ten companies offer counselling before testing, and eight after testing. The counselling is performed via telephone in nine cases, and two companies offer it in an internet-based form.

Seven companies give information on the qualification of the counselling staff. Often it is not clear what is understood by the term "counselling". Terms as "board certified counsellor", "genetic representative" and "genetic consultation expert" are used.

Two companies make reference to a professional code of practice (Smart Genetics/ALZ Mirror and DNA Direct). DNADirect and Smart Genetics/ALZ Mirror make reference to the US National Society of Genetic Counselors' Direct-to-Consumer Guidelines (which include informed consent, privacy guidelines, laboratory certification, etc.), and DNADirect also to the American College of Medical Genetics statement on Direct-to-consumer-genetics (with information on the scientific evidence).

Nineteen companies explicitly do not offer counselling, five websites give no information on this topic, and four websites are not clear. The company Mygenome for example says: "Mygenome information services will provide a simple interpretation of the test results and guidance on how to use these results. We can also refer you to doctors who can provide appropriate care".

Information on Consequences and Actions to Be Taken

Forty-seven percent of the companies' websites present information on consequences and actions to be taken if the test result is positive, and 37% give information on the consequences and the actions to be taken if it is negative.

Some firms offer "specific" products related to the test results, especially dietary supplements. Suracell for example promotes an "age-management program" which consists of taking one or more of their proprietary nutraceuticals and follow-up urine testing.

Information on the Price of Genetic Testing

Seventy-one percent of the websites (27/38) give clear information on the price of the genetic tests, but the heterogeneity in price levels is difficult to interpret. Prices for a genetic test for monogenetic diseases range from US \$70 to \$4200, and for multifactorial diseases from US \$199 to \$3456. General SNP risk factor testing costs between US \$199 and \$3456, pharmacogenetic tests from US \$175 to \$630, and nutrigenomic tests from US \$99 to \$625. The price for a total sequencing of the genome was US \$156 900 (Knome) or US \$350 000 (GATC)⁷.

Other companies are not very clear on the total price of the service. The company SaluGen for example asks customers to agree to a contract for a monthly supply of GenoTrim (US \$99), with a fee for early termination. Consumers who do not read this carefully will have to pay US \$99 every month.

⁷ During the experts' workshop, a representative of GATC doubted that Knome really can perform the total sequencing at that price (or that the company can earn money by doing this), because the chemical reagents needed alone cost more than the offered price.

5.3 Quality Assessment of the Information Available on the Websites

An in-depth quality assessment of the 38 DCGT offers with respect to their scientific foundation, their clinical or other utility for the consumer and the ethical and legal status was beyond the scope of the project. In order to gain detailed and comprehensive data, one would have to perform real tests – an approach which recently has been chosen by some journalists (Fleming 2008; Harmon 2007) and in the year 2006 for the area of nutrigenomic testing by the US Government Accountability Office (GAO 2006). In all these cases, results were more or less shattering (the GAO titled: "Tests purchased from four web sites mislead consumers"; GAO 2006) (see section 6.1). Analysing the content of the specific information or the usefulness for the consumer would have required on the one hand a comprehensive assessment of the possible medical value of the DCGT offers and on the other hand a detailed analysis of how the information on these websites is interpreted by consumers.

Quality Criteria

Thus, the quality assessment of the 38 DCGT web sites could only be performed in a quantitative (and thereby more "superficial" way). For this purpose, the presence or absence of the topic as such was counted on the websites. This approach has recently been used for assessing the quality of information accompanying on-line marketing of home diagnostic tests in general (e.g. for allergies, hepatitis C, HIV or prostate cancer; no genetic testing) (Datta et al. 2008). To our knowledge, our analysis is the first of this kind for DCGT.

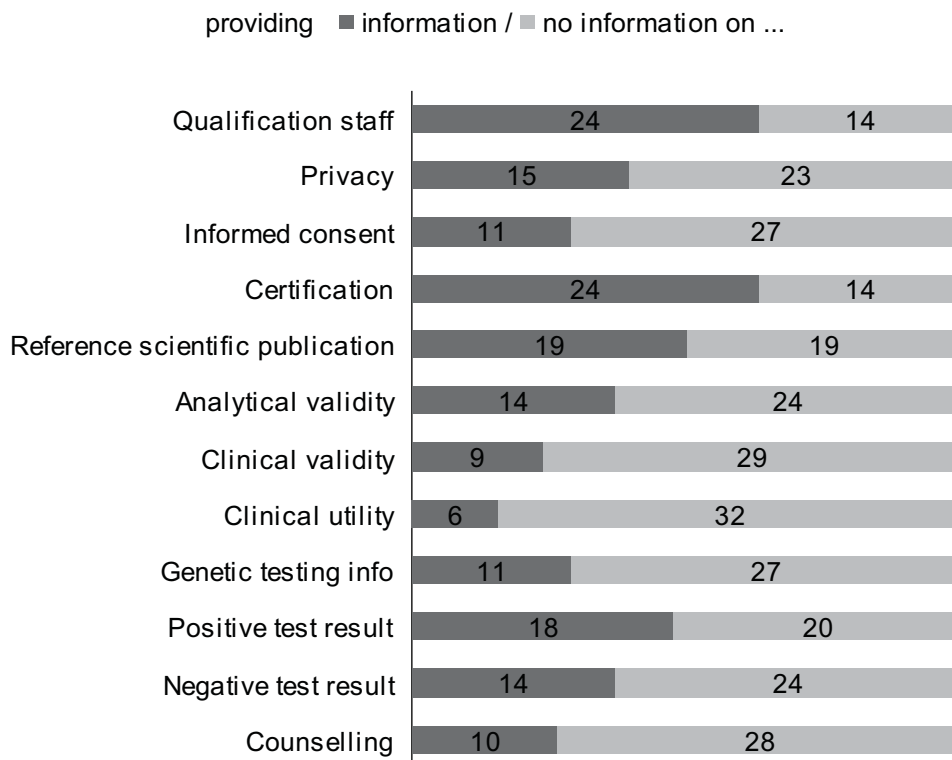
As a basis for the comparison of the 38 websites, 12 "information topics" were defined, the presence of which was counted as a quality item or criterion (see Figure 2):

- Information on the qualifications of management team/scientific staff
- The company mentions guidelines on privacy and data protection
- The company mentions informed consent
- Certification
- Reference to scientific publication
- Information on analytical validity
- Information on clinical validity
- Information on clinical utility
- General information on genetic testing
- Information on consequences and actions to be taken in the case of a positive test result
- Information on consequences and actions to be taken in the case of a negative test result
- The company offers counselling

The comparison (see Table 2) revealed that none of the websites complied with all of the 12 quality criteria, and only one, that of DNADirect, presented information on 11 items (only the information on analytical validity was missing). Six websites (18%) complied with eight criteria, and two with seven. Thus, only a quarter (9/38) complied with seven and more of the 12 quality criteria.

In turn, this means that three-quarters of the websites present information only on six items or fewer (see Figure 3). More than half of the websites (21/38, 55%) complied with four or fewer of the 12 quality criteria, and still one-fifth of the websites (8/38, 21%) complied with only two or fewer of the 12 quality criteria.

These numbers obviously should not be overrated. During the experts' workshop, it was emphasised that irrespective of the quality of information on single topics, an DCGT offer can be senseless or even harmful if only one or two relevant points are missing (e.g. on clinical validity and clinical utility). Thus, the presence of information on six, seven or eight topics is hard to interpret in "positive" terms – but the absence of seven, nine or even 11 "quality criteria" must certainly be interpreted "negatively".

Figure 2: Number Of Companies Meeting Quality Criteria

Thus in general, the quality assessment shows that the majority of websites checked display fundamental information deficits. In the light of the possibly far-reaching consequences for consumers purchasing genetic tests via internet, this seems to be a serious problem, which should be analysed and probably continuously monitored in the future. To be able to understand how the information on these websites is interpreted by consumers, research could be conducted using focus groups with lay people.

