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Direct-to-consumer genetic testing services

In this scientific policy advice report, the Superior Health Council provides recommendations and policy options which are fostering an ethically and medically appropriate offer of direct-to-consumer genetic tests, as the one provided through the healthcare system in Belgium

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1. INTRODUCTION AND ISSUES

I. Introduction

For the purpose of this report, Direct-to-Consumer (DTC) genetic testing is defined as the advertising and selling or (free) provision of genetic tests directly to consumers. Not included in DTC genetic testing as defined for the purpose of this report are genetic tests that are performed in the context of biomonitoring projects, performed by bona fide researchers, authorized by a medical ethical committee and including the implementation of informed consent. As has been suggested by the Human Genetics Commission are also include in this discussion “tests that are commissioned by the consumer” outside the health care system but where a medical practitioner or a health professional is involved in the ordering of the tests or the provision of the test result (HGC, 2010).

Over the last decades the understanding of the genetic background of diseases has increased dramatically. More than 2500 genetic tests (http://www.ncbi.nlm.nih.gov/gtr/qa/) are currently available in clinical practice. The range of DTC genetic tests available is broad, from preconceptional carrier tests for single-gene disorders, such as cystic fibrosis (predicting a high risk of having affected offspring if both partners are carriers) to genetic tests providing information about the predisposition to complex, multifactorial diseases, such as depression and cardiovascular disease. In addition to providing test results, some commercial companies also make recommendations regarding lifestyle changes on the basis of these results, such as changes in diet or use of nutritional supplements. Various genetic tests are currently advertised, sold or provided directly to consumers via internet. Commercial companies offer a broad spectrum of DTC genetic tests: carrier tests for recessive genetic disorders, “life style”-related genetic tests, pharmacogenomics tests, non-invasive DNA--paternity tests or gender testing, romantic relationshiptesting, genomic risk profiles for many conditions, paternity tests, ancestry or genealogical tests.

Genetic tests deserve to be approached carefully for various reasons. From a societal perspective, concerns have been raised that genetic testing may lead to misuse of the genetic information by third parties, including insurers, employers, adoption agencies or others, and/or might lead to stigmatization or discrimination of individuals or groups. In addition, concerns were raised about the private and confidential character of genetic information. At a personal level,

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genetic test results of a person might have direct implications for relatives, including offspring. Moreover, genetic testing might provide information about the medical future of a healthy person, which is generally different from traditional medical diagnosis that says something about the current medical condition of a patient. Finally, it has been reported that a genetic test may also lead to psychological distress, including increased anxiety, depression, changed familial relations, changes in self-image or health perceptions.

Because of these issues genetic tests are performed in a clinical genetics centre or in other entities recognized and/or certified by national healthcare systems in most European countries, where due emphasis is being provided on the individualized medical supervision of patients, the presence of pre-test and post-test counseling, psychological follow-up and quality assurance of the tests performed, as proposed by the European Convention on Human Rights and Biomedicine (1997) and its additional protocol on genetic testing as well as by the Recommendation (CM/Rec(2010)11) on the impact of genetics on the organization of health care services and training of health care professionals of the council of Europe.

In contrast to this practice embedded in health care, in the last three years private commercial companies have been advertising and selling genetic tests directly-to-consumers (DTC) (Hunter et al., 2008). *Nature* reported that “the availability of affordable, direct-to-consumer genetic tests has mushroomed”(Nature, 2009).

The offer of DTC genetic tests creates various concerns about real or potential dangers, including (1) the lack of analytical validity, clinical validity and clinical utility of the tests being sold; (2) the lack of quality control of the tests and laboratories involved in test provision as well as the qualifications of the personnel involved; (3) the (misleading or unfair) advertisement of genetic tests; (4) the inadequate process of informed consent and genetic counseling; (5) the inappropriate genetic testing of children; (6) the lack of individualized medical supervision; (7) the downstream impact on the healthcare system and (8) the potential infringement of research ethics guidelines.

For these reasons, the Superior Health Council (SHC) decided to review of the current offer of DTC genetic testing and of the concerns related to this offer and to develop recommendations and policy options for Belgium which are fostering an ethically and medically appropriate offer of genetic tests, as the one currently provided through the Belgian healthcare system.

In order to formulate recommendations, an ad hoc working group was set up wich consisted of experts in the following fields: medicine, genetics, in vitro diagnostics legislation, toxicology, medical bioethics, medical law, epidemiology, radiobiology, pharmacogenomics.

2. RECOMMENDATIONS

Recommendation 1: Information provision to health care professionals and the general public

In the light of a growing number of companies selling and advertising genetic tests DTC, the SHC considers it crucial that information is available for health care professionals and the general public that gives background on genetic testing and describes the provision of genetic testing services. On the one hand, it is important to underline that clinically validated and medically appropriate genetic tests are offered in clinical services for those that need them and that these are reimbursed by the healthcare system. On the other hand, it is important that information is available about the limitations and concerns of the tests that are currently advertised, provided or sold through the internet.

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This information should be available in English, French, Dutch and German on the websites of the Belgian Ministry of Health and potentially other relevant websites. Moreover, (electronic) leaflets should be elaborated and provided to and for various healthcare professionals and the general public. Good examples of such documents were elaborated by the Federal Trade Commission in the U.S (Federal Trade Commission, 2006) and a patient organization in the U.K. (Genetics Interest Group, 2009). The Council of Europe is currently also preparing an information leaflet on genetic testing where DTC genetic testing is being discussed. The SHC is ready to collaborate to the editing and diffusion of such information leaflets.

Recommendation 2: Existing legislation doesn't cover in a sufficient way direct-to-consumer genetic testing

Compared to countries as Germany, Switzerland, Portugal and France, Belgium does not have a specific legislative framework that regulates the provision of genetic testing services. A Royal Decree of 14 December 1987 (Published in the Belgian Official Journal of 25 December 1987) lays down the rules for the provision of genetic testing in the centres for human genetics in Belgium. Additionally, the Royal Decree of June 7th 2007, modifying the Royal Decree of September 7th 1984, sets requirements for laboratories performing reimbursed molecular biological tests for the determination of acquired pathologies in human genetic material. Belgium has also legislation that addresses the topic of genetics and insurance. A total ban on the use of genetic testing to predict the future health status of applicants for (life) insurance was laid down by article 95 of the Law on Insurance Contract. In addition, the Law on the Rights of Patients of 22 August 2002 describes the rights and duties of physicians and patients. Finally, Flanders has legislation on population screening. Although similar legislation in the Netherlands can partly control the offer of such tests in the Netherlands, DTC genetic testing falls currently outside the remit of the Flemish legislation. The only legal basis applying to DTC genetic tests might be found in article 2 of the Law on the practice of health care professions (Royal decree n°78 (B.S. 14.11.1967)) [1] which stipulates that a physician (recognized by the Belgian health system) should be involved in the provision of medical services requiring an activity considered as a practice of medicine. Hence, if a DTC genetic test falls under the practice of medicine, as a consequence, a physician recognized by the Belgian health system should be involved and the Law on patient rights would apply.

However, most DTC companies write in their 'terms of services' that they are not practicing medicine, and that their tests should not be considered medical information, but only serve "informational purposes." The SHC considers that DTC genetic testing companies state these claims in order to escape regulatory control and considers that most of the tests that are provided by DTC genetic testing companies should be considered medical information and therefore as a practice of medicine.

The current regulations in Belgium don't cover in a satisfactory way the potential provision of genetic testing outside the context of the Centre for Human Genetics and necessitates further action. The SHC considers that a possibility could be to investigate the applicability of the legislation with regard to population screening in Flanders to DTC companies that operate from and in Flanders. However, the SHC also underlines that such an evaluation does not make sense if this would only be happening in one region. A similar evaluation (based on the same criteria) should be operational in all regions.

[1] Article 2: [Koninklijk besluit nr 78 betreffende de uitoefening van de gezondheidszorgberoepen] "Niemand mag de geneeskunde uitoefenen die niet het wettelijk diploma bezit van doctor in de genees-, heel- en verloskunde, dat werd behaald in overeenstemming met de wetgeving op het toekennen van de academische graden en het programma van de universitaire examens, of die niet wettelijk ervan vrijgesteld is, en die bovendien de voorwaarden gesteld bij artikel 7, (...) niet vervult."

Recommendation 3: Strenghtening international regulatory oversight

In Europe medical device regulation is controlled by three E.U. Directives, the third of these is the Directive for In Vitro Diagnostic Medical Devices (IVD) which provides a regulatory framework for all IVDs which are to be placed on the market within the EEA Member States, Switzerland and Turkey. This Directive, which was published in 1998 and came into force in 2003, governs the safety and performance of devices by setting out the essential requirements which have to be addressed before placing a product on the market (e.g. labeling, analytical and diagnostic performances), and, among others, the obligation for post-marketing surveillance.

Genetic tests with a medical purpose fall under the regulation of in vitro diagnostic medical devices. However, at this moment, human genetic testing would generally not fall within Annex II (which defines the tests that need a premarket review), and therefore not be subject to a third party conformity assessment. Foreseen changes of this regulatory framework (with the introduction of a risk model based on four classes running from high to low risk), will most probably move genetic tests into a risk category requiring premarket review.

The Superior Health Council wants to underline, however, that such a premarket review analyzes the safety and performance of the device in the light of the claims of the manufacturer. It does not include an assessment of the clinical usefulness of the device. The introduction of essential requirements addressing the validation of the clinical usefulness of genetic tests in the revised IVD legislation is therefore recommended. It should be acknowledged that the IVD Directive will not provide an assessment whether it is good medical practice to provide a test to a population. It should also be noted that DTC genetic tests that are not intended for medical purpose, such as tests providing information for lifestyle improvement or paternity testing, are excluded from the IVD Directive 98/79/EC. Also, reagents which are produced within health-institution laboratories for use in that environment and are not subject to commercial transactions are not covered by the IVD Directive 98/79/EC. In conclusion, the major weaknesses of the Directive for In Vitro Diagnostic Medical Devices in relation to direct-to-consumer genetic testing should be discussed at an international level.

Recommendation 4: Implementation of a national regulatory oversight

In the light of the loopholes of the applicable legislations, the SHC calls for the elaboration of a regulatory framework that covers the provision of genetic testing services in all potential contexts in Belgium. Although it is impossible to control or restrict an international market of companies that are selling or advertising genetic tests through the internet, the SHC recommends to impose regulatory barriers to companies that would provide or advertise genetic tests for the Belgian market. The impact on public health is becoming more important in the case that companies are marketing and selling tests in the users language and territory, legitimizing regulatory actions.

In light of international efforts elaborated at the Council of Europe, the SHC calls for a translation into national legislation of the content of the "Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing". Specific articles of this Additional Protocol focus on the information provision, genetic counseling, consent procedure, and respect for private life.

Moreover, the SHC recommends making use of the elaborated legislation in other legislations as a starting point for the Belgian legislation. Of particular interest is the Swiss legislation (*Federal Act on Human Genetic Testing* (Federal Assembly of the Swiss Confederation, 2004) from 8 October 2004 (Sprumont, 2004), that provides a framework that aims to prevent improper genetic testing and the improper use of genetic data and to ensure the quality of genetic tests and the way their results are interpreted. It describes general principles such as non-discrimination, consent, right not to know, protection of genetic data, authorization to perform genetic testing. It also describes specific articles with regard to the use of genetic testing in the medical context, in

the context of employment, insurance, liability, and filiation. The genetic tests offered directly-to-consumers correspond to the definition of 'genetic in vitro diagnostic medical devices' as formulated by article 3j of the above mentioned law: "ready-to-use products for the determination of characteristics of human genetic material". Those tests are covered by Article 9 of this Act that reads as follows: "(1) It is forbidden to supply genetic in vitro diagnostic medical devices to individuals for a purpose which cannot be considered part of those individuals' professional or commercial activities; (2) The Federal Council may, having consulted the Expert Commission for Human Genetic Testing, make provision for exceptions to this prohibition provided the products are used under medical supervision and misinterpretation of the test result is not possible." The Act has been completed by two ordinances: the Federal Council Ordinance on Human Genetic Testing from 14 February 2007 (Federal Assembly of the Swiss Confederation, 2007) and the Federal Department of Home Affairs Ordinance on Human Genetic Testing from 14 February 2007 (Federal Department of Home Affairs, 2011). None of these regulations provide for an exception to article 9 of the Act prohibition for DTC genetic testing. In fact, the Act (Sprumont, 2004) makes it a criminal penalty to infringe this prohibition as stated in article 38: "(1) Any person who, in contravention of Article 9 paragraph 1, wilfully supplies genetic in vitro diagnostic medical devices to individuals for a purpose which cannot be considered part of those individuals' professional or commercial activities shall be liable to a fine; (2) If the act is committed for commercial gain, the penalty shall be a custodial sentence not exceeding three years or a monetary penalty."

The SHC recommends that Belgium should implement similar legislation with regard to DTC genetic testing for health purposes as in Switzerland. On the one hand this legislation clearly prohibits the offer of DTC genetic testing, and on the other it provides a procedure for companies that might want to offer DTC genetic tests, and requests that those tests are offered under medical supervision, have demonstrated, validated and published clinical utility, and are offered with respect for patient rights, and with correct information. As in Switzerland, a Belgian federal interdisciplinary committee (comprising expertise in clinical and human and public health genomics, pharmacology, health technology assessment, public health, law, ethics) should be entitled to monitor and evaluate the DTC genetic testing provided to the Belgian market, as well as the fulfillment of the requirements imposed on the companies providing these tests

Recommendation 5: Regulating the offer not its use

The SHC wishes to emphasize the fact that, in imposing restrictions as described in Rec. 4, the focus should be on the companies that advertise and sell genetic tests. Individuals that would order genetic tests for themselves should not be penalized or criminalized. However, ordering a genetic test on material from a third person such as minor if not by an authorized physician, should be penalized by law. Also in the Swiss law, there is no explicit sanction in the law against someone who requests such test for his or her personal use.

Recommendation 6: Further research and discussion is necessary

Firstly, the SHC wants to underline that it did not discuss the specificities of the DTC offer of tests that perform non-invasive prenatal diagnosis. The possibilities of earlier determination of sex during pregnancy, might for example create an increasing demand for abortion for non-medical reasons within the abortion period allowed by the current legislation and might create increased impact on our health care system. Further interdisciplinary discussion on this matter is necessary.

Secondly, the SHC wants to underline that the DTC offer of preconceptional carrier testing questions the offer of preconception care and the systematic offer of carrier tests towards a population of couples that are planning a pregnancy. Such a systematic screening offer doesn't exist in our healthcare system at this moment. It may however even more so create an increased impact on our health care system. Further interdisciplinary discussion on this matter is also necessary.

Thirdly, the SHC wants to underline that various DTC genetic testing companies offer genealogical tests and ancestry tests. Although less problematic in nature than the current offer of DTC genetic testing for health purposes, those tests have shown to be able to trace biological relatives (such as anonymous gamete donors or adoption donors (and their family members)). Further interdisciplinary discussion is necessary on the increasing difficulty to protect anonymity in gamete donors in the context of artificial reproductive technologies and the impact of this in the context of adoption.

KEYWORDS

Keywords	Mesh terms*	Sleutelwoorden	Mots clés	Stichworte
Direct-to-consumer		Rechtstreeks voor de consument	Directement au consommateur	
Genetic testing	Genetic Testing	Genetische testen	Test génétiques	
Biomedical ethic	Bioethics	Biomedische ethiek	Ethique biomédicale	
Regulation	Legislation as Topic	Reglementering	Règlementation	
Healthcare system	Delivery of Health care	Gezondheidszorg systeem	Système de soins de santé	

** MeSH (Medical Subject Headings) is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed.*

3. FURTHER DETAILS AND ARGUMENTATION

List of abbreviations

BRCA :	Breast Cancer
CF :	Cystic Fibrosis
DNA :	Deoxyribose Nucleic Acid
DTC:	Direct-to-consumer
EEA :	European Economic Area
EGAPP :	Evaluation of Genomic Applications in Practice and Prevention
FDA :	Food and Drug Administration
GAO :	Government Accountability Office
GenDG :	The Genetic Diagnosis Act
GHTF:	Global Harmonisation Task Force
GT :	Genetic Test
HbP :	High Blood Pressure
HGC :	Human Genetics Commission
IVD :	In Vitro Diagnostic
LDT :	Laboratory Developed Test
PSA :	Prostate Specific Antigen
SHC :	Superior Health Council
SNP :	Single Nucleotide Polymorphisms

I. Methodology

This advisory report is based on a review of the scientific literature as well as the grey literature, and as well as on the experts' opinion.

II. Direct-to-consumer genetic testing: the offer

1. Types of tests

It is not really possible to provide a complete overview of the genetic tests that are currently advertised or sold directly-to-consumers. However, it is clear that the active companies cover a very broad spectrum of tests, and some companies provide more than one type of test in their offer.

Firstly, various commercial companies presently offer DTC **carrier tests for recessive genetic disorders**. Identifying carriers of autosomal recessive or X-linked disorders before pregnancy has the potential to benefit prospective parents. Couples can become aware of the possible genetic risks to future offspring and of the reproductive options available. These options include not only prenatal diagnosis followed (or not) by termination of the pregnancy in case of an affected fetus or coming to terms with the risk, but also deciding to refrain from having children, adoption, using donor sperm or eggs, or preimplantation genetic diagnosis. In some culturally-related marriage practices, it could also result in choosing a different partner. The details of offer from each company, however, vary greatly. The company *DNA Direct* (www.dnadirect.com) advertised for one individual carrier test (for CF) and one carrier testing panel (for Ashkenazi Jews). The company *DNATraits* says that they are "committed to making all medically validated tests available to consumers rapidly, inexpensively and understandably" (www.dnatraits.com/compare accessed 03/05/2010) and is selling a limited number of individual tests (e.g. for Alpha-1-Antitrypsin Deficiency) as well as panels of disorders (e.g. an Ashkenazi Jewish Genetic Disease Panel or a sickle cell/beta-thalassemia panel). Along with risk assessment information for other disorders, *Pathway Genomics* (www.pathway.com) and *23andMe* (www.23andme.com) include in their full genome testing report the carrier status for 37 and 24 different single-gene conditions respectively. In February 2010 the company *Counsyl* (www.counsyl.com) launched their offer of a prepregnancy 'universal carrier test' which tests an individual or couple for over 100, mostly autosomal recessive, genetic diseases. *Counsyl* considers these activities as " a cause, a campaign to finally end the needless suffering of preventable genetic disease" (https://www.counsyl.com/about/counsyl/ accessed 19/01/2011).

Secondly, various companies provide genetic testing for individual **"life-style"-related genetic traits**. In contrast with the previous category, these tests are focused on particular traits or predispositions. Here some examples. Based on studies suggesting that the ACTN3 gene has an impact on athletic performance, companies as Atlas Sports Genetics (http://www.atlasgene.com/), Genetic Technologies (http://www.gtglabs.com/), American International Biotechnology Services (http://www.sportsxfactor.com/Home.aspx), Inneova (www.inneova.com) and CyGene Direct (http://www.cygenedirect.com/) are selling tests that aim to provide "parents and coaches early information on their child's genetic predisposition for success in team or individual speed/power or endurance sports." (http://www.atlasgene.com/ Accessed 7 June 2011) Companies as Consumer Genetics (http://www.consumergenetics.com/), Gene Planet Limited (http://www.geneplanet.com/), My Gene (http://mygene.com.au/) provide genetic tests that "will tell you if you have the fast or slow caffeine metabolizing gene" (http://www.consumergenetics.com/DNA-Tests/Caffeine-Metabolism-Test.php Accessed 7 June 2011) Companies as Salugen (www.salugen.com), Amway (www.amway.com), Interleukin Genetics (http://www.ilgenetics.com/), Holistic Health International (http://www.holistichealth.com/) offer nutrigenomic tests and combine their genetic tests often with purchasing particular dietary supplements that are recommended and tailored to the individual needs of the consumers depending on the test results.

Thirdly, various companies provide **pharmacogenomic tests**, such as genetic tests for drugs response for inhalers containing beta-agonists (albuterol, solbutamol, salmeterol), Plavix, Tamoxifen or Warfarin. These tests are provided by companies as Consumer Genetics (http://www.consumergenetics.com/), Matrix Genomics (http://www.matrixgenomics.com/), DNAdirect (www.dnadirect.com) or Genelex (http://www.healthanddna.com/).

Fourthly, some companies are offering non-invasive dna-paternity testing or gender testing. This is for example done through companies as the Prenatal Genetics Center

(http://www.prenatalgeneticscenter.com/), ACU-gen Biolabs (www.babygendermentor.com) or Urobiologics (http://www.urobiologics.com/).
Fifthly, a company as Scientific Match (www.scientificmatch.com) is selling a DNA test as complementary way to find a romantic relationship.
Sixthly, some companies such as 23andme (www.23andme.com), Navigenics (www.navigenics.com), deCodeMe (www.decodeme.com) or Pathway genomics (www.pathwaygenomics.com) are offering "genetic profiles" which involves testing over half million single nucleotide polymorphisms (SNPs; these are positions in the genome at which the nucleotide varies within a population), and claim to be able to provide personal information regarding many disorders. They use information from scientific studies to estimate composite risk factors for diseases based on each customer's SNPs. The vision offered here is to convey an all inclusive test for known genetic variants associated with susceptibilities for disease or behavioral traits and abilities. They also provide information about ancestry, carrier status information or pharmacogenomics.
Seventhly, various companies provide non-medically oriented information. This includes the offer of ancestry and genealogical tests, as well as tests identifying familial relationship (e.g. paternity testing). Ancestry testing is done by companies such as Family Tree DNA (www.familytreedna.com), DNA diagnostic Center (www.ancestrybydna.com) or Nimble Diagnostics (http://nimblediagnostics.eu).
Finally, it should also be observed that a company as Myriad launched a few years ago a massive advertisement campaign for a predictive genetic test for breast cancer (BRCA1 and BRCA2). (Matloff & Capaln, 2008;Mouchawar et al., 2005)

2. Vision promoted by DTC companies[2]

The principle notions used in the marketing of DTC genetic tests are autonomy, empowerment, prevention, convenience, and privacy. One of the main aspects outlined in the vision of these companies is that individuals want to have a more active role in the creation, storage and protection of their personal genetic information. They promote the notion that avoiding the traditional encounter with a health care professional will result in a better guarantee of privacy, at least with respect to insurance companies and employers. Moreover, DTC genetic tests allow consumers to collect their own saliva samples (from which DNA is then extracted) from the comfort of their own home. For some tests, the companies argue that it eliminates the hassle of scheduling an appointment with a physician and it eliminates an appointment fee that would otherwise be billed in addition to the laboratory fee (Berg & Fryer-Edwards, 2008) Companies also allege that this model will allow for the increased access of genetic technologies for all consumers. Furthermore, companies advance that this provides "the foundation for truly personalized medicine in which individuals are empowered not only with self-knowledge of their genetic risk, but also with the ability to take informed actions to prevent disease and preserve health"(Ledley, 2002).

3. Success and failure of the DTC market[3]

Presently, little is known about the actual number of genetic tests sold by DTC genetic testing companies. A few American studies have shown that only a relatively small percentage of the US population is aware of the availability of direct-to-consumer genetic tests and only a fraction of these have applied for such tests (Goddard et al., 2006; Goddard et al., 2006; Kolor et al., 2008). In a recent study by Wright and Gregory-Jones, the authors attempted to estimate the size of the DTC whole genome scan market using the Internet traffic on three companies' websites as a proxy for their commercial activity (Wright & Gregory-Jones, 2010). Despite the limited scope of interpretation and generalization allowed by this method, their conclusion that the demand for

[2] Based on Borry P, Cornel MC, Howard HC. Where are you going, where have you been. Direct-to-consumer genetic tests for health purposes. Journal of Community Genetics 2010; 1(3):101-106.
[3] Based on Borry P, Cornel MC, Howard HC. Where are you going, where have you been. Direct-to-consumer genetic tests for health purposes. Journal of Community Genetics 2010; 1(3):101-106.

whole genome scans is fairly small is congruent with the previous studies. That being said, they still estimated the market for the three most prominent genome profiling companies (23andme, deCODE and Navigenics) to be around US $ 10-20 million in 2009.
An analysis of DTC genetic testing companies' activities in this field shows that various genetic tests that were marketed are no longer available for purchase from certain companies. For example, the following tests are no longer available for purchase: tests that predicted AIDS progression based on an analysis of CCR5-Delta 32 and CCR2-64I genes (www.hivgene.com, www.hivmirror.com); nutrigenomic tests (www.mycellf.com, www.genecare.co.za, www.integrativegenomics.com); risk assessment tests of various common disorders such as cardiovascular disease, osteoporosis, immune system defects, Alzheimer Disease (www.genovations.com, www.smartgenetics.com, www.qtrait.com); tests for addiction (www.docblum.com); pharmacogenomic tests (www.signaturegenetics.com); carrier testing for disorders such as cystic fibrosis (www.udlgenetics.com). Meanwhile, some companies retracted their product from the market temporarily for unknown reasons (www.genotrim.com, www.psynomics.com) and it is unclear whether they will be available again. Other initiatives, such as the free "comprehensive genetic test" (www.geneview.com) also disappeared. Since these companies have, for the most part, left the market in silence, it is difficult to understand exactly their reasons for doing so. One may suggest that the consequences of the global financial crisis (starting in 2007-2008) may have contributed to the downfall of some of these companies (i.e: failure to find enough paying customers). That being said, it seems that various companies also struggled with intellectual property protection (Bandelt et al., 2008; Knowledge Wharton, 2009) and the legal requirement that a physician should be involved in the ordering of genetic tests (Wadman, 2008) (which is the case in some states in the USA such as Connecticut and Michigan). Furthermore, companies testing only a few mutations (with each mutation corresponding to one trait) may have had difficulties competing with companies like 23andme, which offer full genome scans (Hayden, 2008). Other companies deliberately chose to focus on ancestry testing, and have avoided making statements about health risks (Altman, 2009). Such companies offering DNA tests for genealogical information now exist in abundance (Bandelt et al., 2008).