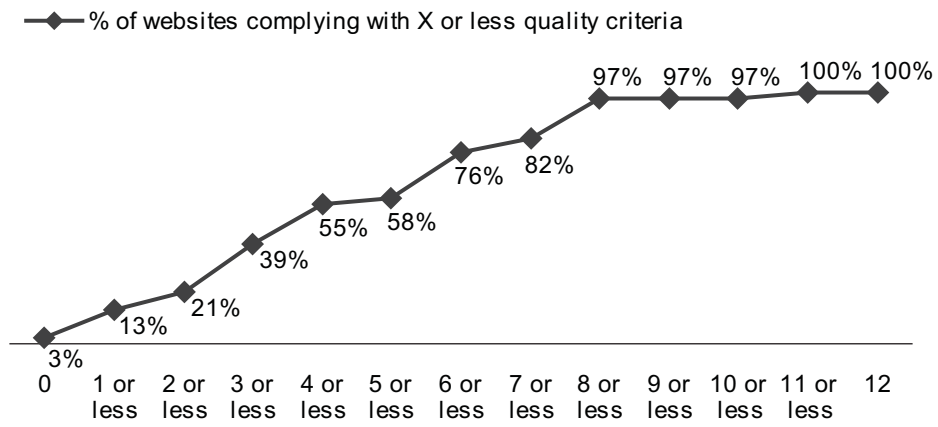
Conclusions and Future Research Needs

The results presented are based on a scan of a non-random sample of websites of companies offering DCGT for health, diet and lifestyle purposes. This approach was based on the assumption that the website is an important information source for consumers and often the basis on which the consumer decides to order a test or not. From the results, we can conclude that the quality of the information posted on websites is unsatisfactory for consumers to make a well-based decision to make use of the services of the company. The transparency of the websites is usually very low, especially for information on analytical validity, clinical validity and clinical utility. The lack of information on the website is not compensated for by the offer of counselling. For the majority of the companies in this assessment, no genetic counselling was offered at all.

In the light of these results, it is not surprising that in our judgement only one-fifth of the websites give the impression of providing a professional health care service, while 50% of the websites show a distinctive advertising style.

Table 2: Number of criteria met by company

How many quality criteria are reached?	By how many websites/companies?	Which ones?
12	0	
11	1	DNADirect
10	0	
9	0	
8	6	23andMe, Navigenics, Psynomics, Sciona/Mycellf, Smart Genetics (ALZMirror), Suracell
7	2	CygeneDirect, Salugen
6	7	Eastern Biotech and Lifesciences, GeneLink Biosciences (Dermagenetics), HairDX, HIVMirror (Smart Genetics), Interleukin Genetics /Alticor /Quixtar, Kimball Genetics, Molecular Diagnostics Laboratories
5	1	Genelex
4	6	Carolyn Katzin's The DNA Diet, Consumer Genetics, deCODE, DNAPrint genomics, HealthCheckUSA, SeqWright
3	7	Acu-Gen Biolab Inc (BabyGenderMentor), GATC, Genetic Health UK, G-nostics, HIVGene, Mygenome, SureGene
2	3	Genova Diagnostics, Health Tests Direct, Proactive Genomics
1	4	Graceful Earth, Knome, Medi-Checks, NeuroMark
0	1	Holistic Health
5	1	Genelex
4	6	Carolyn Katzin's The DNA Diet, Consumer Genetics, deCODE, DNAPrint genomics, HealthCheckUSA, SeqWright
3	7	Acu-Gen Biolab Inc (BabyGenderMentor), GATC, Genetic Health UK, G-nostics, HIVGene, Mygenome, SureGene
2	3	Genova Diagnostics, Health Tests Direct, Proactive Genomics
1	4	Graceful Earth, Knome, Medi-Checks, NeuroMark
0	1	Holistic Health

Figure 3: Percentage of websites complying with x or less quality criteria

6. REGULATION OF DCGT

6.1 Problems and Concerns Regarding DCGT

The debate about DCGT has until now been restricted to groups of experts and some health care policy authorities. There is, however, no doubt that the increasing number of DCGT offers showing up on the internet cause concern to experts, medical authorities and governmental bodies in Europe and in the U.S.. In the U.S. the American College of Medical Genetics (2004) has advised the public to avoid "home DNA tests" as they could be potentially harmful because of inappropriate test utilisation, misinterpretation of results and the absence of follow-up counselling. The Federal Trade Commission (FTC 2006) together with the Food and Drug Administration and the Centres of Disease Control in July 2006 released a consumer alert because of the lack of scientific validity in some gene tests offered. Among U.S. authorities there seems to be serious concern that DCGT may escape from proper quality control and oversight (Smith 2006, Javitt/Hudson 2006; NHGRI 2004). In Europe, DCGT has so far been constantly observed and discussed avidly in the U.K., due to the initiative taken by the Human Genetics Commission (HGC 2003, 2007). DCGT is closely watched by the community of medical genetics and counsellors, and the EU funded Eurogentest Network of Excellence (www.eurogentest.org). In 2008, the German Society of Human Genetics (GfH) in an official opinion judged DCGT offers for SNP testing as scientifically unsound and highlighted that genetic diagnostics in each case should be based on a profound medical consultation (GfH 2008). The Council of Europe has also taken up the issue (COE 2008a and 2008b, see 3.5.4).⁸

As for instance has been shown by statements of representatives of companies offering DCGT (Sciona, Suracell, Genox, Genelex) at the U.S. Senate Hearing on DCGT in 2006, the suppliers of DCGT understand their offers as a means to give consumers access to the newest achievements of human genome research, by this they claim to support progress in health care supply and to foster consumer autonomy by helping them make the long-term behavioural changes required for optimizing health care (U.S. Senate 2006).

⁸ Other official bodies which have discussed the issue of DCGT are the American Medical Association; the European Group on Ethics, the Belgian National Consultative Committee on Bioethics and the French National Consultative Committee on Bioethics.

However, as the internet survey reveals (section 5), only the minority of DCGT offers meet a minimum set of quality criteria that can be regarded as necessary for ensuring adequate information and protection of customers against misleading interpretation of the need for and possible consequences of genetic testing. The majority of observers do not necessarily doubt that DCGT can be a useful service for consumers at all, they are, however, concerned about:

- a) the often poor scientific evidence of the clinical validity and usefulness of the testing offered (particularly for common diseases and lifestyle purposes),
- b) the doubtful quality or usefulness of DCGT testing services,
- c) the problems of providing proper genetic counselling,
- d) the possible negative effects on the public health system.

Poor Scientific Evidence for the Clinical Validity of Tests

As is supported by our internet survey (3.3) the majority of DCGT offers appear to be for susceptibilities to common diseases (based merely on SNPs). This is plausible from an economic perspective, since the market potential for common diseases and lifestyle testing massively exceeds that for rare hereditary diseases and carrier testing.

As discussed above (see Sects. 2.1.1 and 2.1.2), experts regard most offers of testing based on SNPs to be pointless from a scientific point of view, since the clinical validity of most of the tests has not (yet) been sufficiently proven. However, since recommendations that can be drawn (and are drawn by providers) from positive test results usually do not go beyond what a doctor would recommend to any patient as being good for his/her health (e.g. practise sports, avoid fatty foods), some consider offering this directly to consumers to be harmless. Others, however, opine that even this kind of testing may harm clients. If results are negative, the client may gain the false impression of being safe with regard to developing a certain disease and might not see the need for adopting a healthy lifestyle; this would be totally misleading, as the absence of "negative" SNPs tested does not imply an absence of the risk of developing e.g. high blood pressure from bad dietary habits, other behavioural and environmental factors or other (so far unknown) genetic traits (that were not tested).

There is obviously a problem with interpreting the results of susceptibility tests correctly. It has been argued that problems with handling the interpretation of results are also reported from medical tests that are already offered for private (home) use, such as a test for osteoporosis. Also, in such cases the use of tests might lead to false-positive or false-negative results, with negative effects on the consumer's health or psychological condition (e.g. causing serious concerns without reason). On the other hand, it can be argued that there are reasons to treat genetic testing with particular consideration and caution. The relationship between a detected genetic trait and the onset of disease is complex (due to the interrelation of several genes and the environment), and thus the connection between the result of the test and the consequences for the person tested is not straightforward. In addition, the results of genetic testing may be relevant and have an impact not only on the individual tested but also on other family members (HGC 2003, p. 23).

Doubtful Quality of Testing Services

Independent of the question of clinical validity, the quality of testing and information forwarded to consumers (also in case of "lifestyle" testing) is unanimously regarded to be highly relevant to avoid false-positive or false-negative results or any other misleading or meaningless information.

In the US, a quality check of four selected web pages offering diet-related genetic testing conducted by the Government Accountability Office (GAO) provided strong evidence that a lack of quality control by professional or governmental bodies led to serious cases of misleading information or false results being forwarded to consumers (GAO 2006). The GAO submitted 14 DNA samples to the four DCGT suppliers. For all 14 samples, the GAO filled in a questionnaire regarding age, gender and lifestyle information as requested by the suppliers. The GAO thus simulated 14 different (in age, gender and lifestyle) "fictitious consumers" asking for a test, whereas in fact 12 of the 14 DNA samples were taken by cheek swab from a 9-month old girl (with the consent of her parents) and the other two from a 48-year-old man. For the 14 tests, the GAO received results predicting that the fictitious consumers were at risk for a number of diseases: Osteoporosis, cancer, reduced ability to clear toxins, high blood pressure, heart disease and brain aging. Experts consulted by the GAO declared that the predictions given by these results cannot be medically proven. Moreover, if there were really an individual genetic profile prepared as was promised, the nine fictitious consumers "created" from the female DNA should have received the same results and recommendations. They did, however, all receive a number of common sense health recommendations that varied only according to the fictitious lifestyle information given in the questionnaire: where the 'customer' had claimed to be a smoker, 'he' received the recommendation to stop smoking. One of the suppliers combined the report on the results of the test with a suggestion to purchase "personalized" dietary supplements costing approximately \$ 1200 per year. A check of the suggested ingredients showed that they were substantially the same as vitamins and antioxidants that can be purchased for about \$35 per year in grocery stores.

The results of the internet survey provide the impression that most DCGT offers fail to provide proper information on the scientific evidence behind genetic testing services offered to customers (clinical validity and utility). A recently published study on the scientific evidence available for offers of predictive testing for health risks and personalized health interventions from seven companies (Genelex, Genovations, Genosolutions, Integrative Genomics, Salugen, Sciona and Suracell) supports the notion of doubtful or even intentionally misleading information being forwarded to consumers on the basis of genetic testing of susceptibilities to common diseases and dietary related health problems (Janssens et al. 2008). In examining scientific meta studies on the markers used by the seven companies, the study found no or only poor evidence for the clinical validity of tests. The study found the companies' practice of combining tests for a large number of genetic variants into so-called "profiles" to be "... worrisome given the limited predictive value of results from testing single susceptibility genes with small effects" (Janssens et al. 2008, 597).

The study also found the companies' practice of using these profiles to tailor individualized nutrition supplement and lifestyle recommendations to be "another intriguing puzzle", since trials to test gene-diet interactions had thus far only yielded mainly inconclusive results. Moreover, for several genes tested it is known that they increase the risk for some diseases and decrease it for others, thus the health effects of preventive interventions on the basis of a related test may not be entirely beneficial (Janssens et al 2008, 598).

Problems of Providing Proper Genetic Counselling

The salience of medical consultation and genetic counselling in the context of genetic testing and the sensitive nature of genetic testing from the perspective of the general public can be gleaned from the fact that 2/3 of respondents to an opinion poll carried out on behalf of HGC in 2002 would also prefer to consult a doctor for genetic testing that is not related to possible severe diseases but only to lifestyle aspects and paternity (HGC 2003, 24). The main concern regarding DCGT is obviously that the services offered (via internet or over the counter in pharmacies) cannot live up to the high professional standards of medical and genetic consultation required (by statutory regulations or professional guidelines) for normal genetic testing in the context of genetic counselling (ref. 2.3). It can of course be argued that DCGT offers support free access and free choice for consumers by broadening the scope of options for genetic testing. However, at the core of "free choice" is good information to provide informed consent from the customer. This is far from being guaranteed when there is an economic interest in "convincing" a customer that he or she will benefit from testing. According to our internet survey, most companies offering genetic testing services via internet do not include genetic counselling at all in their services. Only a few urge customers to involve an expert before purchasing a gene test, and "counselling" in most cases only is provided as written information via mail or via web-log.

When communication and "counselling" are only provided via mail or web-exchange, it is almost impossible to make sure that the information given has been properly understood by the customer. In testing for complex and serious diseases, personal communication is needed about the individual's situation, relatives that may have to be informed about the test result, and information on possible treatment or preventive measures. The confidentiality and empathy required would probably not be possible via written information and communication (HGC 2003, 28f.). This, according to HGC, does not necessarily imply that the involvement of a doctor is crucial. What is important, however, is the extent to which the setting in which the service is offered and applied allows (or suits) consideration of high-level professional standards. Offers over the counter or via the internet can thus be criticised for not taking place in a context defined by medical consultation in the best interests of the patient/client, but according to a commercial principle, "where the health care professional was simply facilitating a transaction for a kit or self-testing mail order service" (HGC 2003, 25). The standard case of selling genetic testing via the internet is where a laboratory or a private company offers a kit for sampling tissue material (normally from saliva) which is sent to the consumer; the sample is then tested by a laboratory, and the results are sent to the consumer. This must be regarded as not meeting the criteria of "medical consultation", even if the company is run by a medical doctor, since consultation is only offered in the form written advice or personal consultation (e.g. via telephone), or indeed is only offered if explicitly requested by the consumer.

Particular concerns regarding the principle of informed consent have been raised with regard to testing children and in terms of the possibility offered by mail-order testing of sending a specimen from third parties against their will or without their knowledge. The British Human Genetics Commission regards this as such a serious problem that it suggested defining a new criminal offence to deter individuals from taking samples from others without consent (HGC 2003, 30).

Possible Negative Effects on the Public Health System

Apart from the false, misleading, non-substantial or even dangerous recommendations given or drawn from tests offered via the internet, one general danger is, that with low-quality DCGT offers dominating the market, customers might lose confidence in the future in genetic testing overall.

Another more direct effect could be that customers who use DCGT and are left with complex, diffuse or meaningless information will increasingly look for counselling at a publicly funded centre for medical genetics or with their family doctor (HGC 2003, 29). The supply of an entire set of all known SNPs and their association with disease or other features (as offered by 23andMe) may rightly be regarded as being useless for customers. There might, however, be a rebound effect on public genetic services when the "worried well", using this kind of service, go to their doctors to check out the opaque results and recommendations obtained. Thus an expanding market for DCGT could significantly increase the burden on public health services.

Before exploring the options for legal regulation or other authoritative intervention with regard to the use of genetic testing, one must decide whether government has any fundamental right to regulate access to genetic testing. As is the case for genetic testing in general, any consideration of regulatory or statutory intervention by the state must proceed from the question of whether it is legitimate to intervene or to what extent the individual's right to obtain information about himself (regarding his current or possible future state of health) as a natural extension of his autonomy permits intervention. In a liberal society and market economy, it can well be argued that access to and provision of information on an individual's genetic make-up is a right which should not be restricted by the state. An intervention can only be justified when prevention of physical or psychological harm to those requesting genetic information or to third persons is necessary (HGC 2003, 48).

Due to the complexity of genetic information that could well mislead consumers or be used to mislead them, and due to the likely serious health and psychological consequences of this, there is a consensus that principles such as informed consent and quality standards of testing and counselling have to be ensured since DCGT offers via the internet can obviously be associated with consumer protection problems with regard to the prevention of misleading information and bad quality of testing and counselling. Thus it is widely regarded to be legitimate to regulate the market for DCGT. It is, however, a matter of discussion to what extent governmental intervention is needed, and whether regulations should apply in the same way to all different types or purposes of DCGT services.

6.1 Restriction of Genetic Testing to Referral by a Medical Doctor

Most regulations and guidelines on genetic testing were set up in the 1990s and did not envisage that genetic testing would be offered directly to consumers. In most European countries, there are no legal or other binding regulations that explicitly prohibit or otherwise restrict DCGT. Discussions on the need and options for regulating DCGT mainly pertain to restricting the use of genetic testing to the medical context: Testing should be possible only after referral by a medical doctor to ensure the quality of the diagnostic procedure and technique as well as proper genetic counselling before and after testing. If this principle were applied strictly, genetic testing services would not be permitted over the counter or via the internet at all.

It appears that in those European countries which decided to permit genetic testing in general only after referral by a doctor (as stipulated by law), DCGT should be prohibited. This is - as was stated at the European meeting on "Over the Counter Genetic Testing" organised by the Council of Europe in 2007 (COE 2007) - currently the case at least in Switzerland and Austria, and possibly also in France where the Bioethics law of 24 July 1994 stipulates that a genetic study of the characteristics of an individual can only be carried out for medical and scientific reasons. In the case of France there are, however, some uncertainties remaining, since offers via the internet may be made by a medical doctor. Then it could be argued that the diagnosis is in principle offered for medical purposes since a doctor is involved.