4. DTC genetic testing in the European context

It is clear that the majority of the DTC companies are operating at this moment from the United States. However, there are reasons for concerns as these companies will try to attract more consumers from the European market. From a study came out that already at this moment 33% (41/123) of the European clinical geneticists were contacted by patients before undergoing or considering to undergo a DTC genetic test; and 45% (54/121) had been contacted by patients after undergoing a DTC genetic test (European Society of Human Genetics, 2011). The companies most often mentioned were 23andme, Navigenics and decodeme.
Moreover, the number of companies operating from Europe is slightly increasing. Although their mode of operations is not always clear, they all seem to advertise and/or sell genetic tests directly-to consumers. The company Gene Planet Limited (http://www.geneplanet.com/) has its headquarters in Dublin (Ireland), but operates from Slovenia. The company Genetic Health operates in the United Kingdom (http://www.genetic-health.co.uk/). The company My Gene Profile is operating from the U.S. and from the U.K. (http://www.mygeneprofile.com/). A company as Medichecks (U.K.) is advertising over 1200 health checks and blood tests online. (http://www.medichecks.com) For some, a medical prescription is necessary. The company Genepartner GmbH (www.genepartner.com) is operating from Switzerland. The company Genosense is operating in Austria (http://www.genosense.com) In Spain, the company Progenika Biopharma (www.progenika.com) is advertising some tests. A company in Portugal is advertising genetic tests for common disorders, but asks for medical prescription (http://www.genetest.pt). In Belgium, the company Euramedica BVBA/Pharmagenoma Europa is also mentioned as a distributor for a genetic test advertised by the company Hair DX (www.hairdx.com). In the Netherlands, the company Geneticom announced that it would start selling DTC genetic tests, but finally resigned from their plans (www.geneticom.nl). A few companies were operating in Europe, but their websites are currently not available anymore (www.g-nostics.com (U.K.);

www.genosolutions.com (Portugal), www.udlgenetics.com (U.K.). Finally, it is also important to raise the question how commercial laboratories are operating. A Belgian company as Gendia (www.gendia.net), which is not advertising directly-to-consumers, was mentioned in the study (European Society of Human Genetics, 2011) by clinical geneticists as a company where patients could receive genetic tests without remediation by a healthcare professional.

III. Direct-to-consumer genetic testing: concerns

The offer of DTC genetic tests creates various concerns. The main concerns that have been related to the offer of DTC genetic tests are: (1) the analytical validity, clinical validity and clinical utility of the tests being sold; (2) the quality control of the tests and laboratories involved in test provision as well as the qualifications of the personnel involved; (3) the advertisement of genetic tests; (4) the process of informed consent and genetic counseling; (5) the genetic testing of children; (6) the lack of individualized medical supervision; and (7) the downstream impact on the healthcare system. There are still some additional concerns for conclusion.

1. Analytical validity, clinical validity and clinical utility

The majority of currently offered DTC genetic tests are providing a susceptibility or predisposition for common disorders or traits. Huge concerns revolve around issues such the analytic validity and the clinical validity of these tests. Analytic validity refers to "the accuracy with which a particular genetic characteristic (e.g. a DNA sequence variant) can be identified in a given laboratory test" (Burke, 2002). Although there is, as of yet, no report regarding the performance of the genotyping methods within a commercial setting, most researchers consider the analytic validity of the methods used to be rather high (Hunter, 2008). Clinical validity refers to the strength of the association between the genotype and disease. Basically, if the risk-genotype is identified in an individual, what are the chances that he or she will develop the disease (Wade & Wilfond, 2006) ? Within the context of common multifactorial diseases apart from a small number of exceptions, most genotype-disease associations are very weak. Many concerns with regard to the commercial offer of DTC genetic testing are based on the meaningless predictive value of the tests currently offered. As denoted by Janssens et al. (2008), "there is insufficient evidence to conclude that genomic profiles are useful in measuring genetic risk for common diseases or in developing personalized diet and lifestyle recommendations for disease prevention." Similar reports have described the limited value of risk prediction models which are only based on genetic information. (Mihaescu et al., 2009; Janssens & van Duijn, 2010; Janssens et al., 2011; Mihaescu et al., 2011; Palomaki et al., 2010). Likewise, in the U.S.A., the Government Accountability Office (GAO) (Kutz, 2006) investigated the legitimacy of claims made by nutrigenetics companies who advertised being able to provide personalized nutrition and lifestyle recommendations based on genetic information. The GAO concluded that "the tests we purchased [from these nutrigenetics companies] mislead the consumer by making health-related predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers." Multifactorial disorders are hypothesized to occur due to a complex interaction of multiple genes and environmental factors; both individual and compounded factors are poorly understood. Each genetic and environmental factor often contribute only a modest fraction of the risk of developing the disorder, therefore, making it extremely difficult to assign an accurate and meaningful degree of risk to each different factor.

Also in the context of carrier identification of autosomal recessive disorders, concerns with regard to clinical validity may apply. Although the analytical validity of the test for each mutation included in carrier panels offered by DTC genetic testing companies has likely been validated, the clinical validity (i.e. how consistently and accurately the test detects or predicts the intermediate or final outcomes of interest) of the panel of mutations may be far from 100%. Some homozygotes, because of low penetrance, may never develop overt disease, and/or the expression may be variable (Levenson, 2010). For example, this is the case for hereditary haemochromatosis, which is also included in the *Counsyl* test panel (www.counsyl.com). In addition, companies offering large panels of disorders may base their inclusion criteria on technical and economic aspects rather than on policy considerations, which take into account, among other things, carrier

frequency, severity of the disorder and feasibility of testing in a particular population. It also raises doubts about the individual disorders included in these large testing panels, and questions whether 'more is really better' (Leib et al., 2005). Moreover, the question is raised of whether good information and informed decision making (see here below clinical utility) is still possible when the test panel contains such a heterogeneous group of disorders, for which test sensitivity and specificity are variable.

Ultimately, the reason why we would want to undergo genetic testing at all has to do with a test's clinical utility. That is to say, once a genetic variant known to increase one's risk of developing a disease has been identified, how can this be useful in clinical practice? How can this be of any use to the patient who is trying to reduce his/her risk of developing a disease? Will this genetic information add to our knowledge of what should be done to prevent disease? At present, physicians routinely recommend one or more of the following preventive measures for cardiovascular disease, diabetes, and obesity: do not smoke, exercise regularly, eat a nutritious and balanced diet, reduce stress, and control blood pressure. Genetic risk information is not likely to change these recommendations. Companies tend to sell genetic tests as 'knowledge'. Although the clinical utility might not be supported, they claim that tests might have a personal utility (Foster et al., 2009). This interpretation of utility is at odds with tentatives of the professional community of clinical geneticists to develop common standards of clinical utility, for example as those being developed by the UK Genetic Testing Network (Gene Dossiers, http://www.ukgtn.nhs.uk/gtn/Information/Services/Gene+Dossiers), the EU funded Eurogentest network of excellence (Gene Cards, http://www.eurogentest.org/web/info/public/unit3/geneCards.xhtml) or the Evaluation of Genomic Applications in Practice and Prevention (EGAPP, http://www.egappreviews.org/). This interpretation of personal utility might as well be at odds with a "population health validity and utility" as for example defined by a state in its health policy.

2. Quality control and qualifications of personnel involved

As expressed it the statement of the European Society of Human Genetics, "all laboratories offering genetic testing services should implement an internal quality system and be subject to regular external quality assessment. Certification of laboratory procedures and accreditation of the tests offered is the standard for guaranteeing the quality of molecular genetic testing for health purposes. All persons involved in the provision of genetic services (i.e. medical doctors, nurses, genetic counselors, and biologists and technicians working at the laboratories) should have the appropriate qualifications and training and perform their role in accordance with professional best practices and ethical standards" (ESHG, 2010). It is unclear whether all laboratories providing DTC genetic testing fulfill these quality criteria. Worries were for example expressed with regard to the qualifications and impartiality of genetic counselors or health care professionals hired by or linked to these companies.

3. Advertisements

Research on DTC advertising of prescription medicine has shown that this has created an inappropriate demand for medications (Calfee, 2007; Donohue et al., 2007; Schommer & Hansen, 2005; Hamp et al., 2006; Donohue, 2006; Bradford et al, 2006; Mahon, 2006). Moreover, it has been shown that various advertisements for drugs have been misleading. Overstatement of effectiveness or minimization of risk has lead to inadequate or inappropriate changes in medication, diet or lifestyle by consumers. DTC advertising of genetic tests for health-related purposes runs the same risks as DTC advertising of prescription medicine in this regard. Aggressive marketing strategies and slogans for DTC genetic testing might overstate the potential for predictive information of such tests and overrate its future health implications. An example of such an aggressive marketing strategy can be seen at following advertisement http://www.mygeneprofile.com/talent-test.html. All this is likely done to increase test uptake. In most of the company websites there is a huge difference between what can be seen on the start page of a company and in the terms of service. For example at the homepage of deCodeme we can read "Now we have the ability to test someone's genetic risk for certain disease states and then make clinical decisions based on that genetic backdrop" and one can find in their service

agreement and informed consent section “The Genetic Scan product is for informational purposes only, is not medical advice, and is not a substitute for professional medical advice, genetic counseling, diagnosis, or treatment.”(www.decodeme.com). Such examples question the desirability of advertisements for genetic tests and underline anyway the necessity to ensure that advertisements should be accurate and not misleading, claims should be transparent and supported by current evidence, and complete and accurate information about the test limitations, risks and benefits should be provided.

4. Informed consent and genetic counseling

The provision of informed consent implies the presence of two elements: information and voluntary participation. At the level of information, it is crucial that individuals receive the necessary information about the purpose of a test, the (reproductive) choices resulting from a test, the reliability and limitations of a test, the possible psychological impact and the potential consequences of a test for the individual and his/her family members (McQueen, 2002). Privacy and confidentiality of the results, as well as possible consequences related to its disclosure to third parties, such as insurance companies and employers, should also be discussed. Although most DTC companies do foresee in most of this information on their websites, the question is whether, while being commercially driven, the information presented is balanced enough to enable informed choice. Moreover, according to a recent study (Molster et al., 2009), many users would struggle to find and understand the important information on companies websites needed to make an informed decision.

The provision of genetic test results through a website certainly poses various problems. Various studies showed, for example, the difficulties of educating people about carrier status results. The limited knowledge of genetics in the general population (Molster et al., 2009), and the fact that carrier tests have a test sensitivity of less than 100% (causing a residual risk to people who are not found to be carriers) make the goal of transmitting information about these tests a non-trivial matter. Studies have shown that a significant proportion of screen-negative tested participants who underwent preconceptional screening for CF or HbPs wrongly believed that they were definitively not carriers, while some carriers falsely believed that they were only likely to be carriers (Hartley et al., 1997; Honnor et al., 2000; Lakeman et al., 2008; Payne et al., 1997). An offer of DTC testing faces probably the same problems in educating people as has been demonstrated in these screening programs. Multiple studies have also demonstrated that both carriers and non-carriers may experience negative feelings, such as anxiety and worry, when participating in genetic screening, but anxiety levels often decrease after a few months (Lakeman et al., 2008; Bekker, 1994). Genetic results for common complex disorders are similarly complicated by the fact that they are probabilistic in nature, and must be interpreted in the context of family history, present health status and other environmental conditions (e.g. life style, diet, place where someone lives…). Consumers who obtain a test revealing a form of increased risk may over-estimate the risk they have of developing disease and this may cause undue stress and anxiety and unnecessary follow-up tests or treatments. Meanwhile, consumers with results that suggest standard or inferior than average risk of developing a disorder may understand this as meaning that they no longer have to worry about leading a healthy life style. The absence of genetic counseling accompanying the provision of test results might be problematic in some cases. Genetic counseling is the process through which information enables individuals to make their own free decisions about testing. In this understanding, although all companies selling genetic DTC tests require some type of consent form to be signed when ordering a test, the process of informed decision-making cannot be reduced to signing a written document. Genetic counseling is a communication process, which deals with the occurrence, or risk of occurrence, of a genetic disorder in the family. The process involves an attempt by appropriately trained person(s) to help the individual or the family to understand the medical facts of the disorder and the options on how to deal with it. A conflict of interest that may arise when the healthcare professionals involved in the counseling are employed by or linked to the companies selling the tests. In this case impartial health advice might be compromised. Finally, present DTC services are organized in such a way that there is no control over the origin of the samples being analyzed. Most companies send mouth swab kits as these are easier and more practical than

having to send the client to a clinic where blood is drawn Since the mouth swab is done in the privacy of the clients' home, there is no way of controlling for the identity of the sample provider. Testing of third parties, such as incompetent minors or incapacitated adults, becomes possible and rather impossible to control.

5. Genetic testing of children[4]

Clinical guidelines focusing on genetic testing in minors have emphasized that the best interest of the child is paramount and that perceived benefits and risks of testing must be carefully weighed when considering a genetic test in minors. In the context of a genetic test for a late onset disorder, testing has only been recommended when "established, effective, and important medical treatment" (German Society of Human Genetics, 1995) can be offered or when testing "provides scope for treatment which to any essential degree prevents, defers or alleviates the outbreak of disease or the consequences of the outbreak of disease" (Danish Council of Ethics, 2001). The rationale behind this option is that predictive and presymptomatic testing for adult-onset disease "should be delayed until the person is old enough to make an informed choice" (ESHG, 2001). The same notion applies to carrier testing, where it has been advanced that "For carrier status for conditions that will be important only in reproductive decision making, testing of children should be discouraged until the child is able to participate fully in the decision to be tested" (Bioethics Committee Canadian Paediatric Society, 2001).

However, when looking at the policies of DTC genetic testing companies (Borry et al; 2009; Borry et al., 2009) and having surveyed various DTC companies the auteur's have seen that various of these companies definitely test minors (Howard et al., 2011). As alluded to previously, in view of the major ethical considerations that surround predictive genetic testing and carrier testing in minors, one could question whether the same guidelines apply for tests that are described by companies as not being for the purpose of preventing, diagnosing or treating medical conditions. It is interesting to note that many companies offering DTC genetic testing declare that their services are not clinical services and should not be used as a basis for making medical decisions. For example, Consumer Genetics writes in its Authorization and Disclosure form that "all materials and products provided by Consumer Genetics, Inc. are provided for informational purposes only and are not by themselves intended for diagnosis or treatment of any disease or disorder." (www.consumergenetics.com). Various companies state that the predictive value of their genetic tests is insufficient as a useful basis for personalized nutritional and lifestyle recommendations. It remains, however, a possibility that consumers will overestimate the predictive value of the genetic tests (Gollust et al., 2002). Knowledge of an increased disease risk may affect the relationship between parents and children, and engender in the parents a sense of responsibility both for the disorder itself and for protecting the infant from its impact (Lupton, 2001). Excessive attention to genetic risk information could also decrease the attention to non-genetic factors in disease development and lead to an overestimation of (non-validated) risk information (Grob, 2008). Moreover, by accepting children's samples submitted by their parents, some companies are neglecting some of their own positions with regard to the sensitive and private character of genetic information. SeqWright states that "your genetic information is extremely sensitive. In fact, it may be the most sensitive information there is and as new discoveries are made, and more is learned about what your genes say about you, this information is likely to become evermore sensitive over time" (www.seqwright.com). DeCODE claimed that "the only people who should be able to see your genetic information are you and those with whom you choose to share it." (www.decodeme.com). Contrary to the latter two companies, which do provide testing in children, it was precisely because of these "ethical, privacy and informed consent considerations regarding genetic testing of minors for predisposition or carrier status of adult-onset genetic disorders" (www.navigenics.com) that Navigenics decide not to process samples or information from children who have not reached the age of majority.

[4] Based on: Borry P, Howard HC, Senecal K, Avard D. Direct-to-consumer genome scanning services. Also for children? Nat Rev Genet 2009; 10(1):8. Borry P, Howard HC, Senecal K, Avard D. Health-related direct-to-consumer genetic testing: a review of companies' policies with regard to genetic testing in minors. Fam Cancer 2009; 9(1):51-59.Howard HC, Avard D, Borry P. Are the kids really all right? Eur J Hum Genet 2011.

The HGC supports the recommendations of the Advisory Committee on Genetic Testing's Code of Practice (1997) (Advisory Committee on Genetic Testing, 1997) which promotes the practice of not supplying genetic testing services direct-to-the-public to those under the age of 16 or to those not able to make a competent decision regarding testing. The European Society of Human Genetics considered that DTC genetic tests should not be offered to individuals who have not reached the age of legal majority (ESHG, 2010).

6. Individualized medical supervision

Embedding genetic testing in a healthcare setting can ensure adequate information provision to increase informed choice, a more optimal informed consent procedure, a medical follow-up if necessary and psychosocial counseling. The offer of genetic tests through the Internet by commercial companies runs the risk to disconnect these services completely from their usual embedding in a medically supervised context. The absence of medical supervision for most DTC tests may compromise or fail to foster patient health especially in the case of carrier couples who may need intensive counseling on their reproductive choices and on the risks for family members. It is striking that companies are usually interested to sell tests, but not interested in the medical supervision of follow up. Most companies refer consumers to seek medical supervision in the established health care system at the consumer's own discretion. For example *Pathway Genomics*: "You should consult with a physician or other appropriate health care professional regarding the diagnosis, treatment and prevention of any disease or health condition." (http://www.pathway.com/more_info/terms_of_service accessed 04/05/2010) Currently, some companies changed their policies and ask for a medical prescription before a sample can be processed. The company also sends the results directly to the physician for interpretation, thereby, technically no longer selling tests directly to consumers. The offer through physicians may eliminate some of the concerns that were raised about information provision, but does not dissolve the issue about the appropriateness of the test provided.

7. Downstream impact on the healthcare 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 direct-to consumer-genetic testing 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 direct-to-consumer genetic testing and are left with complex, diffuse or meaningless information will increasingly look for counseling at a publicly funded centre for medical genetics or with their family doctor" (Hennen, 2008). In this way, DTC services challenge the organization of public health care systems. DTC services may stimulate consumers to visit healthcare professionals after a measurement of their risk of developing a disorder and therefore, there is a potential risk of overconsumption of health care services. A study (ESHG, 2011) showed that at this moment already there is a downstream impact on clinical geneticists of consumers who have ordered not validated and not clinically indicated tests and who nevertheless look for counseling on their test results. Various companies that sell DTC genetic tests also don't want to be burdened with a medical follow up. They often sell only the genetic tests and refer consumers to the healthcare system. For example, "Consumer Genetics, Inc. strongly urges you to discuss the result of this genetic test with your physician. You should not make any treatment decisions without first consulting your doctor." Or SeqWright: "This service cannot be used for medical diagnostic purposes. … Clients with concerns related to the information provided through this service as it pertains to an increased or decreased likelihood of developing a particular disease state, are encouraged to seek medical advice. (…) SNP data are not commonly interpreted by medical professionals. Therefore, SeqWright understands that your doctor may not be able to discuss your results in detail. It is important that you understand that association studies merely provide a statistical probability of a disease and do not serve to diagnose a disease state. With these thoughts in mind, SeqWright strictly maintains that the information and diagnoses provided by medical professionals take precedence over any information provided through SeqWright's Personal Genomic service."

8. Other concerns

Other concerns with regard to the activities of DTC companies include the research activities of these companies performed on submitted samples and information without adequate informed consent or monitoring by a research ethics committee (Howard et al., 2010). In addition, concerns were raised about what is happening to the samples and data when a company is going bankrupt (Zawati et al., 2011).

IV. Direct-to-consumer genetic testing: various policy options

1. Introduction

With this long list of well-founded apprehensions regarding DTC genetic testing, it is no surprise that a number of professional (American College of Medicine Genetics , 2006; Hudson et al., 2007; ESHG, 2010) and governmental organizations (Gutman, 2005; Federal Trade Commission, 2006) and advisory bodies (HGC, 2003; HGC, 2007) have issued statements and reports warning consumers to be skeptical of the claims made by companies selling these tests.[5] Also the Belgian National Committee for Bioethics (Belgian National Committee for Bioethics, 2004) issued a statement on this issue in 2004. What is more startling and troubling is the lack of any concrete and clear regulatory framework or basic oversight of such services and company practices (Schmidt, 2008; Genetics and Public Policy Center, 2006). Discussions about this phenomenon regularly reveal the deficiencies in the current regulatory frameworks (Kaye, 2008). As many companies operate from the U.S.A., it will be crucial to see how this country will develop regulatory oversight in the future. After the partnership announcement between Pathway Genomics and the drugstore chain Walgreens to sell DTC genetic tests, the US Food and Drug Administration (FDA) decided to investigate the activities of DTC companies more carefully (Allison, 2010; Genetics and Public Policy Center, 2009). Between May and July 2010, the FDA sent letters to various companies telling them that they were unable to "identify any Food and Drug Administration clearance or approval number" (FDA, 2010). Moreover, in mid July 2010, the FDA held a meeting to discuss the oversight of laboratory developed tests (LDTs) (FDA, 2010). The issue of (lack of) oversight of LDTs or "home brews" is closely related to that of DTC genetic testing since many of the tests offered by DTC genetic testing companies could be considered LDTs. Until now, the FDA did not require that most LDTs be reviewed for clinical validity (the exception being those genetic tests that produce a result "for the purpose of diagnosing, treating, or preventing disease" (eg: breast cancer and prostate cancer) (Genetics and Public Policy Center, 2010). Immediately after this FDA meeting, the Committee on Energy and Commerce of the US House of Representatives held a public hearing on July 22 2010 (Committee on Energy and Commerce, 2010), during which the report *Direct-to-consumer genetic tests. Misleading test results are further complicated by deceptive marketing and other questionable practices* by the US Government Accountability Office (GAO) was presented. Although no concrete regulatory changes have taken place since these events, it has to be expected that the FDA might take actions in the future.

In the event that DTC companies might operate more and more in European countries, and in Belgium in particular, in the future it is important that Belgian health authorities take the problems related to DTC genetic testing seriously and consider various policy options. The following sections provides some fields where actions might be necessary at the European, Belgian and regional level.

[5] For an overview see http://www.dtcgenetest.org/

2. Revision of the European Directive on in vitro diagnostic medical devices[6]

In Europe medical device regulation is controlled by three E.U. Directives, the third of these is the Directive for In Vitro Diagnostic Medical Devices (IVD) which provides a regulatory framework for all IVDs which are to be placed on the market within the EEA Member States, Switzerland and Turkey. This Directive, which was published in 1998 and came into force in 2003, governs the safety, quality and performance of devices by setting out the essential requirements which have to be addressed before placing a product on the market (e.g. labeling, analytical and diagnostic performances), and, among others, the obligation for post-marketing surveillance.

Although generally less burdensome than the regimes for pharmaceutical products, these legislations share a number of key features: they are concerned with ensuring the safety and performance of healthcare products. Regulating authorities have the possibility to remove existing products from the market should serious problems arise.

Genetic tests with a medical purpose fall under the regulation of in vitro diagnostic medical devices. It should be noted, however, that reagents which are produced within health-institution laboratories for use in that environment and are not subject to commercial transactions are not covered by the Directive for In Vitro Diagnostic Medical Devices (IVD).

Before placing a device on the market the manufacturer must ensure that it meets the requirements of the Directive. Manufacturers must prepare technical documentation sufficient to demonstrate the conformity of their product, and premarket review of this technical file is a process known as conformity assessment. Conformity assessment procedures vary depending on the risks posed by the device. Annex II to the Directive provides currently lists of a small number of tests which are classified as high (list A) and moderate risk (list B). Only devices listed in Annex II and devices intended for self-testing are subject to a conformity assessment by a third part, a Notified Body. This pre-market review is one way to ensure truth-in-labelling, i.e. that the manufacturer's intended use for the product is supported by the clinical data on the test's performance as set out in the technical file, and summarized in the product label and in promotional material. Human genetic testing would generally not fall within Annex II, and therefore not be subject to a third party conformity assessment.

The Directive sets out three criteria which would determine whether a test should be added to Annex II: "(i) whether total reliance has to be placed on the result obtained with a given device, this result having a direct impact on subsequent medical action, and (ii) whether action taken on the basis of an incorrect result obtained using a given device could prove to be hazardous to the patient, to a third party or to the public, in particular as a consequence of false positive or false negative results, and (iii) whether the involvement of a notified body would be conducive to establishing the conformity of the device." But whilst there is a set of criteria, there appears to be little consistency as regards what is currently classified as moderate-risk and what is low-risk. Thus Chlamydia tests are in Annex II, List B, but no other tests for sexually transmitted diseases; PSA is also on List B, but no other cancer test; there is one heritable disorder, PKU, but no others. Furthermore, experience has shown that a list-based approach to classification is not an effective or future-prove mechanism for risk classification of devices based on novel technologies. Due to the specific wording of Annex II, novel devices may not be subject to the requirements laid down for high risk devices, which thus create inconsistency. For instance, Gen-Probe's PCA3 test

[6] Based on: ESHG - European Society of Human Genetics. Official response of the European Society of Human Genetics to the Public consultation on the revision of Directive 98/79/ec of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices 2010. Internet: https://www.eshg.org/fileadmin/www.eshg.org/documents/ESHG/ESHG-IVD-def.pdf

Eurogentest. Official response of the EuroGentest Network of Excellence in Genetic Testing to the Public consultation on the revision of Directive 98/79/ec of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices 2010. Internet: https://www.eshg.org/fileadmin/www.eshg.org/documents/received/EuroGentestResponseToIVDDRevisionConsultation.pdf

quantifies the PCA3 mRNA in a patient's urine sample as a marker for prostate cancer and thus performing exactly the same clinical function as the PSA test, is not included in Annex II, List B.
In 2008, the European Commission held a public consultation concerning a recast of the medical devices directives. This was complemented by a public consultation held in 2010 focused on the technical aspects of the revision of the In Vitro Diagnostics Medical Devices Directive. The answers provided in the context of this public consultation confirmed the quasi unanimous support regarding the adoption of a risk based classification based on the Global Harmonisation Task Force (GHTF) Model. Such a risk based classification would have a positive impact in terms of flexibility, allowing for a better protection of public health while being able to ensure a timely access to the market for new tests. In addition, the regulatory framework would become more robust to the technological progress. The GHTF model it is a four-class system running from high- to low-risk depending on the potential impact on public health and/or the individual patient. The GHTF model places all genetic tests into the Class C category, requiring a third part conformity assessment.
There is an increasing availability of tests predicting susceptibility to common diseases such as stroke and diabetes. For the most part such tests predict relatively minor modifications of an individual's risk and some believe that such susceptibility tests should *not* be treated with as strict regulatory scrutiny as genetic tests which provide information with much greater clinical impact, such as diagnosis of Huntington Disease or Cystic Fibrosis. However, risk classification is based on *probability* as well as *severity* of harm (see GHTF definitions, section 4), and there is good reason to consider that probability of harm is greater with this class of tests, largely because of the continued uncertainty of the science, the highly polygenic nature of most common disease, the failure to discover as yet more than a small portion of what is estimated to be the heritable component of common diseases and the speed with which genetic discoveries are being placed on the market (often as direct-to-consumer tests). Moreover, there is in some cases the possibility of severe harm. For instance, there is anecdotal evidence of people considering prophylactic surgery in the wake of being told they are at increased risk of cancer, even when the increased risk is relatively minor (Stein, 2010). For these reasons it seems reasonable to require susceptibility tests to be subject to pre-market review of the sort applied to tests at a class C level.
Ambiguity in risk classification may offer significant scope for creative construction of intended uses by manufacturers and discrepancies between the stated intended use and the use promoted in practice (for instance, in the USA the PSA test was approved for monitoring patients diagnosed with prostate cancer but promoted for screening use). With regard to the classification of cancer testing according to the GHTF model, devices intended for diagnosis of cancer would be classified in Class C, whereas screening tests would be within Class B. Such distinction may make sense in principle but may be difficult to implement in practice, and may lead to an intentional down-classification of the device by the manufacturer. Regulatory strategies and a rigorous surveillance of post-market activity would have to be set up to deal with this and would include requiring manufacturers to include prominent warnings about the lack of data/approval for off-label uses on their label/instructions or requiring them to provide evidence on the most common clinical applications. With regard to personalized medicine, assays intended for selective therapy and management would fall in Class C, unless the clinical decision should take account of further investigation or of clinical signs and symptoms. Then a down-classification to Class B is possible. The danger remains that the user, and in case of DTC genetic tests the lay person, would not be able to identify the subtle distinctions in the instructions for use. It is preferable to clearly describe and limit/restrict which devices would fall under Class C. With regard to personalized medicine the revised legislation should clearly define what is understood by 'companion diagnostic'. With regard to the classification of devices intended to be used in screening for or in the diagnosis of cancer, classification of both types of devices in Class C is recommended. Furthermore, there are some categories of tests in development which might raise concern but are not discussed within the GHTF model. For instance, there is a great deal of interest in using new genomic/proteomic biomarkers for early identification of Alzheimer's disease. Such applications are fraught with potential dangers, in part because of the well-established problems associated with the trade-off between clinical sensitivity and clinical

specificity in screening tests, but also because of the difficulties of clinical validation in a condition like dementia which contains a broad spectrum of phenotypic variation. The new risk classification schema should be informed by a horizon-scanning exercise to identify the range of new tests being developed which may not have been considered during the development of the GHTF model. Looking to the future, the classification of novel and ambiguous tests will need an EU-level body able to respond with a harmonized decision within short notice, enabling the prompt implementation of decisions taken, in order to avoid disruption of the market. Decisions made by individual notified bodies or competent authorities would run the risk of creating inconsistency.