In the US, the principle of restricting genetic testing to the medical context and demanding referral by a doctor as obligatory has been guiding recent action taken by public authorities to restrict the activities of DCGT companies. The California Department of Public Health in June 2008 sent out letters to 13 companies offering DCGT (among them deCODE, 23andMe and Navigenics). The letter states that the companies are in violation of California law because they fail to have a clinical laboratory licence in the state, and they offer genetic testing to consumers resident in the state "without a physician's order" (Nature, 26 June 2008). Similar letters were sent by the New York Department of Public Health to 26 companies. In the case of California, the companies were urged to correct this situation within a certain period of time or "face civil and/or criminal sanctions". It is reported that, as regards the laboratory licenses, companies reacted by providing evidence of cooperation with a laboratory certified in the respective state. As a reaction to the complaint, the Iceland-based company deCODE has now included California in a list of states - published at the company's website - for which the company's "Genetic Scan" "may omit certain information" because of state law. With regard to the complaint about carrying out genetic testing without referral by a doctor, some of the companies questioned the rationale and/or necessity of this demand, since a gene test did not include any medical intervention (but only measures a risk). Others such as 23andMe argued - and now state in a respective disclaimer on their webpage - that they are providing genetic information for research and educational use only but not medical advice ("not intended to be used for any diagnostic purpose and is not a substitute for professional medical advice"; www.23andMe.com, "terms of service" as of 03-11-2008).

Among experts in Europe there is some debate on whether the rule for restricting the right to refer or carry out genetic testing to medical doctors or otherwise qualified medical personnel should apply for all genetic tests or whether one should distinguish between tests that are only accessible on referral from a doctor and those that might be amenable to commercial offers direct to consumers. At the above-mentioned seminar of the Council of Europe, the experts (representing several European countries) apparently agreed that the same high standards of quality of testing and counselling must be adhered to in any offer of genetic testing. In the synthesis document, it is stated that:

“The participants all agreed,

- that the test results must be interpreted by an expert bearing in mind: the technical limitations of genetic tests; the fact that, in the case of predictive tests, the results were expressed in terms of probabilities, not certainties; the importance of the medical context and in particular the effect of non-genetic factors on the onset and severity of the disease in question.
- that it was desirable or even vital that patients and their families receive support from multidisciplinary teams, given that: the results might concern other family members; might reveal something inevitable and have a substantial impact on a persons life.
- that individual and family tragedies were likely to arise out of misunderstandings if this practice of free access genetic tests were to develop with no genetic counselling or support.” (Council of Europe 2007, p. 11)

When expressing their concerns with regard to negative effects on consumers, the experts did not, of course, differentiate between types of genetic testing and argue for restriction of the use of any gene test to the medical context. The European Group on Ethics in Science and New Technologies (an advisory body set up by the European Commission) also seems to support a ban on DCGT. The Group (according to HGC 2003, 34) regards advertising for genetic testing directly to the public to be likely to be misleading and expresses concerns that advertising tends to convert genetic testing into a commodity, thus giving rise to a demand that may result in personal and social conflict.

A position held by experts from Eurogentest and the representatives of some consumer organisations, such as the Genetic Interest Group, U.K., suggests making a distinction between types of genetic testing that might or might not be acceptable for offering directly to consumers, depending on the consequences for the consumer and the complexity of the test. Single-gene (inherited) disorders should be only offered in a professional context by specialists. The broad scope of genetic testing for susceptibilities and particularly for lifestyle purposes are regarded as clinically invalid. But, as these tests are meaningless, neither could they cause any severe harm. It thus must be left up to the consumer to decide whether to take up these offers or not. Whereas in for lifestyle testing and the like only general quality criteria should apply, for other predictive testing, more strict rules and quality criteria should be ensured, which could be done by allowing tests to be carried out only by accredited laboratories with staff qualified in genetic counselling.

The central criterion then would not be whether the supplier is a trained doctor, but the quality of testing and information supplied. Even if it were true that predictive testing for slightly increased risks to develop a common disease may do harm, since a negative test result may send the wrong signal of security to the patient (whereas in reality the patient may have another SNP which he has not been tested for), it could (at least for lifestyle testing) be regarded as the consumer's responsibility to search for proper information when purchasing this kind of test.

The same could also apply to testing for an entire set of known SNPs associated with health problems as offered by "23andMe". Such offers are regarded by many experts to be clinically useless and meaningless for a lay person. Thus testing would also probably not do any harm, and one might well leave it to the consumer to decide whether to spend money on it or not.⁹ The case would be different for a total sequence of an individual's genome – which has so far only been envisaged as a possible future service by suppliers. An individual's total genome sequence would carry information about any genetic trait, including predictive monogenetic testing and testing of risks for hereditary multigene diseases: The principle of referral by a doctor should apply, and testing and counselling should be reserved to accredited counselling centres or specialised medical geneticists.

Differentiation on the regulation of tests according to their "informational impact" and the gravity of consequences of results for the client may be appropriate. It must, however, be taken into account that widespread marketing of even relatively "harmless" genetic testing for, e.g. a disposition to develop obesity may give the wrong signal to a public that is often badly informed. DCGT offers (of bad quality) may support the notion of a deterministic connection between genetic traits and disease, whereas from an expert perspective, the connection between genetics and disease for most common diseases (such as cancer and or cardiovascular disease) is complex, and thus it is difficult to draw conclusions with regard to treatment. As has been shown above, some companies offer tests which might not cause serious harm when misinterpreted, but whose clinical validity and utility is doubtful and could be used to mislead consumers. Companies may also take advantage of the public's erroneous deterministic understanding by offering dubious testing (e.g. nutrigenetics) combined with the recommendation to buy expensive dietary drugs or food (HGC 2003, 60).

⁹ There is one single case, the testing for a SNP reported to be related to Parkinson's disease, in which 23andMe demands an opting-in of the customer before viewing the test result ([www. 23andMe.com/health/Parkinson](http://www.23andMe.com/health/Parkinson), accessed on 03-11-2008).

6.3 The Approval of Tests and Offers – Pre-market evaluation

As early as 1997, the former U.K. Advisory Committee for Genetic Testing published a "Code of Practice and Guidance for Genetic Testing Supplied Directly to the Public" (ACGT 1997). This code of practice was meant to give the Committee a basis for evaluating emerging offers of DCGT. Since its recommendations did not have any formal legal status, by releasing the code the committee intended to invite suppliers planning to offer DCGT to present their proposal to the ACGT for evaluation with regard to the compliance of the offer with the stipulations of the Code of Practice. The Commission found that because of the complex nature of genetic diseases and the uncertainties often associated with tests - "about when, if ever, the diseases will strike, how severe it might be, and whether current symptoms ... are in any way linked to the disease in question" - testing should be best carried out on the referral of a patient's medical doctor (ACGT 1997, 4). However, if offers over the counter could not be prevented, quality control should be ensured by applying the Code of Practice as a means of (non-binding) approval of offers. For approval it was requested that information should be provided about the laboratory participating in an accreditation scheme, about procedures to assure confidentiality of customer data, about genetic consulting procedures, and, last but not least, the supplier was asked to provide peer-reviewed evidence of the clinical validity and usefulness of the proposed testing, including population data and copies of referenced papers.

The regulatory approach - as suggested by the ACGT and taken up again by the HGC (2003, 2007) - on the one hand implies the establishment of supervision of companies supplying genetic testing as well as a kind of pre-market evaluation of new tests with regard to their clinical validity and utility before they are allowed to be offered directly to consumers.

- In the US, two bills – the Laboratory Test Improvement Act and the Genomics and Personalized Medicine Act – were introduced in Congress in 2007 that deal with improved supervision of genetic testing, including DCGT. According to the enhanced system of oversight envisaged, the task of pre-market approval would be given to either the Food and Drug Administration or the Centres of Disease Control.
- In Europe, there is currently no specific system of approval for new gene tests before marketing (see Sect. 3.5.3 below). National systems of control are only established for public health care supply, i.e. for services whose costs are covered by public health insurance or public health services. Usually - as in Germany, for instance - insurance companies decide together with professional medical associations which medical service will be covered by health insurance. In Belgium and in the Netherlands, the right to offer genetic testing in the context of public health service is restricted to licensed institutes. The institutes decide which new tests they regard as sufficiently clinically valid and useful to become part of their service. In the Netherlands, these institutes convene to come to an agreement on which services should be standard and which should be excluded.

In the U.K., a Genetic Testing Network was set up by the public authorities to ensure high-quality genetic testing and to decide what is appropriate for inclusion in the National Health Service (HGC 2003, 44f.).

6.4 Quality Control and Evaluation

Behind the discussions about quality control of genetic testing services and a pre-market evaluation of genetic testing lies the question of guiding principles and criteria for control and evaluation. Discussions on the control and supervision of genetic testing focus in general on four quality criteria for evaluating genetic testing services and testing arrays that are referred to by the term ACCE framework (Hogarth et al 2007, 2008, see also Centers for Disease Control and Prevention 2007):

- Analytical validity of a genetic test defines the accuracy of a test identifying the biomarker, i.e. to reliably measure or identify the genotype of interest. This aspect of evaluation focuses on the quality of laboratory work.
- Clinical validity of a genetic test defines its ability to detect or predict the associated disorder (phenotype), i.e. whether the test not only identifies a certain genotype correctly but also correctly measures the relationship between the biomarker and the clinical status of the patient or the patient's risk of developing a disease in the future.
- Clinical utility not only defines the relationship between a certain genetic modification and the (risk of developing a) related disease, but also the likelihood that use of the test will lead to an improved outcome for the patient. Clinical validity thus implies an evaluation of the benefits and the risks for a patient if the test is introduced in routine clinical practice. This would include - among other things - considering the availability and effectiveness of interventions aimed at avoiding adverse clinical consequences.
- Ethical, legal, and social implications denote the wider social effects of introducing a test into practice, such as stigmatization, discrimination, and the privacy/confidentiality of genetic knowledge and data as well as guidelines for genetic counselling such as the principle of informed consent or non-directive counselling.

Ethical, legal and social implications of genetic testing are regulated in some countries by statute. In most countries, they are covered by professional codes of practice.

Regulatory frameworks and authorities for approval and oversight of genetic testing and quality control up to now focus mainly on analytical validity, i.e. whether the test correctly identifies the genetic marker the service provider claims to identify. With regard to the approval of genetic tests (before marketing), it has been argued that evaluation of clinical validity and moreover clinical utility is not applicable, since sufficient information can only be obtained by monitoring the performance of tests in clinical practice. Evaluation of clinical utility - thus it is argued by some - involve judgements which have to take into account the individual situation of the patient, e.g. whether knowledge of his or her genetic status will provide peace of mind despite a lack of treatment options. Thus clinical utility could only be assessed case by case (Hogarth et al. 2008). With more and more susceptibility testing entering the market and with respect particularly to susceptibility testing offered directly to consumers, it is argued that at least clinical validity – if not also clinical utility – must be taken into account for pre-market assessment of genetic testing in order to avoid negative effects for consumers.

Both negative and positive results of tests whose clinical validity is doubtful could lead to consumers drawing the wrong conclusions about their state of health with psychologically or physically harmful consequences. It is thus doubtful that it can be left to the market (i.e. the consumer) to decide whether the information provided by the DCGT company is sufficient, insufficient or even misleading. According to Hogarth et al. (2007, 835f.) the U.S. system of oversight emphasises the importance of pre-market evaluation of clinical validity data which must be provided by service providers, whereas the European system still focuses on analytical validity (see the discussion of the European IVD Directive below).

The recently published OECD Guidelines for Quality Assurance in Molecular Genetic Testing (OECD 2007) also underline the importance of assessing the clinical validity and utility of genetic testing offers and the requirement on laboratories carrying out molecular genetic testing to "make available information on the analytical and clinical validity of tests" (OECD 2007, 14). The focus of the guidelines is, however, the analytical validity and the quality of laboratory work. In this respect too, control and monitoring seem to be insufficient, as there is a lack of efficacy in the quality control of laboratories carrying out genetic testing. The guidelines urge governments of OECD countries to establish a system of accreditation for laboratories that are licensed to carry out molecular genetic testing and to define standards of best practice in terms of the quality control of laboratory work and qualification of staff. The development of the guidelines was urged on by results of a survey carried out in 2002 among eighteen OECD member states. The survey revealed the steady growth and availability of molecular genetic testing offers in OECD countries, together with insufficient regulation and supervision of laboratory quality in some countries, since "regulations with which laboratories must comply are not specifically designed for molecular genetic testing" (OECD 2007, 6). The OECD working group found considerable differences "in the use of licensing, certification, and accreditation procedures", which "poses a number of challenges for molecular testing, particularly with respect to the standards under which test are performed and results are reported for clinical application, and the training and qualifications required by laboratory personnel" (OECD 2007, 6).

In Europe, so far no common requirements for laboratory quality assurance exist and only a few laboratories have a formal accreditation, while many laboratories do not undergo any official inspection (see section 2.1.6). For DCGT, which is carried out outside the framework of public health services (for which quality assurance of laboratory work is taken care of by national public or professional self control), this implies that even the technical quality of testing (analytical validity) cannot be effectively controlled.

6.5 Regulation at the European Level - IVD Directive and Council of Europe

Regulation of DCGT has to face the problem that the reach and value of any regulation on the national level is restricted if the internet is used as the main channel of forwarding testing directly to consumers. Reaching international agreements on regulating genetic testing thus appears to be decisive.

On the European level, the Eurogentest Network of Excellence has taken the initiative to further develop and harmonize professional standards for genetic testing by, for instance, developing guidelines for quality management and setting up a database on quality criteria for laboratories, which allow testing services to be searched for in order to get a quality ranking of the laboratories offering services. Other fields of activities include guidelines for genetic counselling (Eurogentest 2007), information for patients, and assessment of the clinical validity and utility of tests (Schmidtke 2005).

IVD - Directive

With regard to test utility, there seems to be consensus among experts that a European system of assessment and approval of genetic testing is needed prior to marketing, and that for this purpose existing European regulations should be amended (Hogarth/Melzer 2007). At the EU level, diagnostic devices or kits are regulated by the In Vitro Diagnostic Devices Directive (98/79/EC). Subject of the Directive is (Article 1d):

“any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological or pathological state, or
- concerning a congenital abnormality, or
- to determine the safety and compatibility with potential recipients, or
- to monitor therapeutic measures.”

The stipulations of the directive only require that the diagnostic device or kit “performs as stated and does not harm”; wider aspects of the quality of the services offered such as qualifications of personnel are not covered by the directive.

It obviously is unclear or subject of debate to what extent the Directive takes into account the clinical validity or usefulness of a medical device. Whereas some experts holds that the IVD Directive’s regulations concern a test’s safety and accuracy only, others argue that an appraisal of a medical device – if its application implies possible harm for consumers – cannot be evaluated disregarding their clinical validity or usefulness (Melzer/Hogarth 2007).

Whereas the definition of a “diagnostic device” - as cited above - at a first glance should leave no doubt that genetic testing is covered by the Directive, regulatory practice shows that it is obviously not sufficiently clear to what extent which type of genetic testing is covered by the Directive. Thus a working pre-marketing evaluation system for genetic testing is missing in Europe at the moment. Whether genetic testing devices or kits will be subject of pre-market review in the future - in case an amendment makes clear that they are covered by the directive - will be dependent on the risk category they are attributed to.

According to the Directive, only for those diagnostics regarded to carry either “moderate” or “high risk” - and which are thus included in the respective list (list B: moderate; list A: high risk) - are manufacturers obliged to submit information about the test to a notified body for approval. The main reason for excluding gene tests from the pre-market evaluation system is that they are considered to be “low risk” and therefore the directive does not require them to be reviewed before they are marketed.

The only test for a inherited disorder adopted in these lists so far is PKU testing (Phenylketonuria), which is widely applied for neo-natal screening. So far gene tests are treated as being "low risk", they are not regarded as meeting the criteria for being entered into list B. The central criterion for being classified as bearing "moderate risk" according to the Directive is whether action taken on the basis of an incorrect result obtained using a given device could prove to be hazardous to the patient, to a third party or to the public, in particular as a consequence of false-positive or false-negative results.

It is not clear why predictive genetic testing - such as for Huntington's disease or a BRCA test - that have a serious psychological and physiological impact on patients are not included in the list. Whether or not predictive genetic testing is covered by the directive seems to be an open question since predictive testing, as it does not allow for information on the current health status of a person, may not be regarded to serving a medical purpose in the strict sense (Hogarth/Melzer 2007).

Apart from demanding the inclusion of tests for monogenetic inherited diseases, it also is argued that - given the rapid development of new genetic testing, the complexity of information provided by tests and the problems of proper interpretation of results - new genetic test kits generally should be subject of pre-marketing evaluation, independent of the seriousness of the disease tested. Hogarth and Melzer (2007, p. 10) argue that the novelty of tests should be introduced as an additional criteria for classifying tests that otherwise could be regarded as being of low risk since the clinical validity of a test can only be proven in practice and novel tests are thus inherently more likely to lead to incorrect results. The HGC in the UK concluded that the risk classification of the IVD Directive should be reviewed in order to provide for coverage of genetic testing. The Commission also argued that even apparently harmless "lifestyle" tests that might still be classified as low risk should be covered, if not by the IVD Directive, then by some other regulatory mechanisms established to ensure the appropriate oversight (HGC 2007, 24).