Both a EuroGentest document and a document from the European Society of Human Genetics (Eurogentest, 2010; ESHG, 2010) advance that the Directive should be revised in order to address the problems arising from DTC genetic tests on an EU-wide basis. The EuroGentest document believes that concerns about the quality of service and lack of medical supervision should be addressed by identifying those tests which may be made available on a direct-to-consumer basis and those which may only be provided with medical supervision. This should not only be done for genetic tests but all IVD devices. DTC advertising of tests which are classified as prescription-only should be illegal. The Eurogentest document advances that following classes of genetic tests should without exception be classed as prescription-only: diagnostic tests (i.e. tests intended to diagnose a medical condition in a person with symptoms and/or signs); pre-symptomatic tests (i.e. tests intended to predict that an asymptomatic person has a high probability of developing a condition), carrier tests (i.e. tests intended to show that a person is a carrier of a condition, so that although they are not themselves affected, there is a risk they may have affected children). In parallel, this document advances that in some cases tests could be made available DTC: susceptibility/predisposition tests (i.e. tests intended to predict the absolute lifetime risk of an individual developing a condition where the probability is relatively low compared with the types of risks identified by pre-symptomatic tests) and nutrigenetic tests (i.e. tests used to provide information about how an individual responds to a particular nutrient or diet. However, the EuroGentest response also advanced that susceptibility tests for serious or potentially fatal diseases should not be available DTC (e.g. for cancer or stroke), particularly where the test may cause undue anxiety or may result in serious preventive measures (e.g. prophylactic surgery in case of cancer). Although arguments can be provided to try to distinguish between classes of genetic tests that could be classed prescription-only, and classes of genetic tests that could be provided directly-to-consumers, a clear classification is difficult. Therefore, the document of the European Society of Human Genetics pleads for a canalization of all health-related genetic tests through medical supervision. In its recent statement on *Direct-to-consumer genetic testing for health-related purposes,* the European Society of Human Genetics stated that "The offer of genetic tests providing health-related information, in the absence of clinical indications and individualized medical supervision, may compromise patient health. Key concerns are the provision of sufficient information about the purpose and appropriateness of testing, its possibilities and limitations, as well as the clinical significance of testing. An involvement of independent medical professionals could avoid the waste of money on tests that are clinically irrelevant. In addition, the cost and adverse psychosocial effects of unnecessary follow-up or medical investigations could be avoided" (ESHG, 2010). Whether or not the provision of genetic tests is done directly-to-consumer or directly-to-doctors, rule 3 of the GHTF risk-classification model should be followed in order that concerns about the quality of the tests are addressed by subjecting them to pre-market review in order to ensure truth-in-labelling and truth-in-promotion.

3. International framework on the provision of genetic tests[7]

In Europe, the Committee of Ministers of the Council of Europe approved on 7 May 2008 an additional protocol concerning genetic testing for health purposes (Council of Europe, 2008) to the Convention on Human Rights and Biomedicine. This additional protocol deals partly with direct-to-consumer services. In article 7.1., this document states that "a genetic test for health purposes may only be performed under individualized medical supervision." As we can read in

[7] Based on Borry P. Europe to ban direct-to-consumer genetic tests? Nat Biotechnol 2008; 26(7):736-737.

the explanatory report, this article has been "driven by the concern to enable the person concerned to have suitable preliminary information with a view to an informed decision regarding the carrying out of this test and, if appropriate, to have access to an appropriate genetic counseling. 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" (Council of Europe, 2008). If this restriction is enacted in the various Member States, this might create limitations to companies offering currently direct-to-consumer services. This additional protocol emphasizes among other issues the importance of genetic counseling, free and informed consent, the protection of persons not able to consent, the respect for private life and the right to information. This additional protocol should be read in relation with the original Convention. In total, of the 47 Member States of the Council of Europe, 35 signed and 28 ratified (http://conventions.coe.int/Treaty/Commun/ChercheSig.asp?NT=164&CM=8&DF=5/19/2008&CL=ENG) until now the original Convention. Ratification is needed before a State can be bound by a treaty. Belgium did not sign and ratify until now. It is not possible to sign and ratify the additional protocol if the original convention has not been signed and ratified. However, it is possible to take over some of the content of the original convention and the additional protocol in separate legislation. This happened for example in various European countries (see below).

4. National legislation on the provision of genetic tests[8]

Various European countries have legislation that foresees a well elaborated regulatory framework for the provision of genetic tests. We present here in particular the existing legislation in France, Germany, Switzerland and Portugal and how these regulatory frameworks have framed DTC genetic testing.

France

In France, genetic tests are well described and framed in the context of health and this legislation could apply to the DTC context. According to the French Law (Article 16-1 Civil Code) genetic tests can only be performed for an individual for "medical or scientific research purposes". When accomplished in a medical context, the genetic analysis should fulfil one of the following elements: (a) to give, confirm or refute the diagnosis of genetic disease for an individual; (b) to detect characteristics of one or more genes, which may be the cause of developing a disease by a person or family members potentially affected; or (c) to adapt the medical care of a person according to its genetic characteristics (Article R1131-1 Public Health Code). As a consequence there is no possibility in France to access a genetic test for another aim, for example just to obtain information. Moreover, the Public health Code provides some complementary provisions with regard to (a) the quality of laboratories and training of scientists and (b) the respect of the medical relationship. Firstly, in order to perform genetic tests in France, laboratories need to get a specific authorization delivered for 5 years, by the Head of the Regional Agency for Health after consultation of the Biomedicine Agency (Article R1131-14, Public Health Code). In the same way, geneticists must conform to a specific requirement to perform genetic tests. They must be specifically trained to be able to verify the results of a genetic analysis (Articles R1131-6 and R1131-7, Public Health Code). Secondly, the use of genetic tests in the clinical context means that the relationship between the user (patient) and the provider (medical doctor) should be defined as a 'medical relationship'. Any other use outside of this context is outlawed and cannot be covered by the following provisions. The French law gives details on the respect of various duties regarding the terms of the patients (or their family) information, the test prescription and the announcement of the results (Articles R1131-4 and following). The law is also strict on the requirements for consent, which must be obtained in writing after the patient has been informed of the nature and the purposes of the test. This regulation insists on the importance of the quality

[8] The description of the legal provisions from the different countries described are taken over from Borry P, van Hellemondt R, Sprumont D, Fittipaldi Duarte Jales C, Rial-Sebbag E, Spranger TM et al. Legislation on direct-to-consumer genetic testing in seven European countries. in review 2011.

of the information delivered by a medical doctor or explained by a genetics counsellor. During the revision process of the French Bioethics law (Loi n° 2004-800 du 6 août 2004 relative à la bioéthique, JO n° 182 du 7 août 2004 modifiant la Loi n° 94-653 du 29 juillet 1994 relative au respect du corps humain et la Loi n° 94-654 du 29 juillet 1994 relative au don et à l'utilisation des éléments et produits du corps humain, à l'assistance médicale à la procréation et au diagnostic prénatal), some of the preparatory reports underlined the necessity to elaborate specific provisions with regard to DTC genetic testing. Considering that DTC tests are being offered internationally and that anticipating the scope of the consumer demand in France will be very difficult, these reports have encouraged the legislator to adopt two kinds of provisions. The conclusions of the reports proposed that, first, prohibition for individuals to use the results of these tests in France should be enshrined in law and, second, that the Biomedicine Agency should be charged to watch the websites offering these tests to ensure their quality and validity. (Office parlementaire des choix scientifiques et technologiques (« L'évaluation de l'application de la loi du 6 août 2004 relative à la bioéthique », 20 novembre 2008), Agence de la biomédecine (« Le bilan d'application de la loi de bioéthique du 6 août 2004 », 2008) ; mission d'information sur la révision des lois bio éthiques (Rapport d'information n° 2235 déposé le 20 janvier 2010).
Finally, the new Bioethics law which entered into force on July the 7th 2011(Law n°2011-814 of July the 7th 2011, published JORF n°0157 July the 8th 2011, page 11826) has implemented most of these proposals. The most significant of these is that from the persons' rights perspective, for the first time the French Public Health code prohibits a person from requesting a genetic test for herself, or for a third person, or for identification through her DNA profile, outside the conditions laid by the law (Article L.1133-4-1). This action is punishable under the article 226-28-1 of the criminal code by a fine of 3.750 Euro. Second, from the institutional perspective, the French Bioethics law reinforces the conditions to be fulfilled by the laboratories which perform genetic tests. In particular, the new article L. 1131-2-1 (Public Health Code) specifies that the study of the genetic characteristics of a person, or the identification of a person through his DNA profile can only be performed by authorized and accredited laboratories (which excludes companies which are not considered as laboratories). Finally, the Biomedicine Agency is unlikely to be in charge of website surveillance due to the difficulty of such a management. Nevertheless the new law added a new mission for the Agency to "make information about the uses of direct-to-consumer genetic tests available to the public and to elaborate a benchmark for the evaluation of their quality" (Article L. 1418-1 paragraph 9, Public health code). The modalities to implement this measure are not given by the law. It will be up to the Biomedecine Agency to act as an independent body and to choose the best way to ensure and fulfil this mission.

Germany
In Germany, there is no legislation that specifically addresses the issue of DTC genetic testing. However, on 24 April 2009 the German Bundestag passed the Human Genetic Examination Act (The Genetic Diagnosis Act, GenDG) (Bundesrat, 2009), which covers some aspects of these genetic testing services. A prior aim of this law, which came into effect on the 1st of February 2010 (Sec. 27 para. 1; for divergences see sec. 27 paragraph 2 to 4), is on the one hand the strengthening of the right to informational self-determination concerning the execution of diagnostic or predictive genetic tests, and on the other hand, the protection against abusive use of the information originating from genetic testing and screening. The Act however focuses on tests carried out under specific circumstances. As art 2 sec. 1 points out, the act only applies to genetic examinations and genetic analyses conducted within the framework of genetic examinations involving born natural persons, as well as embryos and foetuses during pregnancy and the handling of genetic data and genetic samples gained thereby for medical purposes, for purposes of determining descent as well as in the insurance and employment sectors. This Act does not apply to genetic analyses or the handling of genetic samples or genetic data conducted for research purposes, or on the basis of applicable regulations relating to criminal procedures or the Infection Protection Act.

According to sec 7 paragraph 1 of the Act, a diagnostic genetic examination may only be undertaken by physicians and a predictive genetic examination may only be undertaken by

medical specialists in the field of human genetics or other physicians who have qualified themselves via the acquisition of some specialist designation for genetic examination within their specialist area. Paragraph 2 states that the genetic analysis of a biological sample may only be carried out within the scope of a genetic examination and by the medical person in charge or by person or institution commissioned by the responsible medical doctor. Paragraph 3 finally declares that genetic counselling according to sec 10, may only be undertaken by physicians named in paragraph 1 and who are qualified to provide genetic counselling.

Furthermore, a precondition for valid informed consent is the clarification presented in sec. 9 para. 1-3: "Before obtaining consent, the medical person in charge must inform the person concerned on the nature, meaning and consequences of the genetic examination. After being informed the person concerned must receive sufficient time for consideration before deciding to provide consent. The clarification covers in particular: (1) the purpose, type, scope and significance of the genetic examination including the results attainable in the course of the purpose of the examination and with the designated means of examination; the foregoing also includes any genetic characteristics which are to be examined and which are significant in terms of avoiding, preventing or treating any illness or health condition; (2) the health risks for the person concerned which are connected to the knowledge of the results of the genetic examination and the procurement of the necessary biological sample (…); (3) the intended use of any sample as well as the results of any genetic examination or analysis; (4) the right of the person concerned to revoke his or her consent at any time; (5) the right of the concerned person to not have to know results (…)."

Under this legislation, the DTC provision of genetic tests in Germany is clearly restricted. Genetic tests can only be carried out by a medical doctor after the provision of sufficient information concerning the nature, meaning and consequences of the genetic test and after the consent of the person concerned. The German law described in this article does not regulate tests for research purposes, but companies cannot just avoid this legislation by suggesting that their tests are for research and educational purposes only. However, the mere sale of test kits and the application of DTC GT outside the areas described are not prohibited per se, and individuals purchasing tests from abroad will not be penalized. Finally, it must also be noted that the legal discussion of the DTC problem has just begun and therefore many questions are still open. In particular, the relevance of self-determination as a legal concept and the degree to which German law requires protection of the person concerned from their own decisions remains to be clarified.