The IVD Directive is currently undergoing a procedure of amendment, and a public consultation has been started by European Commission (DG Enterprise) asking among others for hints at additional medical devices that so far are not but should be covered by the Directive in the Future.

Recently a new model of risk assessment for in-vitro diagnostics has been drafted by the Global Harmonization Task Force (GHTF). The GHTF is a partnership of public authorities and industry with the aim of achieving greater uniformity among national medical device regulatory systems. Besides the US, Canada, Australia and Japan, the European Union is a founding member of the partnership. If the recommended system were adopted by European regulatory bodies, it would most likely imply that pre-market review would become compulsory for many genetic tests (GHTF 2007, Hogart/Melzer 2007). The draft explicitly mentions that genetic testing should be classified as "class C" (high individual risk/moderate public health risk) where it comprises IVD devices that are intended for use "... in predictive genetic screening, when the outcome of the test would ordinarily result in a substantial impact on the life of the individual. Examples: Guthrie test for phenylketonuria, Huntington's disease, cystic fibrosis" (GHTF 2007, 13). It appears to be likely that SNP-based testing for an increased risk for cancer would also fall in this category. It is doubtful, however, whether so-called "lifestyle" tests would be covered by category C.

The draft suggests classifying all IVD devices for self-testing as “class C”, except those “from which the result is not determining a medically critical status”. The latter are classified as B (moderate individual risk) but according to the draft may also undergo a somewhat less strict pre-market assessment.

Amending the IVD Directive in a way that does not allow for uncertainties about the classification of genetic testing devices would certainly improve the system of supervision at the European level. However, even an amendment of the IVD Directive with regard to risk classification of genetic testing would probably leave some questions open regarding the approval and evaluation of DCGT:

- It is not clear to what extent “lifestyle” testing kits can be included in the Directive in a way that they undergo pre-market evaluation.
- It remains unclear to which extent laboratory developed tests (home brew tests) that are only applied by the laboratory itself and are not offered to other suppliers as a “device” or test kit are covered by the directive (Hogarth/Melzer 2007).
- It has to be discussed how a system of pre-market evaluation of clinical validity of gene tests should and could be established on a European level. Such a system could oblige suppliers of genetic testing to give scientific evidence on the clinical validity of tests to a European authority such as the European Medicine Agency (EMA), which is responsible for the scientific evaluation of medical products for European marketing authorisation.

The Council of Europe’s Additional Protocol on Genetic Testing

With regard to the regulation of DCGT, recent activities by the Council of Europe (COE) can be regarded as preparing the ground for a harmonised European solution. In May 2008, the Committee of Ministers of the COE authorised the publication of an “Additional protocol to the Convention on Human Rights and Biomedicine, concerning genetic testing for health Purposes” (COE 2008). Since the Council is aware of “concerns that exist regarding possible improper use of genetic testing”, the intention of this document is to provide general rules for the use of genetic testing in Europe. The subject of the protocol is thus genetic testing in general, and it proposes rules and principles for dealing with a broad range of problems such as proper genetic counselling, informed consent, data protection and others, as they have been discussed by many advisory and political bodies at the national level in Europe (Section 2.3 of this report). It is, however, obvious that when drawing up the protocol, the Council also took account of recent developments in DCGT. In the “Explanatory Report” to the protocol, it is stated that one motivation for drawing up the Protocol (by the COE’s Steering Committee on Bioethics) was the observation, that “genetic tests are to become more and more an integral part of medical practice, but at the same time a direct commercial offer of genetic tests outside any health system is developing” (COE 2008b, Introduction, paragraph 3).

It is obviously with an eye on DCGT that Article 7.1 of the protocol states that “a genetic test for health purposes may only be performed under individualized medical supervision” (COE 2008a). By using the term “individualized” - as the Explanatory Report reveals - the Council wanted to stress the need for personal genetic counselling in order to ensure proper preliminary information of any person concerned and to enable an informed decision:

"A precise evaluation of the situation of the person concerned, involving direct contact with him or her, is a determining element in that respect. A mere telephone conversation with a medical doctor, for example, does not allow for such evaluation." (COE 2008b, Article 7, paragraph 64). This clearly excludes the practice of indirect or remote counselling conducted by many DCGT companies. If the rules of the Protocol were enacted in the various European member states, this clearly would affect DCGT companies' business and would probably result in the prohibition of DCGT (Borry 2008).

However, as Borry argues, the practical effect of the Protocol on regulatory practice is not guaranteed and remains to a certain extent unclear. A Europe-wide, harmonised regulation on the basis of the Protocol requires the Protocol to be signed by the member states. So far the basic document, the Bioethics Convention, has only been signed by 34 out of 46 member states of the Council and has been ratified by only 21. Apart from this, it remains unclear to what extent the protocol will cover the practice of DCGT. The protocol applies to "tests, which are carried out for health purposes". Some DCGT companies, however, claim that their offers do not involve information directly related to health purposes. Companies like 23andMe, offering a scan of SNPs, include a disclaimer on their website stating that the information provided about potential health conditions should not be used to estimate an overall health risk and is "not intended to be medical advice" (Borry 2008).

7. CONCLUSIONS - POLICY OPTIONS

Offering genetic testing services direct to consumers is a new form of supplying genetic testing to the public that is associated on the one hand with well-known problems which have been discussed in relation to genetic testing in general. This applies for instance to the question of the clinical utility of susceptibility testing for common diseases, whose pros and cons can be discussed independently of the framework (private or public) within which the services are offered. On the other hand, there is no doubt that, given the private character of the offers, barriers and control mechanisms regarding the quality of services and restriction of the use of genetic testing to medically defined cases, which exist in the public health services or medical context (either statutory or self-regulatory), do not apply to DCGT. As the above discussion on DCGT as well as the results of the internet scan show, many DCGT offers fail to meet quality standards of services – as regards, e.g. genetic counselling – which determine the practice of genetic testing in the medical sector, at least in the form of guiding principles. It is also obvious that some gene tests offered via the internet are of a doubtful or even misleading character in terms of clinical validity and utility. There are also (albeit few) examples of DCGT companies that do a lot to meet established quality standards, and there are indications that companies react to criticism by reconsidering and improving their services. There is, however, also evidence that serious concerns remain about whether offering genetic testing direct to consumers via internet can in any way provide the transparency and reliability of information and the individual quality of counselling that is necessary due to the complex nature of genetic testing.

Regulation of DCGT is a complex matter because of the heterogeneity of tests offered and the different models of promoting and delivering gene tests and the associated services to the public. The challenge (and at the same time the guiding principle) for any intervention by policy makers, as formulated by Hogarth et al. (2008, 178), is “to create standards that adequately protect consumers from harms associated with unsafe tests, while ensuring access to tests that are analytically and clinically valid in a manner that provides appropriate context and counselling. Regulatory requirements must be proportionate to the risks posed by the tests, and must recognize that some tests carry greater risks than others”.

Taking this as a basic rule for policy intervention, there is still a conceivably broad range of measures to be taken. Depending on how one assesses the risks or possible negative outcomes associated with tests offered to consumers, the degree of intervention and the model of regulation will differ. It can well be argued that due to the complexity of the subject matter and the possibly misleading signals given to consumers, all genetic testing should be restricted to a medical setting and to referral by a doctor. This would most probably imply the general prohibition of DCGT. There is also the option of leaving the decision to purchase certain “non-risk” gene tests up to consumers, while restricting the use of genetic testing to the medical context for those tests (e.g. predictive tests) that are defined as associated with risks and/or involve complex information that only can be supplied by qualified individual genetic counselling.

The work on DCGT that has been done by the British Human Genetics Commission can be regarded as the most profound exploration of the problems connected with DCGT that has so far been made¹⁰ available and the HGC's conclusions on policy options therefore are presented here as a general orientation for decisions on political intervention. There is no other document at hand that gives a comparable overview of policy options to be considered with regard to DCGT.

The HGC concludes that it would be inappropriate to forbid DCGT altogether due to the individual's right to know. On the other hand, however, most tests available are regarded as lacking sufficient evidence to be clinical valid or being too complex in nature to be offered to people without a medical consultation.

The following summary of the HGC's policy recommendations provides a kind of check list for further discussions on options for policy interventions also on the European level (HGC 2003 pp. 47 ff.; HGC 2007 pp. 23 ff.; HGC 2008):

- **Develop public supply for genetic testing**
Since the commission feels that it is not possible to restrict DCGT completely and open access of consumers to genetic testing has to be ensured, it is recommended the public supply be supported by the public health system (NHS) as much as possible. A good public supply is, so to speak, a means to prevent consumers from making use of (low-quality) private offers.
- **Restrict predictive testing to prescription by a medical doctor**
The Commission does not support statutory prohibition of DCGT. It sees, however, the need to restrict access to most predictive testing by requesting a prescription by a doctor and by stipulating that certain genetic tests should only be offered by particularly qualified health professionals. Other, "low risk" genetic testing may be offered directly to consumers via pharmacies or via the internet.
- **Approval of gene tests and direct offers to consumers**
The Commission supports initiatives to create approval procedures for new gene tests before they are allowed to enter the market. In this context it is recommended that private companies offering genetic testing directly to consumers have to convince an authority of the clinical validity and appropriateness of the offer. It also should be ensured that laboratories carrying out genetic testing undergo a licensing process.

¹⁰ Due to further development of new predictive genetic tests and new reports about offering of "lifestyle" genetic testing direct to consumers, the HGC held a meeting in 2007 to review the findings and recommendations laid down in an extensive report that had been provided in 2003. The policy recommendations from 2003 were consolidated in a report on the review meeting published in December 2007. In June 2008 the HGC organised a seminar with experts and representatives of DCGT companies to follow up on the issue and discuss options for regulation.

- **Quality of services**

A code of practice related to genetic testing services should be developed to support the quality of services. It should be ensured by statutory regulation or by professional self-regulation that personnel carrying out genetic testing and genetic counselling are appropriately qualified and trained. The development of a code of practice was widely supported at a meeting on DCGT with experts and representatives of DCGT companies which was held by the HGC in June 2008 (HGC 2008).

- **Control of the quality of DCGT services and advertisement**

DCGT offers should be subject to control as regards standards of fair trading. Advertisements for genetic testing should be controlled by advertising standard authorities which so far are lacking knowledge and advice to apply control to genetic testing offers. Advertising directly to the public those genetic tests which are "prescription only" should be prohibited.

- **Informing and educating the public**

The government should ensure that consumers are properly informed on the pros and cons of genetic testing. For this purpose it is deemed appropriate to set up public web-based information offers or support existing independent information web pages of high quality.

- **International/European regulation**

The Commission is aware that DCGT offers made via the internet and from foreign sources cannot easily be controlled. Efforts to harmonize regulation internationally are needed. The European IVD Directive should be amended in a way that genetic tests should require an independent pre-market review, and complementary mechanisms should be established for "lifestyle" tests.

Most of the options explored and suggested by the HGC are intended for adoption by national authorities. Development, regulation and control of health care are mainly the tasks of national governments and authorities in the EU member states. There is, however, an increased demand by experts as well as stakeholders for Europe-wide harmonisation of guidelines and rules for genetic testing practice in general. As shown in the present report, DCGT in particular seems to require international or European efforts of regulation and quality control, since the internet offers are in principle accessible to citizens across national boundaries. When setting up the Additional Protocol on Genetic Testing, the European Council obviously felt the need for a Europe-wide harmonisation of standards for genetic testing. The ramifications of the Council's Additional Protocol (6.5) will become apparent in the future. It might well be that the protocol will prove to impose major restrictions on DGCT offers when ratified by the member states. Apart from the Protocol, at present three areas appear to be most prominent with respect to policy intervention at the European level.

- **IVD Directive**

As outlined above, the IVD Directive which is currently undergoing a process of amendment, is addressed as the European regulatory framework for pre-market approval of genetic testing (6.5). In the course of the amendment, decisions will have to be taken as to what extent genetic testing can and should be covered by the rules of the Directive and how different types of gene tests are assigned to the different risk categories; this in turn will determine whether pre-market approval is mandatory. It seems crucial in this respect to include clinical validity (and utility) as criteria for the evaluating gene tests. The role of monitoring of IVD medical devices that is attributed to the European Medicines Agency (EMA) in the future will also be important for the control of DCGT. So far, applications for pre-market approval of devices have to be submitted by providers to national notifying bodies, which, however, might not have the expertise to assess the clinical validity and utility of gene tests. The time schedule for amending the Directive is not settled yet. DG Enterprise intends to publish a summary of the answers received from the currently running public consultation on its website in November 2008.

- **European Code of Practice**

Even if a European framework for the approval of genetic testing is established via the IVD Directive, there still might be a need for controlling DCGT offers for those tests for which no marketing restrictions have been stipulated. It might be appropriate to consider establishing a European code of practice for DCGT, which would imply commitment of service providers to standards of scientific evidence for the clinical validity of tests offered, of advertising and properly informing consumers, and of genetic counselling. A European initiative in this respect (probably under the guidance of the Eurogentest Network) would be helpful to enforce national activities to establish a code of practice (as currently undertaken by the British HGC). A code of practice would be of a voluntary nature. The code, however, could be enforced by an independent regulatory body equipped to deal with complaints and entitled to intervene if companies are found not to be complying with the code. It must be considered whether this supervisory function could be assigned to a European authority.

- **Quality Control and Accreditation of Laboratories**

As outlined above, the current system of quality control for laboratories carrying out molecular genetic testing in Europe is inconsistent, if not insufficient (6.4). It might be appropriate to try to set up a European system of quality control and accreditation of laboratories, or at least to explore appropriate means of supporting and enforcing national efforts to improve quality control and adopt the OECD guidelines

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ANNEX

1. Assessment form for the evaluation of websites offering DCGT

General information about company:

Name of the company:

Website:

Q0 Founded/launched

Q A Home country of provider:

Q B Information about in which countries the company offers test:

Q C Information about in which countries the company does not offer tests:

Q D Is there an explicit link to other companies? Which ones?

Q1 Offering direct-to-consumer genetic testing is

(1) ⁸ The only field of activity of the company: Single-purpose company offering DCGT services

(2) ⁸ Only one of the company's activities/services:

Q1.2. (Yes 1 /No 2) ⁸ Research Company active in the field of human genetics

Q1.3. (Yes 1/No 2) ⁸ The Company offers non-genetic tests as well

Q1.4. (Yes 1/No 2) ⁸ The Company offers dietary supplements

Q1.5 ⁸ Others:

Q2 The company offering the test

(1) ⁸ also carries out the laboratory work

(2) ⁸ outsources the laboratory work

(3) ⁸ No information

(4) ⁸ Not clear

Characterisation of DCGT services offered

Which types of genetic testing are offered?

Q3 Indicate the diseases, susceptibilities for which genetic testing is offered by name

...

Type of offers

- | | |
|----------------------------------|---|
| Q 3.1 (Yes 1/No 2) ⁸ | Monogenetic Mendelian diseases |
| Q 3.2 (Yes 1/No 2) ⁸ | Monogenetic Mendelian diseases with late onset (Huntington) |
| Q 3.3 (Yes 1/No 2) ⁸ | Testing for genetic variants for multifactorial disease/susceptibilities |
| Q 3.4 (Yes 1/No 2) ⁸ | Risk factors (SNPs) for cancer |
| Q 3.5 (Yes 1/No 2) ⁸ | Risk factors for cardiovascular disease |
| Q 3.6 (Yes 1/No 2) ⁸ | Risk factors for diabetes |
| Q 3.7 (Yes 1/No 2) ⁸ | Risk factors for mental /neurological diseases/disorders |
| Q 3.8 (Yes 1/No 2) ⁸ | Risk factors for other diseases |
| | |
| Q 3.9 (Yes 1/No 2) ⁸ | Response to medical treatment (pharmacogenetic testing) |
| Q 3.10 (Yes 1/No 2) ⁸ | Risk factors for nutrition genetic factors related to personal diet (nutrigenomics), personalised nutrition |
| Q 3.11 (Yes 1/No 2) ⁸ | Offer of a general check of the genome (SNPs) |
| Q 3.12 (Yes 1/No 2) ⁸ | Total sequence of genome |
| | |
| Q 3.13 (Yes 1/No 2) ⁸ | Genetic factors related to athletic performance |
| Q 3.14 (Yes 1/No 2) ⁸ | Genetic factors related to addiction |
| Q 3.15 (Yes 1/No 2) ⁸ | Genetic factors related to cosmetics |
| | |
| Q 3.16 (Yes 1/No 2) ⁸ | Paternity testing |
| Q 3.17 (Yes 1/No 2) ⁸ | Ancestry testing |
| Q 3.18 (Yes 1/No 2) ⁸ | Family inheritance |
| Q 3.19 (Yes 1/No 2) ⁸ | Others |