Switzerland

In Switzerland, the conditions under which human genetic testing may be performed has been regulated under the *Federal Act on Human Genetic Testing* (Federal Assembly of the Swiss Confederation, 2004) from 8 October 2004 (Sprumont, 2004). The genetics tests offered directly-to-consumers correspond to the definition of 'genetic in vitro diagnostic medical devices' as formulated by article 3j of the above mentioned law: "ready-to-use products for the determination of characteristics of human genetic material". Those tests are covered by Article 9 of this Act that reads as follow: "(1) It is forbidden to supply genetic in vitro diagnostic medical devices to individuals for a purpose which cannot be considered part of those individuals' professional or commercial activities; (2) The Federal Council may, having consulted the Expert Commission for Human Genetic Testing, make provision for exceptions to this prohibition provided the products are used under medical supervision and misinterpretation of the test result is not possible."
The Act has been completed by two ordinances: the Federal Council Ordinance on Human Genetic Testing from 14 February 2007 (Federal Assembly of the Swiss Confederation, 2007) and the Federal Department of Home Affairs Ordinance on Human Genetic Testing from 14 February 2007 (Federal Department of Home Affairs, 2007). None of these regulations provide for an exception to article 9 of the Act prohibition for DTC genetic testing. To the best of our knowledge, no one has yet requested from the competent authorities the right to benefit from the exceptions mentioned in the Act. One could therefore conclude that such tests remain unlawful in Switzerland.

In fact, the Act makes it a criminal penalty to infringe this prohibition as stated in article 38: "(1) Any person who, in contravention of Article 9 paragraph 1, wilfully supplies genetic in vitro diagnostic medical devices to individuals for a purpose which cannot be considered part of those individuals' professional or commercial activities shall be liable to a fine; (2) If the act is committed for commercial gain, the penalty shall be a custodial sentence not exceeding three years or a monetary penalty."
Yet, it should be underlined that the prohibition or at least the severe restriction of the law is limited to putting those devices on the market, not the use of them. There is no explicit sanction in the law against someone who imported such test for his or her personal use. The issue is indeed very similar to the one of importing any therapeutic products. In practice, this is tolerated by the law as long as it remains limited to personal use and does not present a risk in terms of public health. For genetic testing, there is still another dimension as there are many companies advertising on the Internet that offer simple and rather inexpensive paternity tests (Sprumont, 2003). The key point in this case is that the test requires testing not only the potential father(s) but also the child. When the latter is a minor, there is a clear conflict of interest for the "father" to consent for him or her, especially when he is not actually the legal father. Courts have already decided that such tests are invalid and could not be used to challenge the family links between a man and a child. There could also be an issue of liability as the test could be considered as an infringement of the personal rights of each person whose DNA is analyzed without their consent (Büchler, 2005) – without mentioning his or her legal parents if their family relationship is denied – and therefore open the way for obtaining indemnities.

Portugal

In Portugal, the Law n°12/2005 of 26 January 2005 defines the concept of health information and genetic information, and sets forth rules for the collection and preservation of biological products for genetic testing for clinical or research purposes. In article 10 of this law, different genetic tests are categorized based on use: tests to be used for the detection of carriers of recessive disorders; pre-symptomatic tests for monogenic diseases; predictive tests allowing the detection of susceptibility genes; pharmacogenetic tests; prenatal tests and tests used for screening. According to article 9.2 of the Law nº12/2005, the detection of the heterozygosity status of recessive diseases, the presymptomatic diagnosis of monogenic diseases and the tests for genetic susceptibility in healthy persons can only be carried out by request of a medical geneticist, following a genetic counselling consultation and subject to the express written and informed consent of the person in question. Article 9.7 also advances that in situations of risk of severe, late-onset diseases that appear in the beginning of adulthood and that have no cure or proven effective treatment, the performance of any presymptomatic or predictive testing must be preceded by a previous psychological and social evaluation and by the follow-up of the patient after the delivery of the tests results. Besides, Article 17.3 also states that every citizen has the right to receive genetic counselling and, if appropriate, psychological and social support, before and after heterozygosity, presymptomatic, predictive or prenatal genetic tests. In this context, it is also important to state that Portugal ratified the Oviedo Convention (Council of Europe, 1997), through Presidential Decree nº 01/2001, which means that the aforementioned Convention has force of law throughout the national territory. According to article 12 of this convention, "tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling" (Council of Europe, 1997). Finally, in July 2008, the National Council of Ethics for the Life Sciences issued an opinion that genetic testing for health purposes should not be offered directly to the public, in compliance with fundamental ethical principles. This document is not a legally binding document.

Based on these provisions, various jurists advance that DTC genetic testing is forbidden in Portugal (Sequeiros, 2011). However, article 15 of Law nº 12/2005 still attributes responsibility to the Government to regulate the conditions of availability and performance of genetic testing. This

is meant to prevent that tests are made available by national or foreign laboratories that do not have the support of a proper and multidisciplinary medical team, and to avoid the possible over-the counter marketing of this type of tests. Notwithstanding this legal provision and an Order, issued in September 2008, by the Ministry of Health, creating a work force to regulate the Law nº 12/2005, there are still no regulations that determine measures for accreditation, certification and licensing of public and private laboratories responsible for genetic testing. As a consequence, there is no specific legislation addressing DTC genetic testing enacted yet and according to some authors, no real legal provisions prohibiting DTC genetic testing services.

Belgium

In Belgium, no specific legislation forbids or regulates the provision of DTC genetic tests. A Royal Decree of 14 December 1987 (Published in the Belgian Official Journal of 25 December 1987) lays down the rules for the provision of genetic testing in the Centres for medial Genetics in Belgium. Additionally, the Royal Decree of June 7th 2007, modifying the Royal Decree of September 7th 1984, sets requirements for laboratories performing reimbursed molecular biological tests for the determination of acquired pathologies in human genetic material. The only legal basis applying to DTC genetic tests could be found in article 2 of the Law on the practice of health care professions (Royal decree n°78 (B.S. 14.11.1967)) [9] which stipulates that a physician should be involved in the practice of medicine. Hence, if a DTC genetic test falls under the practice of medicine, as a consequence, a physician should be involved and the Law on patient rights would apply. In this respect, it is important to determine whether a DTC genetic test could be considered the 'practice of medicine'. As we know, most DTC companies write in their 'terms of services' that they are not practicing medicine, and that their tests should not be considered medical information, but only serve "informational purposes." Whether or not this statement would stand further legal or judicial scrutiny has yet to be proven.

In Flanders, the Flemish regulatory framework on screening has been laid down in the Flemish Parliament Act of 21 November 2003 concerning the preventative health policy. Within the framework of disease prevention and based on the Decision of the Flemish Government of 12 December 2008 on population screening in the framework of the prevention of illness, Flanders organizes population-based screening programmes, which are generalized and structured forms of detection, or screenings for specific diseases or risks in people who are, in principle, free of health complaints. This method allows for advancing the time of diagnosis and thus either obtaining a better treatment results, or preventing complications. The Flemish Government aims to protect the population against unessential or unproven screening and to ensure the quality of population based screenings. Although DTC genetic testing might fall under this regulatory framework, the Flemish authorities (until now) have not stipulated that DTC genetic tests fall under the application of this legislation. That being said, in the case where healthcare professionals or pharmacists would be involved in the provision of DTC tests, then this practice would fall under this legislation.

5. Screening legislation[10]

The Netherlands has no legislation that specifically addresses DTC genetic testing (van Hellemont et al., 2011). In principle, companies are allowed to offer DTC genetic tests to the public. However, the Dutch Act on population screening (henceforth Act), by way of a permit system, seeks to protect individuals against screening programmes that may be a threat to

[9] Article 2: **[**Koninklijk besluit nr 78 betreffende de uitoefening van de gezondheidszorgberoepen] "Niemand mag de geneeskunde uitoefenen die niet het wettelijk diploma bezit van doctor in de genees-, heel- en verloskunde, dat werd behaald in overeenstemming met de wetgeving op het toekennen van de academische graden en het programma van de universitaire examens, of die niet wettelijk ervan vrijgesteld is, en die bovendien de voorwaarden gesteld bij artikel 7, (...) niet vervult."

[10] The description of the legal provisions in the Netherlands is taken overr from Borry P, van Hellemondt R, Sprumont D, Fittipaldi Duarte Jales C, Rial-Sebbag E, Spranger TM et al. Legislation on direct-to-consumer genetic testing in seven European countries. in review 2011.

health. This legal framework was introduced to establish and guarantee a fair balance between the right of self-determination of individuals and the need to protect them against (potentially) harmful screening programmes (Van der Maas et al., 2000). Hence, although the Act on population screening was not developed to regulate the access and the use of DTC genetic tests specifically, it does apply to certain of these tests.
In this Act, population screening is defined as "a medical examination which is carried out in response to an offer made to the entire population or to a section thereof and to detect diseases of a certain kind or certain risk indicators, either wholly or partly for the benefit of the persons examined'. The key word in the definition is *'offer'*. DTC genetic tests which predict diseases based on risk indicators fit within this definition due to the fact that companies advertise and offer their genetic tests directly to the public in magazines, newspapers and through the Internet. The fact that individuals visit the website or the web shop of 'test companies' on their own initiative makes no difference when classifying DTC genetic tests as population screening.
According to the Act, some forms of DTC genetic tests can only be carried out with a permit issued by the Dutch Minister of Welfare and Sports. Offering and practicing DTC genetic tests for detecting (risk factors of) cancer and (risk factors of) 'incurable' diseases –which can neither be treated nor prevented- without a licence is against the law in the Netherlands. Moreover, performing these tests without permission is a punishable offence (article 3 (1) and article 13). Based on article 7, the responsible Dutch Minister can refuse to a provide licence if a test is scientifically unsound, is not in accordance with the professional medical practice standards or if the expected benefit is not in balance with the (potential) health risks. The Act does not set up quality norms for the information to be provided to consumers of DTC genetic tests, nor for consent to use samples and counselling to be provided. Nevertheless, DTC genetic testing companies wishing to sell genetic tests for detecting (risk factors of) cancer and (risk factors of) 'incurable' diseases have to comply with the professional medical practice standards which entail the main rights of patients laid down in the Dutch Civil Code.
Furthermore, the Dutch 'Medical Treatment Contracts Act' as part of the Dutch Civil Code, applies to all contracts whereby a health care provider undertakes to provide medical services. The main purpose of this 'Act' is to clarify and strengthen the legal position of the patient. It lays down the rights and obligations of care providers and the patient. Among other rights, it sets up quality norms for the information to be provided, for obtaining consent and how to deal with confidential patient data. According to the 'Medical Treatment Contracts Act', health care providers have to give information about the indication, the proposed treatment, alternatives, prognoses, risks and possible side-effects prior to starting with a medical intervention. The Dutch permit system guarantees normative criteria for DTC genetic tests aimed at detecting (risk indicators of) cancer and (risk indicators of) 'incurable' diseases. This legal framework effectively prevents individuals from getting access to some DTC genetic tests with a questionable validity and clinical utility in the Netherlands.

However, from the beginning there was confusion about the scope of the Act, and thus uncertainty about the requirement of obtaining a licence. The Health Council -a scientific advisory body- has been allotted the task of advising the Minister on the provision of a licence to applicants under the Act (article 6). The Dutch Health Council has written several reports to clarify the scope of the Act. Despite these helpful reports certain uncertainties remain that are probably inherent to the use of terms like 'population screening', 'offer' and 'incurable'. In the light of these difficulties, already more than 10 years ago there was a call to revise the Act in order to enhance its effectiveness (Van der Maas, 2000).

Flanders has as well an Act on Screening. However, contrary to the Dutch regulatory framework, the Flemish authorities did not consider DTC genetic tests to fall under the application of the Flemish Act on Screening at this moment (unless they would be provided by healthcare professionals or pharmacists). In Wallonia or Brussels, no legislation is in place that regulates the provision of DTC genetic tests in the context of screening legislation.

6. Implementation of existing legislation on information services[11]

In this context, the advice elaborated by the Belgian Advisory Committee is relevant: "As regards the bringing of genetic tests onto the market in Belgium via the Internet, reference should be made to the law of 11 March 2003 on certain legal aspects of the services of the information society (*Belgian Official Journal* of 17.03.2003) and relevant royal decree of enforcement of 7 May 2003 (*Belgian Official Journal* of 07.07.2003), as well as the law of 8 December 1992 for the protection of personal privacy, in respect of the processing of personal data (*Belgian Official Journal* of 18.03.1993). The law of 11 March 2003 is applicable to all "information services". This therefore means: all services provided by electronic means, i.e. which are originally sent and received by the recipient with the aid of computer equipment, even if for example a part of the service is provided physically. The sale of predictive genetic tests via web sites thus falls under this law, even if the blood samples or results are sent by post. Pursuant to Article 5 of this law, the provision of services of the information society by a service provider established on Belgian territory must comply with the requirements in force in Belgium. Every site which offers this kind of service and is established in Belgium, is thus subject to Belgian law and in particular the law on the protection of privacy (*confer infra*). The royal decree of 7 May 2003 implementing the law of 11 March 2003 moreover determines that the services of the General Board of Control and Arbitration of the federal Department for Economic Affairs can take specific measures for the limitation of the free traffic of a service of the information society provided by a service provider established in another European Union Member State. In addition to the fairly cumbersome procedure which this rule provides for, the limitation solely to web sites established on the territory of EU countries clearly appreciably curtails its scope. As regards sites which sell genetic tests and are not established in Belgium but are accessible on Belgian territory, the law of 11 March 2003 makes it possible in some cases for service providers who "host" these sites to be held liable. A "hoster" established in Belgium of sites on which genetic tests are offered for sale, could be held liable if it/he did not take prompt action to remove the information or render access to it impossible as soon as it/he became aware of the illegal nature of the activity or information on its/his server. Data such as the biological samples needed to carry out a genetic analysis, constitute personal data within the meaning of the law of 8 December 1992 on the protection of privacy in respect of the processing of personal data. This law is applicable to the processing of personal data in the framework of activities by a body established on Belgian territory (site selling genetic tests which is established in Belgium), but also when the party responsible for processing the personal data is not established within the European Union, but calls upon automated or non-automated resources which are located on Belgian territory for the processing of personal data. All cases of genetic data being collected on Belgian territory by such sites selling genetic tests consequently fall under the scope of the law, irrespective of the nationality of the person concerned. The law and its implementing decree of 13 February 2001 (Belgian Official Journal of 13.03.2001) lay down a number of principles that apply to every case of processing of personal data. For example, these texts regulate the way in which the collected data should be stored, as well as the subsequent use of this data. But for written consent on the part of the person concerned, personal data on health may only be processed under the responsibility of a professional practitioner in the healthcare sector and certain information should be given to the person concerned at the time the data is collected. The law provides for penalties for failure to observe the legal provisions. The same principles for the protection of personal data are applied in other countries of the European Union. These principles are based on European directive 95/46/EC on the protection of natural persons in respect of the processing of personal data and on the free circulation of these data."

7. Information provision to healthcare professionals and the general public

As with any new market, commercial success for DTC GT companies will depend greatly on the public demand for these services. This consumer demand, in turn, will depend on many factors,

[11] This section has been copied from: Belgian Advisory Committee on Bioethics. Opinion no. 32 of 5 July 2004 on the free availability of genetic tests. 2004. www.health.fgov.be/bioeth.

including consumers' desire or need to obtain genetic testing services outside of the traditional health care system. With this in mind, the DTC model of genetic testing may have underestimated the consumer's attachment to their physician. A report by the investment bank Burril & Company (San Francisco) revealed that physicians remain the most likely source to which individuals will turn for health and genetic information (www.burrillandco.com). A few studies also showed that two thirds of consumers who ordered genetic tests directly to consumer shared their test results with their healthcare professional or were planning to do so (McGuire et al., 2009). In general, the DTC model creates concerns for potential consumers regarding credibility of tests, security of DNA use, privacy of genetic risk information, and lack of confidence in non face-to-face genetic counseling (Wilde et al., 2010). With this in mind, it is not surprising that some companies have recently opted for DTC *advertising* instead of DTC *sales* of their services. They have combined the DTC advertising along with the involvement of regular healthcare professionals who then order the test for their patients. Depending on the test, some companies require an order from a physician (e.g. www.hairdx.com) or an oncologist (e.g. www.collabrx.com). The company Counsyl, (www.counsyl.com) which offers pre-conceptional carrier testing, changed its policy since its launch in February 2010. At the time, Counsyl underlined the possibility of ordering the test directly from the company: "You can order the test directly from our website to receive your kit immediately. Everyone has a prescription: the American College of Medical Genetics (ACMG) recommends that adults of reproductive age be offered carrier testing for cystic fibrosis and spinal muscular atrophy, two of the many conditions assayed by the Universal Genetic Test. Alternatively, you may get the test through your doctor." (https://www.counsyl.com/learn/easy/ accessed 04/05/2010) Since May 2010, however, testing from Counsyl can only be requested through a physician and therefore consumers first need to find a physician that offers the test. The company also sends the results directly to the physician for interpretation, thereby, technically no longer selling tests directly-to-consumers. (https://www.counsyl.com/learn/easy/ accessed 06/06/2010). The offer through physicians may eliminate some of the concerns that arose about information provision, but does not remove the issue of the appropriateness of the test provided. In this context it becomes important whether physicians will take a role of gatekeeper for tests that may prove to be inappropriate. In that regard it is worrisome that some of these companies have lists of medical doctors on their website through which the tests (that are advertised directly to consumers) can be ordered.

Superior Health Council
rue de l'Autonomie 4 • 1070 Brussels • www.css-hgr.be

4. REFERENCES

ACGT - Advisory Committee on Genetic Testing. Code of Practice and Guidance on Human Genetic Testing Services Supplied Direct to the Public 1997. London: Health Departments of the United Kingdom.

ACMG - American College of Medicine Genetics. ACMG statement on direct-to-consumer genetic testing. Genet Med 2006; 6(1):60.

Allison M. Genetic testing clamp down. Nat Biotechnol 2010;28(7):633.

Altman RB. Direct-to-consumer genetic testing: failure is not an option. Clin Pharmacol Ther 2009;86(1):15-7.

Belgian Advisory Committee on Bioethics. Opinion no. 32 on the free availability of genetic tests 2004.
Internet:http://www.health.belgium.be/eportal/Healthcare/Consultativebodies/Commitees/Bioethics/Opinions/index.htm

Bandelt HJ, Yao YG, Richards MB, Salas A. The brave new era of human genetic testing. Bioessays 2008;30(11-12):1246-51.

BR - Bundesrat. Gesetz über genetische Untersuchungen bei Menschen (Gendiagnostikgesetz-GenDG) [Human Genetic Examination Act (The Genetic Diagnostis Act)].
Internet:http://www.gfhev.de/de/startseite_news/2009_GenDG_mit_freundl_genehmg_Baz_Verlag.pdf

Berg C, Fryer-Edwards K. The Ethical Challenges of Direct-to-Consumer Genetic Testing. Journal of Business Ethics 2008;77(1):17-31.

Bekker H, Denniss G, Modell M, Bobrow M, Marteau T. The impact of population based screening for carriers of cystic fibrosis. J Med Genet 1994;31(5):364-8.

Borry P, Howard HC, Senecal K, Avard D. Direct-to-consumer genome scanning services. Also for children? Nat Rev Genet 2009;10(1):8.

Borry P, Howard HC, Senecal K, Avard D. Health-related direct-to-consumer genetic testing: a review of companies' policies with regard to genetic testing in minors. Fam Cancer 2010;9(1):51-9.

Bradford WD, Kleit AN, Nietert PJ, Steyer T, McIlwain T, Ornstein S. How direct-to-consumer television advertising for osteoarthritis drugs affects physicians' prescribing behavior. Health Aff (Millwood) 2006;25(5):1371-7.

BR - Bundesrat. Gesetz über genetische Untersuchungen bei Menschen (Gendiagnostikgesetz-GenDG) [Human Genetic Examination Act (The Genetic Diagnostis Act)].

Internet:http://www.gfhev.de/de/startseite_news/2009_GenDG_mit_freundl_genehmg_Baz_Verlag.pdf

Büchler A. Aussergerichtliche Abstammungsuntersuchungen - Die neuen Bestimmungen des Bundesgesetzes über die genetischen Untersuchungen beim Menschen (GUMG). ZVW 2005;32-44.

Burke W, Atkins D, Gwinn M, Guttmacher A, Haddow J, Lau J, et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. Am J Epidemiol 2002;156(4):311-8.

Burril & Company/Change Wave Research. Personalized Medicine and Wellness Survey. Executive Summary 2008. Internet:
http://www.burrillandco.com/content/CWSurvey_61708.pdf

Calfee JE. An assessment of direct-to-consumer advertising of prescription drugs. Clin Pharmacol Ther 2007;82(4):357-60.

Committee on Energy and Commerce. Hearing on "Direct-To-Consumer Genetic Testing and the Consequences to the Public Health" . Washington; 2010. Internet:.http://energycommerce.house.gov/index.php?option=com_content&view=article&id=2083:hearing-on-direct-to-consumer-genetic-testing-and-the-consequences-to-the-public-health&catid=133:subcommittee-on-oversight-and-investigations&Itemid=73

CE - Council of Europe. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the application of Biology and Medicine: Convention on Human Rights and Biomedicine. Oviedo; 1997.

CE - Council of Europe Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes 2008. Internet:
http://conventions.coe.int/Treaty/EN/Treaties/Html/TestGen.htm

CE - Council of Europe. Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes 2008. Internet: http://conventions.coe.int/Treaty/EN/Reports/Html/TestGen.htm.

Consumer Genetics. Authorization and Disclosure form 2009. Internet:
http://www.consumergenetics.com/pdfs/Asthma-Brochure.pdf

CPS – Canadian Paediatric Society. Bioethics Committee. Guidelines for genetic testing of healthy children. Paediatr Child Health 2003; 8(1):42-5.

DCE – Danish Council of Ethics. Genetic Investigation of Healthy Subjects - Report on Presymptomatic Gene Diagnosis2001. Internet: http://www.etiskraad.dk/sw293.asp

Decode. The deCODEme concept 2009. Internet:
http://www.decodeme.com/index/about_concept .

deCODEme Genetic Scan Service Agreement and Informed Consent 2010. Internet:
http://www.decodeme.com/service-agreement

Donohue J. A history of drug advertising: the evolving roles of consumers and consumer protection. Milbank Q 2006;84(4):659-99.

Donohue JM, Cevasco M, Rosenthal MB. A decade of direct-to-consumer advertising of prescription drugs. N Engl J Med 2007;357(7):673-81.

ESHG – European Society of Human Genetics. Provision of Genetic services in Europe - current practices and issues 2001. Internet: www.eshg.org .

ESHG – European Society of Human Genetics. Statement of the ESHG on direct-to-consumer genetic testing for health-related purposes. Eur J Hum Genet 2010; 18(12):1271-3.

ESHG - European Society of Human Genetics. Survey of European clinical geneticists on awareness, experiences and attitudes towards direct-to-consumer genetic testing. Amsterdam; 2011.

ESHG - European Society of Human Genetics. Official response of the European Society of Human Genetics to the Public consultation on the revision of Directive 98/79/ec of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices 2010. Internet: https://www.eshg.org/fileadmin/www.eshg.org/documents/ESHG/ESHG-IVD-def.pdf

Eurogentest. Official response of the EuroGentest Network of Excellence in Genetic Testing to the Public consultation on the revision of Directive 98/79/ec of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices 2010. Internet: https://www.eshg.org/fileadmin/www.eshg.org/documents/received/EuroGentestResponseToIVDDRevisionConsultation.pdf

Federal Assembly of the Swiss Confederation. Federal Act on Human Genetic Testing 810.12; 2004. Internet: http://www.admin.ch/ch/e/rs/8/810.12.en.pdf

FDA – Food and Drug Administration. Letters to Manufacturers Concerning Genetic Tests 2010. Internet:www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm219582.htm

FDA – Food and Drug Administration. FDA/CDRH Public Meeting: Oversight of Laboratory Developed Tests (LDTs 2010. Internet: www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm#webcast

Federal Assembly of the Swiss Confederation. Federal Act on Human Genetic Testing 810.12; 2004. Internet: http://www.admin.ch/ch/e/rs/8/810.12.en.pdf

Federal Assembly of the Swiss Confederation. Federal Council Ordinance on Human Genetic Testing. 810.122.1; 2007. Internet: http://www.admin.ch/ch/f/rs/8/810.122.1.fr.pdf

Foster MW, Mulvihill JJ, Sharp RR. Evaluating the utility of personal genomic information. Genet Med 2009;11(8):570-4.

FTC - Federal Trade Commission,. CDC - Centers for disease control and prevention. At home genetic tests: a healthy dose of skepticism may be the best subscription 2006. Internet: http://www ftc gov/bcp/edu/pubs/consumer/health/hea02 pdf

GIC - Genetic Interest Group. Over-the-counter Genetic Susceptibility Tests. Information for individuals, families and non-specialist health professionals 2009. Internet: http://www.geneticalliance.org.uk/docs/OTCbooklet09.pdf

Goddard KA, Duquette D, Zlot A, Johnson J, Annis-Emeott A, Lee PW, et al. Public awareness and use of direct-to-consumer genetic tests: results from 3 state population-based surveys, 2006. Am J Public Health 2009;99(3):442-5.

Goddard KA, Moore C, Ottman D, Szegda KL, Bradley L, Khoury MJ. Awareness and use of direct-to-consumer nutrigenomic tests, United States, 2006. Genet Med 2007;9(8):510-7.

Gollust SE, Hull SC, Wilfond BS. Limitations of direct-to-consumer advertising for clinical genetic testing. JAMA 2002;288(14):1762-7.

GPPC – Genetics and Public Policy Center. Direct-to-consumer genetic testing: empowering or endangering the public? 2006. Internet:http://www.dnapolicy.org/policy.issue.php?action=detail&issuebrief_id=32

GPPC – Genetics and Public Policy Center 2009. Internet: http://www.dnapolicy.org/resources/DTCcompanieslist.pdf

Genetics and Public Policy Center. FDA Regulation of Genetic Tests 2010 . Internet:www.dnapolicy.org/images/issuebriefpdfs/FDA_Regulation_of_Genetic_Test_Issue_Brief.pdf

Grob R. Is my sick child healthy? Is my healthy child sick?: changing parental experiences of cystic fibrosis in the age of expanded newborn screening. Soc Sci Med 2008;67(7):1056-64.

GSHG - German Society of Human Genetics. Statement on genetic diagnosis in children and adolescents1995. Internet: http://www.gfhev.de/en/gfh/;

Gutman S. Warning Letter to Access Genetics 2005. Internet:http://www fda gov/cdrh/oivd/letters/080105-access html

Hampl JS, Bramlett-Solomon S, Wharton CM. Direct-to-consumer advertising of prescription medications: Do you see what the public sees? J Am Diet Assoc 2006;106(12):1937-40, 42-3, 45-6.