Q4 Type of testing procedure

Q 4.1 (Yes 1/No 2) ⁸ Test kit for home use with the result provided directly at home

Q 4.2 (Yes 1/No 2) ⁸ Test kit for home use with DNA probe (cheek swab or saliva / blood) to be sent to the provider for analysis

Q 4.3 (Yes 1/No 2) ⁸ Test kit to be used under supervision of a doctor

Q4.3.1 (1) patients doctor, (2) company doctor (3) both are possible

Q5 How are the results submitted

Q 5.1 (Yes 1/No 2) ⁸ Results are obtained directly at home

Q 5.2 (Yes 1/No 2) ⁸ Results are submitted to the client by letter

Q 5.3(Yes 1/No 2) ⁸ Results can be accessed by the client on line / by E-mail

Q 5.4 (Yes 1/No 2) ⁸ Results can be accessed by the client by telephone

Q 5.5 (Yes 1/No 2) ⁸ Results are submitted to the doctor given

Q6 Connection of result submission to consultation

(1) ⁸ Results are submitted to the client without the option of consulting an expert

(2) ⁸ Results are submitted to the client with the option of consulting an expert

(3) ⁸ Results are submitted to client with consultation as a mandatory part of the process

(4) ⁸ No information

(5) ⁸ Not clear

Comments on testing procedure:

Assessment of information available on website

Is any information available on the following issues?

Q 7 ⁸ Qualification of institute and personnel

Q 7.1 (Yes 1 / No 2) ⁸ More general assurance of good quality

Q 7.2 (Yes 1 / No 2) ⁸ More detailed information about qualification of management team/scientific staff

Q 7.3 (Yes 1 / No 2) ⁸ Membership of professional bodies

Q 7.5 (Yes 1 / No 2) ⁸ Subject to control public authorities/ FDA regulation?

Q 7.6.1 (Yes 1 / No 2) ⁸ The company highlights their advisory board: ⁸ scientific

- Q 7.6.2 (Yes 1 / No 2) ⁸ ethical
- Q 7.7 (Yes 1 / No 2) ⁸ The company mentions ⁸ privacy guidelines (data protection)
- Q 7.8 (Yes 1 / No 2) ⁸ informed consent
- Q 7.9 (Yes 1 / No 2) ⁸ other ethical guidelines
- Q 7.10 (Yes 1 / No 2) ⁸ Certification / If yes, which one?
- Q 7.11 (Yes 1 / No 2) ⁸ Accreditation of company

Q 8 ⁸ Information on genetic testing

- Q 8.1 (Yes 1 / No 2) ⁸ General information on genetic testing
- Q 8.2 (Yes 1 / No 2) ⁸ General information on risk factors related to SNPs
- Q 8.3 (Yes 1 / No 2) ⁸ General information on pharmacogenetics
- Q 8.4 (Yes 1 / No 2) ⁸ General information on nutrigenetics

Q 9 ⁸ Test-specific information

- Q 9.1 (Yes 1 / No 2) ⁸ Information on science behind test for lay people
- Q 9.2 (Yes 1 / No 2) ⁸ Information on subgroup of population suitable for testing (when is genetic testing useful and when not)
- Q 9.3 (Yes 1 / No 2) ⁸ Reference to scientific publication
- Q 9.4 (Yes 1 / No 2) ⁸ Information on which SNPs are tested
- Q 9.5 (Yes 1 / No 2) ⁸ Information on algorithm used to predict risk

Q 10 ⁸ Accuracy of test data

- Q 10.1 (Yes 1 / No 2) ⁸ Information on analytical validity (accuracy of test identifying the biomarker)
- Q 10.2 (Yes 1 / No 2) ⁸ Information on clinical validity (relationship between the biomarker and the clinical status)
- Q 10.3 (Yes 1 / No 2) ⁸ Information on clinical utility (likelihood that test will lead to an improved outcome)
- Q 10.4 (Yes 1 / No 2) ⁸ Reference to expert knowledge /scientific evidence

Q 11 ⁸ Information on consequences and actions to be taken

- Q 11.1 (Yes 1 / No 2) ⁸ If a positive test result is obtained
- Q 11.2 (Yes 1 / No 2) ⁸ If a negative test result is obtained

Q12.1 ⁸ Necessity and quality of counselling

Is counselling offered?

(1) ⁸ Yes

Q12.1.1 (Yes 1 / No 2) ⁸ Via telephone

Q12.1.2 (Yes 1 / No 2) ⁸ Via internet

Q12.1.3 (Yes 1 / No 2) ⁸ Before testing

Q12.1.4 (Yes 1 / No 2) ⁸ After testing

Q12.1.5 The company offering the genetic test

(1) does the genetic counselling itself

(2) outsources the genetic counselling

Q 12.1.6 (Yes 1 / No 2) ⁸ Reference to a professional code of practice

Q 12.1.7 (Yes 1 / No 2) ⁸ Staff qualified for counselling

(2) ⁸ No

(3) ⁸ No information

(4) ⁸ Not clear

Price of laboratory and counselling services

Q 13 Is there information on price?

(1) ⁸ Yes

Q13.1 What is the price (EURO) of genetic testing (USD)?

Q13.1.1 ⁸ Test for monogenetic disease

Q13.1.2 ⁸ Test for multifactorial disease

Q13.1.3 ⁸ Risk factors SNPs test

Q13.1.4 ⁸ Pharmacogenetic test

Q13.1.5 ⁸ Nutrigenomic test

Q13.1.6 ⁸ Other

Q13.2 Is counselling included in the price? (1) ⁸Yes

(2) ⁸ No, the counselling costs extra

Q13.2.1 How much (USD)?

(2) ⁸ No

(3) ⁸ Not clear

2. Overview of testing services offered via internet

Firm	Men- delian	Late onset Mendelian	Multi- factorial	Cancer SNPs	Cardio- vascular	Diabetes	Neurologic al/ Mental	Pharmac- o- genetic	Nutri- genetics	Genome Check	Sequenc e of genome	Athleti c	Addictio n	Cosmeti cs	Paternit y	Ancestry	Inheritance	Other	
23and Me	1		1	1	1	1				1		1	1			1	1	Chron's disease	
Acu-Gen Biolab																		Sex testing foetus	
C. Katzin's The DNA Diet									1										
Consumer Genetics								1	1						1				
Cygene Direct			1		1				1			1						Osteoporosis	
decode	1		1	1		1				1							1		
DNADirect	1		1	1	1	1									1		1	Infertility	
DNAPrint genomics																	1		
Eastern Biotech and Lifesciences	1		1	1	1	future	1									1	1	1	premarital screening, prenatal DNA test
GATC											1								
Genelex			1				1	1	1							1	1		
Genova Diagnostics			1		1		1												
G-nostics													1						
GeneLink Biosciences Dermagenetics														1					
Genetic Health UK			1	1	1	1		1	1										
Graceful Earth							1												
HairDX																1			
HealthCheckU SA	1		1		1													Hereditary hemochromatosis, thrombosis, celiac disease	
Health Tests Direct	1		1	1	1													MTHFR test, associated with cardiovascular disease, pregnancy loss, schizophrenia, herpes virus 6 detection	
HIVGene																		HIV resistance	
Holistic Health									1										
Interleukin			1		1				1									Genetic susceptibility test	

Firm	Men- delian	Late onset Mendelian	Multi- factorial	Cancer SNPs	Cardio- vascular	Diabetes	Neurologic al/ Mental	Pharmac- o- genetic	Nutri- genetics	Genome Check	Sequenc- e of genome	Athleti- c	Addictio- n	Cosmeti- cs	Paternity	Ancestry	Inheritance	Other
Genetics /Altior /Quixtar																		for periodontal disease
Kimball Genetics	1		1		1		1	1										
Knome											1							
Molecular Diagnostics Laboratories			1		1			1	1									
Medi-Checks	1	1	1	1											1			Many tests for prenatal or chromosomal analysis, also sex testing unborn child and testing for (developmental) disorders of unborn child.
Mygenome			1		1		1	1										Osteoporosis
Navigenics			1	1	1	1	1		1	1								
NeuroMark								1										
Proactive Genomics			1	1														
Psynomics							1	1										
Salugen									1									
Sciona/Mycellf									1			1						
SeqWright			1	1	1	1	1			1					1	1	1	MS, restless legs syndrome, rheumatoid arthritis, macular degeneration, Crohn's disease
HIVMirror (Smart Genetics)																		HIV resistance
Smart Genetics /ALZ Mirror							1											
Suracell									1					1				
SureGene			1				1	1										