Hartley NE, Scotcher D, Harris H, Williamson P, Wallace A, Craufurd D, et al. The uptake and acceptability to patients of cystic fibrosis carrier testing offered in pregnancy by the GP. J Med Genet 1997;34(6):459-64.

Hayden EC. Alzheimer's tests under fire. Nature 2008;455(7217):1155.

Hennen L, Sauter A, van den Cruyce E. Direct to consumer genetic testing. European Technology Assessment Group (ETAG) 2008.

HGC – Human Genetics Commission. Genes direct. Ensuring the effective oversight of genetic tests supplied directly to the public 2003. Internet: http://www.hgc.gov.uk

HGC – Human Genetics Commission. More Genes Direct. A report on developments in the availability, marketing and regulation of genetic tests supplied directly to the public 2007. Internet: http://www.hgc.gov.uk.

HGC – Human Genetics Commission. A Common Framework of Principles for direct-to-consumer genetic testing services 2010. Internet: http://www.hgc.gov.uk/Client/document.asp?DocId=280&CAtegoryId=10

Honnor M, Zubrick SR, Walpole I, Bower C, Goldblatt J. Population screening for cystic fibrosis in Western Australia: community response. Am J Med Genet 2000;93(3):198-204.

Howard HC, Knoppers BM, Borry P. Blurring lines. The research activities of direct-to-consumer genetic testing companies raise questions about consumers as research subjects. EMBO Rep 2010;11(8):579-82.

Howard HC, Avard D, Borry P. Are the kids really all right? Direct-to-consumer genetic testing in children: are company policies clashing with professional norms? Eur J Hum Genet 2011;19(11):1122-6.

Hudson K, Javitt G, Burke W, Byers P. ASHG Statement* on direct-to-consumer genetic testing in the United States. Obstet Gynecol 2007;110(6):1392-5.

Hunter DJ, Khoury MJ, Drazen JM. Letting the genome out of the bottle--will we get our wish? N Engl J Med 2008;358(2):105-7.

Janssens AC, Gwinn M, Bradley LA, Oostra BA, van Duijn CM, Khoury MJ. A critical appraisal of the scientific basis of commercial genomic profiles used to assess health risks and personalize health interventions. Am J Hum Genet 2008;82(3):593-9.

Janssens AC, van Duijn CM. An epidemiological perspective on the future of direct-to-consumer personal genome testing. Investig Genet 2010;1(1):10.

Janssens AC, Wilde AA, van Langen IM. The sense and nonsense of direct-to-consumer genetic testing for cardiovascular disease. Neth Heart J 2011;19(2):85-8.

Kaye J. The regulation of direct-to-consumer genetic tests. Hum Mol Genet 2008;17(R2):R180-3.

Kolor K, Liu T, St Pierre J, Khoury MJ. Health care provider and consumer awareness, perceptions, and use of direct-to-consumer personal genomic tests, United States, 2008. Genet Med 2009;11(8):595.

Koninkrijk der Nederlanden. Wet op het bevolkingsonderzoek [Dutch Act on Population Screening] 1992. Internet: http://wetten.overheid.nl/BWBR0005699/geldigheidsdatum_09-02-2010

Kutz G. Nutrigenetic testing. Tests purchases from four web siets mislead consumers. Washington: United States Government Accountability Office 2006.

Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. Genet Med 2008;10(11):820-30.

Ledley F. A consumer charter for genomic services. Nat Biotechnol 2002;20(8):767.

Leib JR, Gollust SE, Hull SC, Wilfond BS. Carrier screening panels for Ashkenazi Jews: is more better? Genet Med 2005;7(3):185-90.

Levenson D. New test could make carrier screening more accessible. Am J Med Genet A 2010;152A(4):vii-iii.

Lupton D. Risk as moral danger: the social and political functions of risk discourse in public health. In: Conrad P, editor. The sociology of health and illness. New York: Worth Publishers; 2001;394-403.

Mahon SM. Impact of direct-to-consumer advertising on healthcare providers and consumers. Clin J Oncol Nurs 2006;10(3):417-20.

Matloff E, Caplan A. Direct to confusion: lessons learned from marketing BRCA testing. Am J Bioeth 2008;8(6):5-8.

McGuire AL, Diaz CM, Wang T, Hilsenbeck SG. Social networkers' attitudes toward direct-to-consumer personal genome testing. Am J Bioeth 2009;9(6-7):3-10.

McQueen MJ. Some ethical and design challenges of screening programs and screening tests. Clin Chim Acta 2002;315(1-2):41-8.

Mihaescu R, van Hoek M, Sijbrands EJ, Uitterlinden AG, Witteman JC, Hofman A, et al. Evaluation of risk prediction updates from commercial genome-wide scans. Genet Med 2009;11(8):588-94.

Mihaescu R, Meigs J, Sijbrands E, Janssens AC. Genetic risk profiling for prediction of type 2 diabetes. PLoS Curr 2011;3:RRN1208.

Molster C, Charles T, Samanek A, O'Leary P. Australian study on public knowledge of human genetics and health. Public Health Genomics 2009;12(2):84-91.

Mouchawar J, Hensley-Alford S, Laurion S, Ellis J, Kulchak-Rahm A, Finucane ML, et al. Impact of direct-to-consumer advertising for hereditary breast cancer testing on genetic services at a managed care organization: a naturally-occurring experiment. Genet Med 2005;7(3):191-7.

Navigenics. Privacy Policy 2009. Internet: http://www.navigenics.com/policies/Privacy/

NCELS - National Council for Ethics in the Life Sciences. Opinion n° 56 on direct marketing of genetic tests to the public 2008. Internet: http://www.cnecv.pt/admin/files/data/docs/1273504469_56CNECV2008_EN.pdf

Palomaki GE, Melillo S, Neveux L, Douglas MP, Dotson WD, Janssens AC, et al. Use of genomic profiling to assess risk for cardiovascular disease and identify individualized prevention strategies--a targeted evidence-based review. Genet Med 2010;12(12):772-84.

Payne Y, Williams M, Cheadle J, Stott NC, Rowlands M, Shickle D, et al. Carrier screening for cystic fibrosis in primary care: evaluation of a project in South Wales. The South Wales Cystic Fibrosis Carrier Screening Research Team. Clin Genet 1997;51(3):153-63.

PSP - People Science and Policy Ltd. The supply of genetic tests direct to the public: supporting the public consultation 2002. Internet:http://www.hgc.gov.uk/UploadDocs/DocPub/Document/evidence_focusgroup.pdf

Putting DNA to the test. Nature 2009;461(7265):697-8.

República Portuguesa. Lei n°12/2005. Informação genética pessoal e informação de saúde [Personal genetic information and health information law] 2005. Internet: http://dre.pt/pdf1sdip/2005/01/018A00/06060611.pdf

República Portuguesa. Direcção-Geral da Saúde. Despacho N° 22784/2008;2011. Internet: http://dre.pt/pdf2sdip/2008/09/172000000/3874338743.pdf

Schmidt C. Regulators weigh risks of consumer genetic tests. Nat Biotechnol 2008;26(2):145-6.

Schommer JC. Direct-to-Consumer advertising for prescription drugs. Minn Med 2005;88(3):32-3, 45.

Sequeiros J. Personal Communication 2011.

SeqWright. Privacy Policy 2008. Internet: http://www.seqwright.com/gps/privacy.php .

Sprumont D. Quelle réglementation des trousses d'analyse génétique. In: Joye C, editor. L'analyse génétique humaine: quelles perspectives législatives. Geneva: Schulthess; 2004. p. 71-88.

Sprumont D, Quéloz N, Benoît A, Schaller F. Conditions de liciéité des tests de paternité par l'analyse d'ADN en dehors du cadre judiciaire. Pratique juridique actuelle 2003;11:1280-90.

Stein R. Mix-ups spur calls for regulation of genetic test kits. Invalid claims, errors prompt FDA hearing 2010. Internet: http://www.boston.com/news/health/articles/2010/07/19/mix_ups_spur_calls_for_regulation_of_genetic_testing_kits/

U.S. GAO - United States Government Accountability Office. Direct-to-Consumer Genetic Tests Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices 2010. Internet: http://energycommerce.house.gov/documents/20100722/Kutz.Testimony.07.22.2010.pdf

Van der Maas PJ, Gevers JKM, Roscam Abbing HDC. Evaluatie Wet op het Bevolkingsonderzoek. Zorg Onderzoek Nederland 2000; Den Haag.

van Hellemondt RE, Hendriks AC, Breuning MH. Regulating the use of genetic tests: is Dutch law an example for other countries with regard to DTC genetic testing? Amsterdam Law Forum 2011; 3(1):13-24.

Wade CH, Wilfond BS. Ethical and clinical practice considerations for genetic counselors related to direct-to-consumer marketing of genetic tests. Am J Med Genet C Semin Med Genet 2006;142C(4):284-92, discussion 93.

Wadman M. Gene-testing firms face legal battle. Nature 2008;453(7199):1148-9.

Wilde A, Meiser B, Mitchell PB, Schofield PR. Public interest in predictive genetic testing, including direct-to-consumer testing, for susceptibility to major depression: preliminary findings. Eur J Hum Genet 2010;18(1):47-51.

Wharton School. Can anyone make sense - or money - out of personal DNA testing?. Knowledge@Wharton 2007. Internet: http://knowledge.wharton.upenn.edu/article.cfm?articleid=1757

Wright CF, Gregory-Jones S. Size of the direct-to-consumer genomic testing market. Genet Med 2010;12(9):594.

Zawati MH, Borry P, Howard HC. Closure of population biobanks and direct-to-consumer genetic testing companies. Hum Genet 2011;130(3):425-32.

5. COMPOSITION OF THE WORKING GROUP

All experts joined the working group ***in a private capacity.*** The names of the members and experts of the Superior Health Council are indicated with an asterisk*.

The following experts were involved in drawing up the advice :

ANTOINE-POIREL Hélène	Human Genetics - Oncogenetics	UCL
BAATOUT Sarah	Radiobiology	SCK- CEN
BLAUMEISER Bettina	Genetics - Gynecology	UA
BORRY Pascal	Biomedical Ethics	K.U.Leuven
CASSIMAN Jean Jacques*	Human genetics	K.U.Leuven
dE THIBAULT DE BOESINGHE Léopold	Industrial Medecine, oncologist radiotherapy nuclear medecine	UGent - Member of the Consulting Bioethics Committee of Belgium
FONDU Michel*	Chemistry, additives, contaminants	ULB
GODDERIS Lode	Occupational Health Physician, Toxicologist	K.U. Leuven

HAUFROID Vincent	Pharmacogenomics	UCL
HULSTAERT Frank	Medicine	KCE
KIRSCH-VOLDERS Micheline*	Cellular and environmental genetics	VUB
LIEBAERS Inge	Medical Genetics	VUB - former president of the High council on human genetics - Member of the Consulting Bioethics Committee of Belgium
LOEYS Bart	Human Genetics	UA
POPPE Bruce	Medical Genetics	UGent
SCHAMPS Geneviève,	Biomedical Law	UCL - Member of the Consulting Bioethics Committee of Belgium
VAN LAREBEKE Nicolas	Carcinogenesis and cancer prevention	UGent
VAN NEROM Anne	IVD competent authority	Scientific Institute of Public Health
VAN OYEN Herman*	Public Health, epidemiology	Scientific Institute of Public Health
VERELLEN-DUMOULIN Christine	Human Genetics	UCL, IPG
VIKKULA Mikka	Molecular Human Genetics	UCL

The working group was chaired by Herman VAN OYEN, the scientific secretary was Sylvie GERARD

About the Superior Health Council (SHC)

The Superior Health Council is a federal body that is part of the Federal Public Service Health, Food Chain Safety and Environment. It was founded in 1849 and provides scientific advisory reports on public health issues to the Ministers of Public Health and the Environment, their administration, and a few agencies. These advisory reports are drawn up on request or on the SHC's own initiative. The SHC takes no decisions on the policies to follow, nor does it implement them. It does, however, aim at giving guidance to political decision-makers on public health matters. It does this on the basis of the most recent scientific knowledge

Apart from its 25-member internal secretariat, the Council draws upon a vast network of over 500 experts (university professors, members of scientific institutions), 200 of whom are appointed experts of the Council. These experts meet in multidisciplinary working groups in order to write the advisory reports.

As an official body, the Superior Health Council takes the view that it is of key importance to guarantee that the scientific advisory reports it issues are neutral and impartial. In order to do so, it has provided itself with a structure, rules and procedures with which these requirements can be met efficiently at each stage of the coming into being of the advisory reports. The key stages in the latter process are: 1) the preliminary analysis of the request, 2) the appointing of the experts within the working groups, 3) the implementation of the procedures for managing potential conflicts of interest (based on the declaration of interest, the analysis of possible conflicts of interest, and a referring committee) and 4) the final endorsement of the advisory reports by the Board (ultimate decision-making body). This coherent set of procedures aims at allowing the SHC to issue advisory reports based on the highest level of scientific expertise available whilst maintaining all possible impartiality.

The advisory reports drawn up by the working groups are submitted to the Board. Once they have been endorsed, they are sent to those who requested them as well as to the Minister of Public Health and are subsequently published on the SHC website (www.css-hgr.be), except as regards confidential advisory reports. Some of them are also communicated to the press and to target groups among healthcare professionals.

The SHC is also an active partner in developing the EuSANH network (European Science Advisory Network for Health), which aims at drawing up advisory reports at the European level.

In order to receive notification about the activities and publications of the SHC, you can send a mail to info.hgr-css@health.belgium.be.

Superior Health Council
rue de l'Autonomie 4 • 1070 Brussels • www.css-hgr.be